

A Longitudinal Study of the Effects of a Gluten-Free Diet on Glycemic Control and Weight Gain in Subjects With Type 1 Diabetes and Celiac Disease

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OBJECTIVE — To describe the longitudinal growth characteristics and glycemic control in type 1 diabetic children diagnosed with celiac disease and started on a gluten-free diet (GFD).

RESEARCH DESIGN AND METHODS — Data on growth and glycemic control for 11 case subjects diagnosed with celiac disease (cd⁺ group) and started on a GFD were collected prospectively, and two control subjects without celiac disease matched for age, sex, and duration of diabetes (cd⁻ group) were selected for comparison.

RESULTS — In the period between diagnosis of type 1 diabetes and start of a GFD in the cd⁺ compared with the cd⁻ group, BMI standard deviation score (SDS) was lower (−0.2 vs. 0.7, $P = 0.015$), as was HbA_{1c} (8.9 vs. 9.8%, $P = 0.002$). In a regression model the cd⁺ group had lower BMI SDS ($P < 0.001$) and lower HbA_{1c} ($P = 0.04$), independent of other variables. On a GFD, BMI SDS increased by 12 months in the cd⁺ group and then was no different than the cd⁻ group (1.1 vs. 1.0, $P = 0.11$), whereas HbA_{1c} improved further within case subjects compared with pre-GFD (8.9 vs. 8.3%, $P = 0.002$). On a GFD, case subjects in contrast to control subjects showed no deterioration in HbA_{1c} during the years of puberty (8.3 vs. 10.0%, $P = 0.022$).

CONCLUSIONS — In children with type 1 diabetes, untreated celiac disease resulted in lower BMI SDS and lower HbA_{1c}. Recovery of BMI SDS with a GFD was associated with further improvement in HbA_{1c} as compared with pre-GFD, with no expected deterioration in glycemic control during puberty. These apparent clinical benefits need confirming by larger studies.

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With the advent of sensitive and specific serological testing, it is clear that celiac disease is more common than previously thought (1–3). In children with type 1 diabetes, prevalence rates are in the region of 1–10% compared with 0.01–0.03% in the general population (1–6). A significant proportion of these patients is clinically asymptomatic or have atypical features only recognized in retrospect (7). The co-

existence of both conditions may reflect a similar genetic background and an association with HLA haplotypes; in particular, the DQB1 locus is well-recognized (8).

Screening for anti-gliadin antibodies (AGA) and anti-endomysial antibodies (EMA) as part of routine diabetes care provides an opportunity to diagnose celiac disease at an early preclinical silent stage. However, screening in this popula-

tion has not been universally adopted, and controversy exists as to whether it is of any clinical benefit (9). Previous reports on the influence of celiac disease on growth and metabolic control in type 1 diabetic patients have been mainly cross-sectional, and thus far results are conflicting (10–20). In addition, the benefit of a gluten-free diet (GFD) in silent case subjects is also in doubt. The full impact of screening for celiac disease and intervention with a GFD would require a longitudinal study comparing those on a GFD against untreated control subjects; however, this may be impractical and unethical. An alternative is to use a longitudinal case-control design, comparing outcome in those type 1 diabetic patients with celiac disease against those without celiac disease.

We report the results of longitudinal study of growth and metabolic control in 11 children with type 1 diabetes who were subsequently diagnosed with celiac disease (cd⁺ group) and started on a strict GFD. At diagnosis of celiac disease, each case was matched for age, sex, and duration of diabetes with two children with type 1 diabetes but no celiac disease (cd⁻ group).

Study design

Population. Between 1994 and 1998, the pediatric diabetic clinic at John Radcliffe Hospital, Oxford, consisted of 230 children who were all seen every 3 months. Screening for celiac disease was performed annually from the first year after diagnosis of type 1 diabetes by obtaining a sample of blood from each patient for the determination of serum IgA EMA and total IgA levels. Serum from subjects with low total IgA levels (<0.5 g/l) was assayed for IgG AGA antibodies.

Celiac-positive case subjects. A total of 10 children were EMA positive and 1 child with low total IgA levels was AGA positive, accounting for 4.8% of the clinic population (10). Of these 11 case sub-

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Abbreviations: AGA, anti-gliadin antibodies; CV, coefficient of variation; EMA, anti-endomysial antibodies; GFD, gluten-free diet; SDS, standard deviation score.

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

Table 1—Comparison of case and control subjects

	Case subjects	Control subjects
At diagnosis of type 1 diabetes		
n	11	22
Sex (male/female)	5/6	10/12
Height SDS	0.1 ± 0.2	0.7 ± 0.3
Weight SDS	-0.7 ± 0.3*	0.5 ± 0.3*
BMI SDS	-1.2 ± 0.1†	-0.1 ± 0.1†
C-peptide (pmol)	72.8 ± 23	76.1 ± 13
Age (years)	8.1 (1.2–16.1)	7.4 (1.3–14.8)
At diagnosis of celiac disease in cases		
Age (years)	13.8 (2.6–17.3)	13.2 (2.2–18.0)
Duration of type 1 diabetes (years)	4.2 (0.9–7.2)	4.0 (1.0–10)

Data are means ± SEM and median (range). * $P = 0.002$; † $P = 0.005$.

jects, 3 were detected on their first annual screening test. Only one patient demonstrated symptoms typical of celiac disease, presenting at the time of screening with failure to thrive and steatorrhea. Also, four subjects had retrospective histories of mild abdominal discomfort and diarrhea. All subjects were counseled regarding a jejunal biopsy, which was carried out by endoscopy under sedation. Multiple biopsy specimens were obtained from the distal duodenum and proximal jejunum. The specimens were examined by a hospital pathologist and pediatric gastroenterologist. All 11 case subjects showed classical histological features of celiac disease and were commenced on a GFD under supervision of a dietitian.

Celiac-negative control subjects. At the time of diagnosis of celiac disease, each case was matched for age, sex, and duration of diabetes with two type 1 diabetic control subjects from the same clinic who had negative AGA/EMA status (Table 1).

Data collection. Height, weight, and HbA_{1c} were measured on all subjects every 3 months from diagnosis of diabetes, and C-peptide levels were measured every year. These data, together with daily insulin requirements and insulin regimen, were recorded in subject case notes at each clinic appointment. Data were collected retrospectively from the case records of both celiac-positive case subjects and matched control subjects from the time of diagnosis of diabetes to diagnosis of celiac disease, and were collected prospectively from start of a GFD in case and control subjects for 4 years. Once a diagnosis of celiac disease was confirmed and a GFD was started in case subjects, AGA/EMA levels were tested every 3 months until negative and every year

thereafter as a marker of good dietary compliance. In control subjects, AGA/EMA levels were tested yearly and to date remain negative. Height and weight were measured by a single observer.

Assays. EMAs were detected using indirect immunofluorescence on cryostat sections of lower third primate esophagus. Sera were screened at a 1:5 dilution and were reincubated with rabbit anti-serum IgA-specific fluorescein conjugate (Dako). Sections were examined under UV light immunofluorescence. Positive sections were identified by characteristic perivascular endomysial staining. Total serum IgA levels were determined by immunochemical quantification (Beckman). IgG AGA were analyzed using rodent stomach tissue cryostat sections preincubated in gliadin. Sera were screened at a 1:10 dilution and incubated on sections at room temperature for 30 min before being washed and reincubated with fluorescinated anti-human IgG conjugate (Dako). Sections were read under UV light immunofluorescence for characteristic staining patterns. HbA_{1c} was measured by high-pressure liquid chromatography (Diamat). The intra-assay coefficients of variation (CVs) were 1.9 and 2.2% at HbA_{1c} levels of 6.9 and 11.5%, respectively. The inter-assay CVs were 2.7 and 2.3% at HbA_{1c} levels of 7.0 and 11.6%, respectively. Normal population range was 4.0–6.5%. C-peptide was measured using a double-antibody radioimmunoassay from DPC Ltd. The intra-assay CV at C-peptide levels of 294 and 2,614 pmol/l were 3.4 and 3.0%, respectively. Equivalent inter-assay CVs were 1.9 and 10.0%, respectively.

Statistics. Data for BMI standard deviation score (SDS) and HbA_{1c} were nor-

mally distributed (as confirmed by the One-Sample Kolmogorov-Smirnov Test). Each case was matched against two control subjects. All analyses compared the mean data from case subjects (weight, height, insulin dose, C-peptide level, and HbA_{1c}) against the mean data from the two matched control subjects. A general linear ANOVA model was used for comparison of data between the groups and data within case subjects. For each individual, the proportion of the observed period spent on a particular insulin regimen was expressed as a percentage of the total observation period. These data were then compared between the groups using the χ^2 test. An ANOVA model was used to determine the influence of celiac disease on both HbA_{1c} and BMI SDS, allowing for factors such as insulin dose, insulin regimen, and time. Time was expressed as months relative to onset of celiac disease. Data are presented as mean values ± SEM unless otherwise stated, and a P value <0.05 was considered significant.

Height, weight, and BMI SDS (measured as kilograms per meter squared) scores were calculated using reference data based on the British 1990 Growth Reference and Cole's LMS method supplied by the Childhood Growth Foundation (21). SPSS version 10 was used for all statistical analysis and significance.

RESULTS

At diagnosis of diabetes

Cohort characteristics are described in Table 1. In case subjects compared with control subjects, mean BMI SDS was significantly lower (-1.2 ± 0.1 vs. -0.1 ± 0.1 , $P = 0.005$), as was mean weight SDS (-0.7 ± 0.3 vs. 0.5 ± 0.3 , $P = 0.002$) (Table 1). There was no difference between the groups in mean height SDS (0.1 ± 0.2 vs. 0.7 ± 0.3 , $P = 0.19$) or mean C-peptide level (72.8 ± 23 vs. 76.1 ± 13 pmol/l, $P = 0.32$) (Table 1). For case subjects diagnosed at first antibody testing (i.e., within 1 year of onset of diabetes) compared with case subjects diagnosed in >1 year of onset of diabetes, no difference was found in BMI SDS.

At diagnosis of celiac disease

Cohort characteristics at diagnosis of celiac disease are described in Table 1. The mean age of diagnosis of celiac disease was 11.2 years (range 2.2–17.3). The

Table 2—Characteristics of case and control subjects for the period from diagnosis of type 1 diabetes to diagnosis of celiac disease in case subjects and for the period of follow-up on GFD

	Period from diagnosis of type 1 diabetes to diagnosis of CD		Period of follow-up on GFD in cases	
	Cases	Controls	Cases	Controls
BMI SDS	$-0.2 \pm 0.2^*$	$0.7 \pm 0.2^*$	1.1 ± 0.1	1.0 ± 0.1
HbA _{1c} (%)	$8.9 \pm 0.3^\ddagger$	$9.8 \pm 0.3^\ddagger$	$8.3 \pm 0.2^\ddagger$	$10.0 \pm 0.2^\ddagger$
Insulin ($\text{units} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$)	0.8 ± 0.1	0.8 ± 0.1	1.0 ± 0.04	1.0 ± 0.03
Insulin regimen	81/19/0§	64/16/20§	55/41/4	55/20/25

Data are means \pm SEM, and insulin regimen is expressed as percentage of time on two-, three-, and four-a-day injections, respectively. CD, celiac disease. * $P = 0.015$; $^\ddagger P = 0.002$; $^\ddagger P = 0.022$; $§P = 0.019$.

mean duration of diabetes at diagnosis of celiac disease was 3.8 years (range 0.9–7.2). Of the 11 case subjects, 3 were detected on their first annual screening test.

The mean number of annual screening tests was four per subject, range 1–7. In the period between diagnosis of type 1 diabetes and the diagnosis of celiac dis-

ease, mean BMI SDS remained significantly lower in case subjects compared with control subjects (-0.2 ± 0.2 vs. 0.7 ± 0.2 , $P = 0.015$) (Table 2) (Fig. 1), as was mean HbA_{1c} (8.9 ± 0.3 vs. 9.8 ± 0.3 , $P = 0.002$) (Table 2) (Fig. 2). Clinical mean HbA_{1c} for this age group was 9.3%. There was no difference in daily insulin dose between the groups (0.8 ± 0.1 vs. 0.8 ± 0.1 $\text{units} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, $P = 0.54$ for cd^+ vs. cd^-), but case subjects received less-intensive insulin regimens compared with the cd^- group (as expressed by the proportion of the total observation period spent on a particular regimen, $\chi^2 = 7.6$, $P = 0.019$) (Table 2). There was no difference in mean C-peptide levels (13.2 ± 2.0 vs. 26.5 ± 5.6 pmol/l , $P = 0.22$ for cd^+ vs. cd^-).

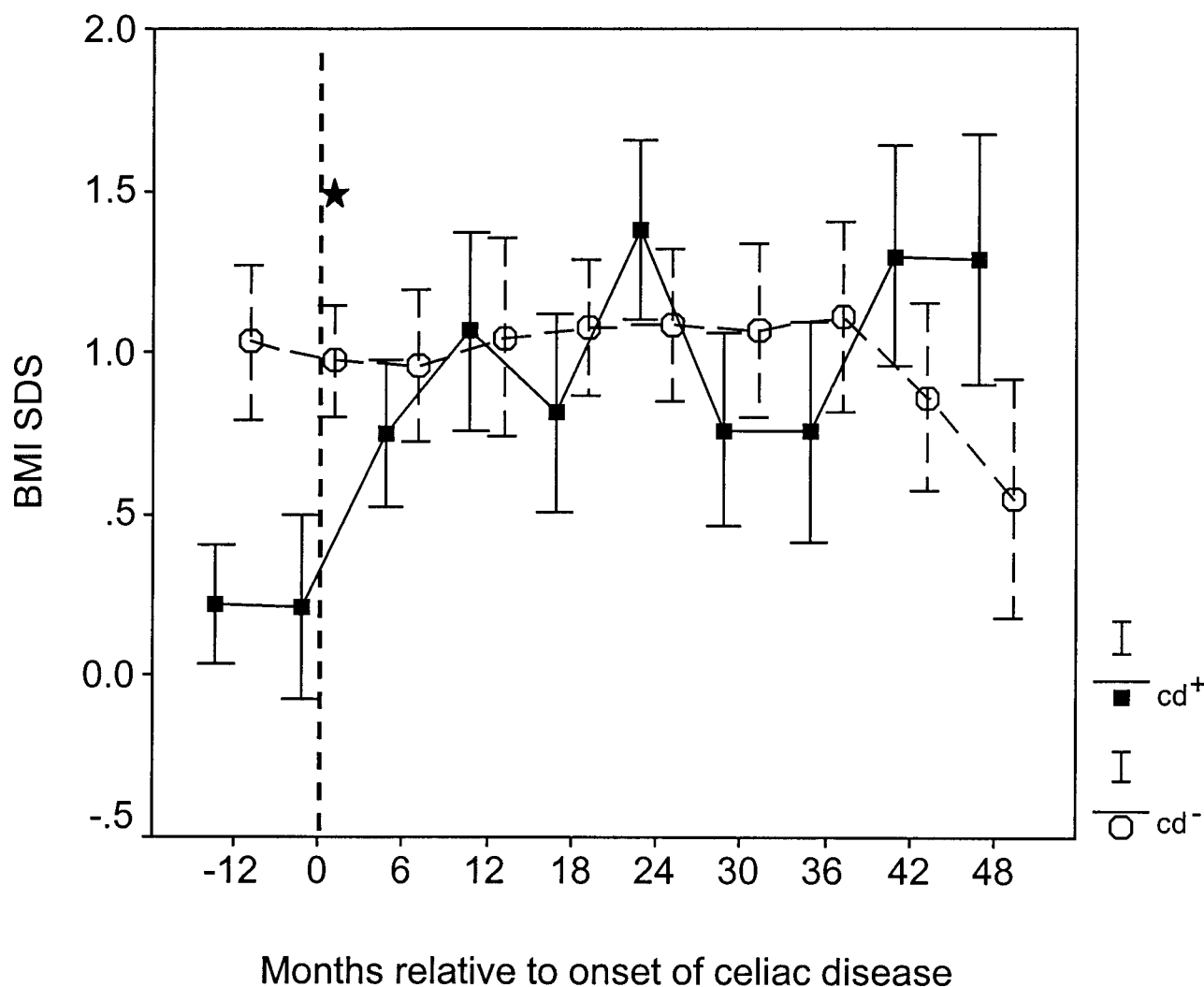


Figure 1—BMI SDS (\pm SEM) in case subjects with type 1 diabetes and celiac disease (cd^+) compared with control subjects without celiac disease (cd^-). Time 0 indicates diagnosis of celiac disease, after which time GFD was started in case subjects. *, Significant difference at this time point, $P < 0.05$.

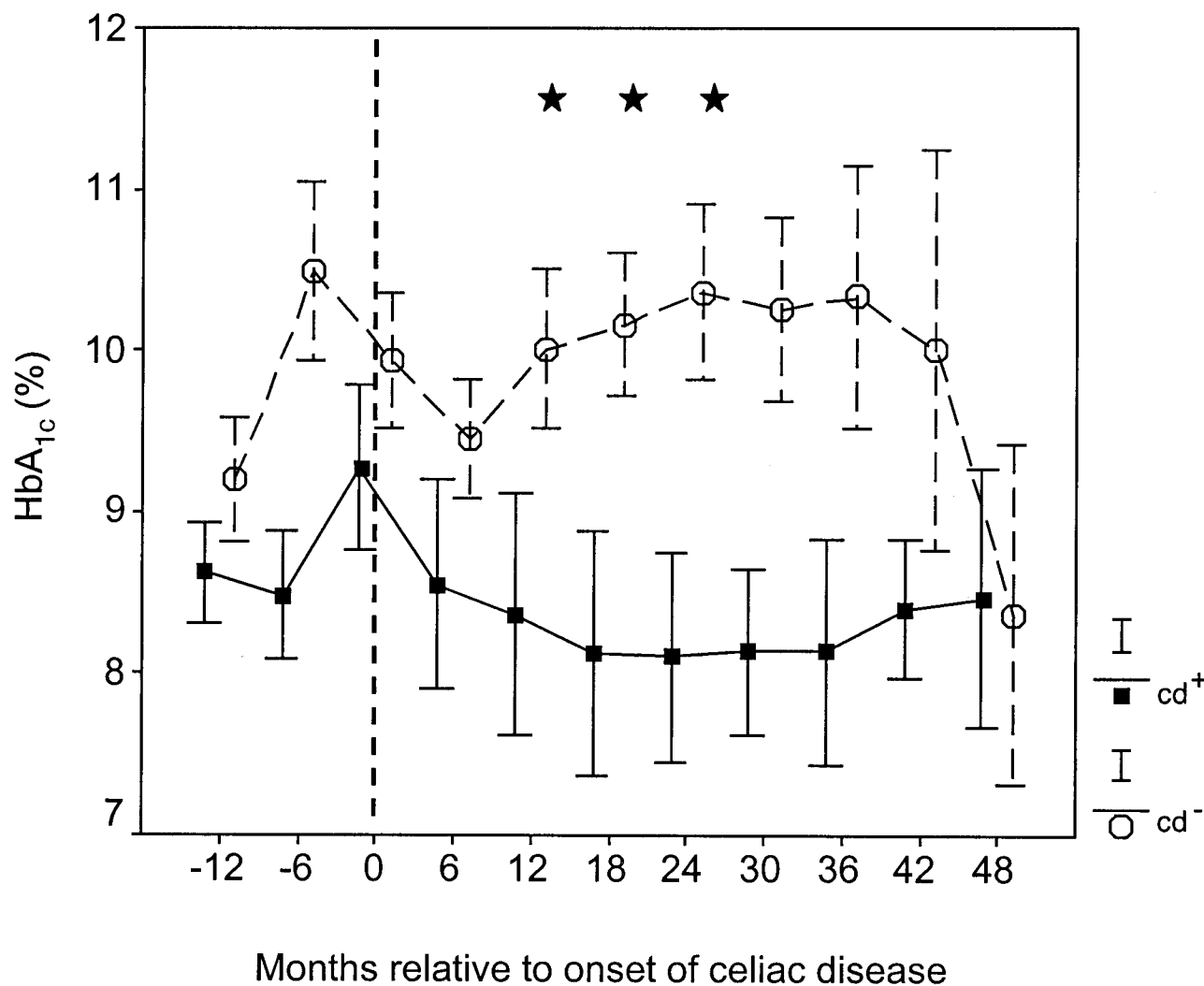


Figure 2—HbA_{1c} levels (\pm SEM) in case subjects with type 1 diabetes and celiac disease (cd^+) compared with control subjects without celiac disease (cd^-). Time 0 indicates diagnosis of celiac disease, after which time a GFD was started in case subjects. \star , Significant difference at this time point, $P < 0.05$.

Effect of GFD

Of the 11 case subjects, 6 agreed to a repeat small bowel biopsy on a GFD that was consistent with the diagnosis of celiac disease and successful treatment. All subjects reverted to antibody-negative status within 3–6 months of starting a GFD and have remained negative to date. Symptoms resolved in the single subject who was symptomatic at diagnosis of celiac disease. The difference in mean BMI SDS between case subjects and control subjects at diagnosis of celiac disease was reversed over 12 months after the start of a GFD (1.1 ± 0.13 vs. 1.0 ± 0.1 , $P = 0.11$) (Table 2). Thereafter, there was no significant difference in mean BMI SDS between the groups. To date, the control subjects remain antibody negative on annual screening.

For case subjects, mean HbA_{1c} levels were lower for the period on a GFD compared with before diagnosis of celiac disease (8.9 ± 0.1 vs. 8.3 ± 0.1 , $P = 0.002$). Furthermore, on a GFD, mean HbA_{1c} levels remained significantly lower in case subjects compared with control subjects (8.3 ± 0.2 vs. $10.0 \pm 0.2\%$, $P = 0.02$) (Table 2).

In both groups, insulin requirements increased compared with before a GFD was started (0.8 ± 0.1 vs. 1.0 ± 0.04 , $P < 0.001$ for pre- vs. post-GFD), but there was no difference in daily insulin dose (units \cdot kg⁻¹ \cdot day⁻¹) between the groups (1.0 ± 0.04 vs. 1.0 ± 0.03 , $P = 0.33$ for cd^+ vs. cd^-). In the follow-up period after a GFD was started, there was no statistical difference in the proportion of time spent on a particular insulin

regimen between the groups ($P = 0.20$) (Table 2).

Influence of celiac disease on BMI SDS and HbA_{1c}, allowing for other covariates

From diagnosis of diabetes to diagnosis of celiac disease, in using a general factorial linear model, celiac disease was associated with lower BMI SDS ($F = 32.6$, $P < 0.0001$) and a lower HbA_{1c} ($F = 4.2$, $P = 0.04$) across time (months relative to onset of celiac disease), independent of other factors, namely insulin dose and insulin regimen. Similarly, in the period on the GFD, celiac disease was associated with lower HbA_{1c} ($F = 5.1$, $P = 0.027$), independent of BMI SDS, insulin dose, and insulin regimen.

CONCLUSIONS— We report results from a longitudinal case-controlled study detailing the impact of celiac disease on children with type 1 diabetes before and after intervention with a GFD. Untreated celiac disease was associated with lower BMI SDS and lower HbA_{1c}. Introduction of a GFD led to recovery of BMI SDS and further improvement in HbA_{1c}. In contrast to control subjects, in case subjects there was no deterioration in glycemic control during the pubertal years.

Symptomatic celiac disease shows a dramatic response to intervention with a GFD (15,22); however, serological testing now permits an earlier diagnosis of celiac disease (23,24). Prevalence rates in the region of 1.7–10% have been reported in the pediatric diabetes clinic setting (2–5), with many case subjects being asymptomatic or having atypical features only recognized in retrospect (7).

Previous studies investigating the effect of celiac disease on type 1 diabetes and the benefit of treatment with GFD have been cross-sectional or confounded by lack of control subjects (5,11,14,17,20–22), relied on inadequate longitudinal follow-up data (10–13,19,25), or were disrupted by poor compliance to a GFD (13,14); thus, data are conflicting. A question therefore remains as to whether it is worthwhile to screen for silent celiac disease and whether subjects benefit from a GFD in terms of metabolic control and growth.

At diagnosis of diabetes, our data show lower BMI SDS in case subjects compared with control subjects, and as far as we know, this has not been previously described. Although we have no information on EMA/AGA status at diagnosis of diabetes, this may indicate the presence of silent celiac disease. This may be further evidence of a possible common immunopathology in genetically susceptible individuals; however, the pathogenetic mechanisms remain unexplained (23,26).

From diagnosis of type 1 diabetes to diagnosis of celiac disease, lower BMI SDS in our case subjects has again been inadequately described in previous studies. Some report short stature with no differences in weight (4,5,11,16), whereas others have shown no differences in height or weight (15–17,19,25). During the same period, HbA_{1c} levels were lower in case subjects despite no difference in C-

peptide levels. Both these features may be consistent with the effects of villous atrophy secondary to celiac disease and subsequent carbohydrate malabsorption.

Once established on a GFD, the difference in BMI SDS took 12 months to disappear, presumably reflecting slow recovery of small bowel morphology. Others have previously shown no difference in growth parameters regardless of dietary compliance (20). Within case subjects, the start of a GFD resulted in further significant improvement in mean HbA_{1c} levels compared with pre-GFD, confirming findings of some studies (24,27) but not others (13,14,19,25). Furthermore, mean HbA_{1c} levels were also lower when compared with control subjects. The period of follow-up on a GFD was in the pubertal age range, when even well-motivated intensively treated patients invariably demonstrate worsening glycemic control compared with prepuberty, which in part is related to increased insulin resistance (28). As expected, this occurred in the control group, with a gradual rise in HbA_{1c}. In contrast, those with celiac disease did not show any worsening of glycemic control, suggesting that intervention with a GFD is associated with improvement (or lack of deterioration) in glycemic control compared with control subjects. We found no difference in C-peptide levels, insulin dose, or regimen to account for these findings, which may be due to small sample size and increased dietetic input received by case subjects. An alternative explanation is that a GFD may influence insulin sensitivity. The glycemic index of gluten-free and gluten-containing foods is similar (29). However, data suggest that the type of carbohydrate may be important in influencing insulin sensitivity (30). The gain in BMI SDS and lack of deterioration in HbA_{1c} in case subjects during puberty while on a GFD, with no difference in insulin dose between the groups, would be compatible with this explanation. No difference in HbA_{1c} between the groups was found at the end of the follow-up period, and this may signify that puberty is complete and differences in insulin sensitivity are less pronounced.

This study is limited by small sample size, yet detailed follow-up is longer than previously published data, with case subjects being tightly matched to control subjects. Mean HbA_{1c} levels in the control group were higher than the clinic mean, which may reflect unmatched factors that

impact glycemic control. In addition, initial data are potentially skewed by the presence of three case subjects diagnosed within 1 year of diagnosis of diabetes. However, comparisons of these against the remaining case subjects revealed no significant differences and therefore our initial observations remain valid. Only six subjects were re-biopsied on a GFD to ensure compliance with diet, although all case subjects maintained a negative antibody status throughout the study period.

A recent review by Holmes (9) recommended routine antibody screening on the basis of the high prevalence of silent celiac disease in type 1 diabetic subjects and the availability of a cost-efficient method for screening. The long-term sequelae of untreated celiac disease, such as gastrointestinal malignancy, lymphoma, infertility, and osteoporosis, would also suggest long-term benefit from a GFD (31–33). We have demonstrated in a longitudinal case-controlled study in children with type 1 diabetes that silent celiac disease results in poor weight gain and lower HbA_{1c} independent of daily insulin dose and regimen. Intervention with a GFD causes BMI SDS to recover and HbA_{1c} to improve further within case subjects compared with before the GFD. In addition, case subjects in contrast to control subjects did not demonstrate the deterioration in glycemic control that invariably occurs during puberty. These apparent clinical benefits need confirming by larger, similarly designed studies before routine antibody screening is universally adopted.

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