High Prevalence of Microvascular Complications in Adults With Type 1 Diabetes and Newly Diagnosed Celiac Disease

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OBJECTIVE—The implications of celiac disease (CD) in adult patients with type 1 diabetes are unknown, with respect to diabetes-related outcomes including glycemic control, lipids, microvascular complications, quality of life, and the effect of a gluten-free diet (GFD). We identified CD in adults with type 1 diabetes and investigated the effect of a GFD on diabetes-related complications.

RESEARCH DESIGN AND METHODS—This was a case-control study conducted at a U.K. teaching hospital. Patients with type 1 diabetes aged >16 years (n = 1,000) were assessed for CD. HbA_{1c}, lipid profile, quality of life, retinopathy stage, nephropathy stage, and degree of neuropathy before and after 1 year on a GFD were assessed.

RESULTS—The prevalence of CD was 33 per 1,000 subjects (3.3% [95% CI 2.3–4.6]). At diagnosis of CD, adult type 1 diabetic patients had worse glycemic control (8.2 vs. 7.5%, P = 0.05), lower total cholesterol (4.1 vs. 4.9, P = 0.014), lower HDL cholesterol (1.1 vs. 1.6, P = 0.017), and a higher prevalence of retinopathy (58.3 vs. 25%, P = 0.02), nephropathy (41.6 vs. 4.2%, P = 0.009), and peripheral neuropathy (41.6 vs. 16.6%, P = 0.11). There was no difference in quality of life ($P > 0.1$). After 1 year on a GFD, only the lipid profile improved overall, but in adherent individuals HbA_{1c} and markers for nephropathy improved.

CONCLUSIONS—Adults with undetected CD and type 1 diabetes have worse glycemic control and a higher prevalence of retinopathy and nephropathy. Treatment with a GFD for 1 year is safe in adults with type 1 diabetes and does not have a negative impact on the quality of life.

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Long-term microvascular and neurologic complications are responsible for major morbidity and mortality in type 1 diabetes (1). Intensive glycemic control reduces these complications and improves quality of life (1). Even patients with good glycemic control have complications, suggesting that other factors increase the risk (2). Coexisting medical problems may be a confounding factor when managing glycemic control (2). The association between celiac disease (CD) and type 1 diabetes was recognized over 30 years ago, particularly by pediatricians. The prevalence of CD in patients with adult type 1 diabetes has been reported as 1.8–8.4% (3–6). Despite a large number of prevalence studies, other important clinical factors have not been well investigated, including glycemic control, quality of life, microvascular complications, cardiac risk factors, and bone mineral density.

Investigations of the effect of CD on glycemic control have been conflicting, with some studies showing improvement (7) and some deterioration (4,8) and others showing no effect (9). The difficulty in interpreting these studies is that most involve pediatric populations and are small, retrospective, and uncontrolled, leaving this question unanswered. There have been no quality-of-life assessments before and after the diagnosis of CD to assess the impact of the diagnosis and a subsequent gluten-free diet (GFD) (3). Adapting to a GFD with the restrictions of a diabetic diet may negatively impact quality of life.

Peripheral neuropathy affects up to 30% of patients with adult type 1 diabetes and is a major cause of morbidity (1). Neuropathy is associated with both type 1 diabetes and CD; therefore, patients with both conditions may have a higher prevalence (10,11). In gluten-sensitive neuropathy, the pathophysiological changes lie in the humoral immune response, and a GFD seems to be beneficial (12,13). There are no studies examining neuropathy in patients with type 1 diabetes and CD or the effect of a GFD. One study examined whether CD may contribute to autonomic neuropathy in a cohort of patients with type 1 diabetes. They found no difference in the prevalence of positive antibodies in patients with and without autonomic neuropathy (14).

Two previous studies have examined the effect of CD on diabetic nephropathy but were conflicting (15,16). There are currently no studies examining the prevalence of retinopathy in individuals with both type 1 diabetes and CD.

Recent data in nondiabetic CD cohorts have shown a reduced risk of ischemic heart disease, possibly attributed to lower cholesterol levels and a lower prevalence of hypertension (17). Reduced bone mineral density has been associated with both CD and type 1 diabetes, but there are little data on people with both conditions (18). The aim of our study was to identify undetected CD in adult patients with type 1 diabetes and investigate the effect on diabetes-related complications before and after a GFD.

RESEARCH DESIGN AND METHODS

—The Sheffield Diabetes Centre operates at both the Royal Hallamshire Hospital and the Northern General

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Hospital. This covers a population of ~500,000 people and provides tertiary referral services for the South Yorkshire region. There are ~2,000 patients with type 1 diabetes, defined using the American Diabetes Association position statement. Approximately 95% of patients with type 1 diabetes are managed by the diabetes center in secondary care.

Inclusion criteria were patients with type 1 diabetes aged >16 years. Exclusion criteria were patients aged <16 years, inability to consent, or affliction with diabetes other than type 1. Where diabetes type was uncertain, the notes were reviewed with the treating consultant and a decision made concerning diabetes type. If diabetes type still was uncertain, then the individual was excluded.

Patients were prospectively recruited when attending for annual review, the foot clinic, or the Dose Adjustment for Normal Eating Clinic. Study participants completed a health questionnaire and the short-form 36 (version 2) quality-of-life assessment questionnaire (Quality Metric). Data were prospectively collected, including age, sex, ethnicity, drug history, and other medical comorbidities. Blood was taken for glycosylated hemoglobin (HbA_{1c}), renal profile, lipid profile (including total and HDL cholesterol), full blood count, IgA endomysial antibody (EMA), IgA anti-tissue transglutaminase antibody (tTG), and total IgA levels.

Diagnosing CD

Participants with either a positive antibody or a low IgA level were recalled and offered a duodenal biopsy. Histological features consistent with CD were classified according to Marsh staging (0–3), with grade 3 changes (villous atrophy) considered diagnostic of CD (19).

Newly identified CD study group investigations

Participants with newly identified CD underwent additional investigations to determine the effect of unrecognized CD. In addition to HbA_{1c} (measured by boronate affinity chromatography and high-performance liquid chromatography), quality-of-life assessment, and lipid profile, assessment of microvascular complications and bone mineral density were made.

The presence of nephropathy was assessed using renal protein excretion, estimated glomerular filtration rate (eGFR), and diabetes nephropathy stage. Renal protein excretion was measured using the urinary protein-to-creatinine ratio (albumin-to-creatinine ratio [ACR]), and eGFR was calculated and a chronic kidney disease stage was assigned. Retinopathy was assessed by notes review and graded as no retinopathy, background changes, preproliferative changes, or proliferative changes, as described by the National Screening Committee for Diabetic Retinopathy. Patients underwent annual retinal photography and were reviewed within 3 months of diagnosis and then 1 year later.

Peripheral neuropathy was assessed by a combination of quantitative sensory-threshold tests, cardiac autonomic function tests, and electrophysiological tests of four nerves. Quantitative sensory-threshold tests were performed using the Computer-Aided Sensory Evaluator (CASE IV version 4.27), which provides cold, vibration, and heat-pain detection thresholds on the dorsum of the right foot.

Cardiovascular autonomic function tests were measured using the O'Brien protocol. A three-lead electrocardiogram was attached to the subject while lying in the supine position. After a rest period, measurements of the time between R waves on the electrocardiogram were made, and changes in heart rate based on RR variation over time were recorded. The degree of variation was calculated using the RR ratio and was corrected for age. RR ratios were measured at rest, during deep breathing, during the Valsalva maneuver, and after rising from the supine position. The change in blood pressure from lying down to standing also was measured. Autonomic dysfunction was diagnosed if two or more of these tests were abnormal.

Electrophysiological tests were performed on the radial nerve, sural nerve, common peroneal nerve, and the tibial nerve using surface electrodes (Synergy version 10.0; Oxford Instruments). The nerves were subjected to supramaximal stimulation to allow measurement of the amplitude and latency. Neuropathic symptoms were assessed using the Neuropathy Symptom Score (20) and the Neuropathic Impairment Score of the Lower Limbs (NISLL) questionnaires. The NISLL+7 score was calculated to determine the presence and severity of neuropathy for comparison between groups (20).

Bone mineral density was assessed using dual-energy X-ray absorptiometry (DEXA). In the previously undetected CD patients with type 1 diabetes, these measurements were made prior to starting a GFD. Apart from bone mineral density, all measurements were repeated at 1 year of following a GFD.

Control groups

The control population to compare the prevalence of CD was taken from screening 1,200 healthy volunteers recruited from five separate general practices in Sheffield. These five practices serve different socioeconomic backgrounds. These individuals were a mix of patients attending the practice and those attending with a patient to reduce bias from health care–seeking behavior. These individuals represent a similar group because the majority of patients with type 1 diabetes are seen as "well" outpatients. This population has been previously described (21).

To provide control subjects for subjects with type 1 diabetes and newly identified CD, individuals from the type 1 diabetic cohort without CD were randomly selected from those who matched by age, sex, weight, and diabetes duration, with a ratio of two control subjects to one case subject. These individuals also underwent the same additional investigations (with the exception of DEXA scanning), and comparisons were made at baseline and 1 year.

Statistical analysis and power calculation

Statistical analyses were performed using SPSS version 13.0. A comparison of the prevalence of CD between cohorts was performed using a Fisher exact test, and odds ratios were calculated. A comparison of clinical parameters was performed using the Mann-Whitney *U* test at both baseline and 1 year. Comparisons of changes in parameters within each group over time were performed using the Wilcoxon signed-rank test.

Assuming that the prevalence of CD is 1% for the control subjects (21) and the prevalence of CD in patients with type 1 diabetes is 3%, a sample size of 1,000 will give 85% power to detect a difference at the $P = 0.05$ level. Assuming that the prevalence of neuropathy is 30% in patients with type 1 diabetes and 50% in patients with type 1 diabetes and CD, a sample size of 50 will give 90% power to detect a difference at the $P = 0.05$ level. To determine whether there were differences in the progression of neuropathy (and subsequent outcomes on a GFD) between patients with type 1 diabetes and CD compared with control subjects, the Wilcoxon signed-rank test was used. Assuming a two-point difference in the mean composite score between case and control subjects, a sample size of 50 will have 95% power to detect a difference at the $P = 0.05$ level.

Ethical approval

Ethical approval was obtained from the South Sheffield Research Ethics Committee, and written informed consent was obtained.

RESULTS—Figure 1 shows the flow of participants through the study. A total of 1,043 individuals were approached, of which 1,000 agreed to take part (95.8% uptake). The mean age of the group was 43.2 years, and there were 439 female subjects. During this period, 21 individuals were identified with established CD and type 1 diabetes. These patients had been identified as a result of overt gastrointestinal symptoms or gross anemia. They were included in the analysis to enable the calculation of the prevalence of CD in the entire cohort.

Serological results

We diagnosed 12 new cases of undetected CD (Fig. 1), of which 6 had gastrointestinal symptoms, 4 were anemic, and 2 were negative for EMA. With the inclusion of the 21 patients with established CD (already on a GFD) identified during the period of study, the prevalence of CD in this cohort of people with type 1 diabetes was 3.3% (33 of 1,000) (95% CI 2.3–4.6). Compared with the population control group (21), in which the prevalence of CD was 1% (12 of 1,200) (0.5–1.7), there was an increased prevalence of CD in people with type 1 diabetes (odds ratio 3.3 [95% CI 1.7–6.6], $P < 0.0001$).

There were four patients with positive antibodies who refused to be biopsied. If these individuals had undergone investigation, and if all four were found to have CD, then the prevalence would have been 3.7% (37 of 1,000) (95% CI 2.6–5.1).

A total of 21 patients tested positive for EMA but had nondiagnostic biopsies and were considered to have potential CD and entered into clinical follow-up. A total of 18 of these individuals had completely normal biopsies, whereas 3 individuals had increased intraepithelial lymphocyte counts (Marsh grade 1). These individuals were excluded from the subsequent investigations in the study because they did not meet the diagnostic criteria for CD.

Newly identified CD comparisons

The case (n = 12) and control (n = 24) subjects were well matched for age, sex, diabetes duration, average insulin dose, and weight at baseline. Table 1 summarizes the observations in those with both type 1 diabetes and CD and control subjects at baseline and after 1 year on a GFD. Table 2 summarizes the observations in those with type 1 diabetes and CD stratified by adherence to the GFD at 1 year.

At baseline, individuals with type 1 diabetes and CD had higher HbA_{1c}, lower total cholesterol, lower HDL cholesterol, lower diastolic blood pressure, and a higher prevalence of advanced nephropathy and retinopathy. There was a trend toward higher urinary protein excretion and peripheral neuropathy. There was no difference in quality of life in any of the domains (all $P > 0.1$), the cholesterol-to-HDL ratio, triglycerides, sensory detection thresholds, autonomic function testing, electrophysiological testing, or NISLL+7 scores (12.5 vs. 11.0, P = NS).

After 1 year on a GFD for individuals with type 1 diabetes and recently detected CD, there was no longer a difference in HbA_{1c}, blood pressure, or prevalence of nephropathy. Of interest, there was clinically significant improvement in the prevalence of advanced nephropathy after 1 year on a GFD. This occurred as three patients had improvements in their renal protein excretion, but this did not achieve statistical significance ($P > 0.1$). There was a trend toward lower total cholesterol, lower HDL cholesterol, and peripheral neuropathy. There still was a higher prevalence of advanced retinopathy. Quality-of-life scores at 1 year were not significantly different compared with baseline (all $P > 0.1$).

Outcomes also were stratified by adherence to the GFD, as judged by positive antibodies at 1 year (positive for EMA or tTG >15), clinical assessment with the patient, and dietetic review. Nine individuals were judged to be adherent to the diet, and these data are shown in Table 2. In these groups, the difference in the baseline and 1-year value for each variable was calculated and averaged, showing the mean direction of change with respect to adherence to the GFD. Those judged adherent to the GFD had a significant increase in HDL cholesterol compared with those who were not. Also, HbA_{1c}, the cholesterol-to-HDL ratio, triglycerides, and urinary ACR changed favorably in adherent individuals, whereas these changes were unfavorable or less marked in the nonadherent subjects. These numbers are very small and therefore must be interpreted with caution.

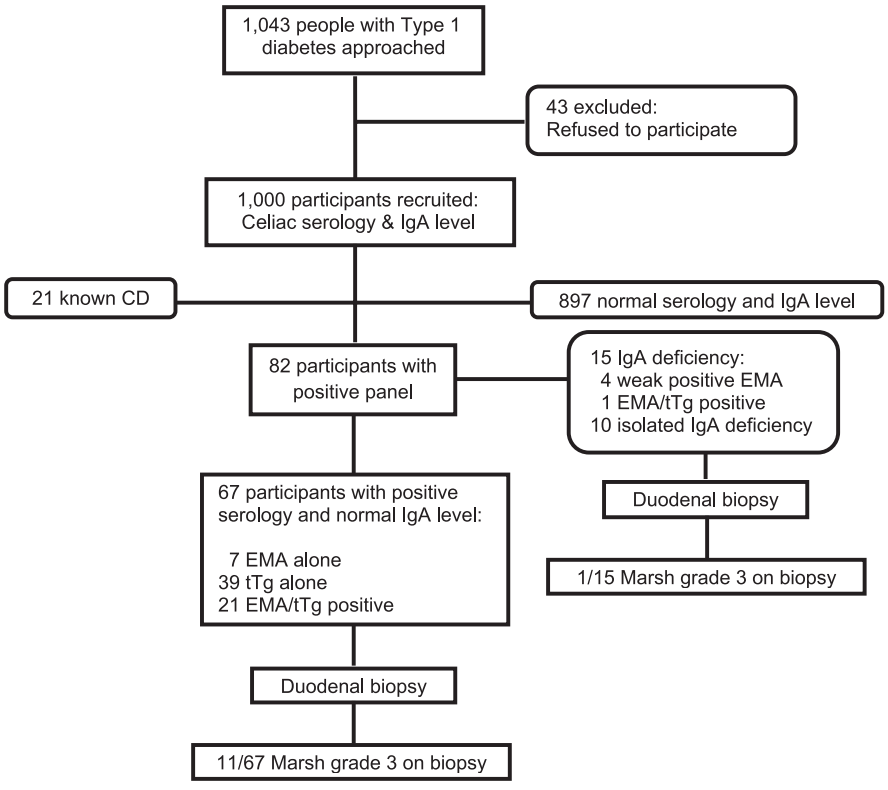

Figure 1—*Study participant flow diagram. Four individuals refused the duodenal biopsy (all were positive for EMA/tTG).*

Table 1—*Summary of the findings at baseline and 1 year following a GFD in case and control subjects*

Variables	CD and type 1 diabetes	Control subjects	*P*
Baseline values			
Age (years)	41	41	NS
Duration (years)	22.5	28.5	NS
Weight (kg)	71	72.3	NS
Insulin dose (units/kg)	0.69	0.66	NS
HbA_{1c} (%)	8.2 (2.5)	7.5 (1.93)	0.05
Cholesterol (mmol/L)	4.1 (1.43)	4.9 (1.13)	0.014
HDL (mmol/L)	1.1 (0.6)	1.56 (0.8)	0.017
Cholesterol-to-HDL ratio	3.4 (1.7)	2.8 (1.8)	NS
Triglycerides (mmol/L)	0.85 (0.8)	0.75 (0.6)	NS
eGFR	95.5 (35.8)	89.5 (28.3)	NS
ACR	1.8 (36.2)	1.0 (2.0)	0.06
Nephropathy stage >3 [*n* (%)]	5/12 (41.6)	1/24 (4.2)	0.009
Advanced retinopathy [*n* (%)]	7/12 (58.3)	6/24 (25)	0.02
Peripheral neuropathy [*n* (%)]	5/12 (41.6)	4/24 (16.6)	0.11
1-Year values			
Weight (kg)	69.9	77.5	NS
Insulin dose (units/kg)	0.69	0.64	NS
HbA_{1c} (%)	8.5 (1.65)	8.45 (1.5)	NS
Cholesterol (mmol/L)	4.1 (1.2)	4.8 (1.25)	0.08
HDL (mmol/L)	1.2 (0.6)	1.6 (0.8)	0.07
Cholesterol-to-HDL ratio	3.4 (1.5)	2.8 (1.9)	NS
Triglycerides (mmol/L)	0.85 (0.4)	0.65 (0.7)	NS
eGFR	84.0 (31.0)	87.5 (33.0)	NS
ACR	1.5 (10.0)	0.5 (0.8)	NS
Nephropathy stage >3 [*n* (%)]	2/12 (16.6)	1/24 (4.2)	NS
Advanced retinopathy [*n* (%)]	7/12 (58.3)	6/24 (25)	0.02
Peripheral neuropathy [*n* (%)]	5/12 (41.6)	4/24 (16.6)	0.11

Data are median (interquartile range), unless otherwise indicated. NS, not significant.

Other factors

At the 1-year follow-up, there were no significant differences between case and control subjects when comparing age, sex, diabetes duration, and average insulin dose or weight. Analysis of these factors by comparing them with baseline values found no significant changes in those with both type 1 diabetes and CD, but there was a trend toward weight gain in the control group (72.3 vs. 77.5 kg, $P = 0.053$).

Table 2—*Findings at follow-up stratified by compliance to the GFD in those with type 1 diabetes and CD*

Variables	Adherence	Poor Adherence	*P*
HbA_{1c} (%)	8.5	9.1	NS
Mean difference	−0.98	+0.85	NS
Total cholesterol (mmol/L)	4.0	4.0	NS
Mean difference	+0.2	−0.45	NS
HDL cholesterol (mmol/L)	1.2	1.4	NS
Mean difference	+0.3	−0.2	0.029
Cholesterol-to-HDL ratio	3.4	2.9	NS
Mean difference	−0.6	0.0	NS
Triglycerides (mmol/L)	0.9	0.8	NS
Mean difference	−0.6	−0.3	NS
eGFR	84	70	NS
Mean difference	−15	−11	NS
ACR	1.0	1.3	NS
Mean difference	−7.4	+5.8	NS

Bone mineral density

All patients with newly identified CD were sent for a DEXA scan to assess bone mineral density. A total of 3 of 12 individuals had abnormal bone mineral density, with 2 of 12 (16.7%) having osteoporosis and 1 of 12 (8.3%) having osteopenia.

CONCLUSIONS—This is the first study to assess the effect of newly diagnosed CD in adults with type 1 diabetes and to provide follow-up of important clinical outcomes on a GFD. Prior to starting a GFD, case and control subjects were well matched for age, sex, weight, average insulin dose, and duration of diabetes. At baseline, people with both type 1 diabetes and undetected CD had significantly worse glycemic control, lower total cholesterol, lower HDL cholesterol, lower diastolic blood pressure, more renal disease, and more retinopathy compared with control subjects.

After 1 year on a GFD, the only difference was the prevalence of advanced retinopathy. Adherent individuals had a significant increase in HDL cholesterol and favorable changes in parameters, such as glycemic control and renal protein excretion. There was no detriment of a GFD in type 1 diabetes, particularly in glycemic control, in keeping with previous studies (4,9).

Quality of life showed no differences at baseline or following a GFD. Improvement in gastrointestinal symptoms needed balancing against a more complicated diet, and improvements in HbA_{1c} were modest. Social isolation as a result of the GFD has been previously described (22).

The finding of increased prevalence of microvascular complications is novel. With respect to nephropathy, people with both type 1 diabetes and CD had significantly higher ACRs at baseline, and a trend remained at 1 year, with eGFR being reduced significantly compared with control subjects. Two patients had significant deterioration in their renal profile, with one starting dialysis.

There are two studies examining the association of CD and diabetic nephropathy. A study of 967 people with type 1 diabetes, of which 462 had nephropathy, found no difference in the prevalence of CD (15). A study of children with type 1 diabetes and established CD on a GFD

was compared with a control group with diabetes alone. Those with CD had lower urinary protein loss, suggesting that a GFD was protective (16). Our results are in keeping with Malalasekera et al. (16), who suggest that dietary modifications of a GFD might be beneficial and a reduced dietary intake of advanced glycation end products may be responsible.

Recent epidemiological studies suggest that patients with CD have a lower risk of developing ischemic heart disease, possibly as a result of lower cholesterol levels (17). Another study showed that in newly diagnosed CD, total cholesterol was lower at diagnosis and after 12 months on a GFD, and despite no change in total cholesterol, HDL cholesterol increased by an average of 12% (23). This is more important for patients at increased cardiac risk, such as those with type 1 diabetes.

Renal and retinal changes commonly mirror each other and are related to underlying endothelial dysfunction. The prevalence of retinopathy was similar in people with type 1 diabetes and undetected CD compared with control subjects, but the prevalence of more advanced retinopathy was significantly higher in the CD group, with one subject undergoing laser therapy.

An association between CD and neuropathy has been previously described but not in the context of type 1 diabetes (10,11). We found that individuals with newly identified CD and type 1 diabetes had a higher prevalence of neuropathy, but this was not statistically significant. After 1 year on a GFD, there was no significant improvement of the neuropathy. This may be because of the short period of follow-up or because the impact of diabetes on peripheral nerve damage is more substantial than CD (1,2). It would be interesting to follow-up this cohort of patients to see whether their neuropathy eventually improves. All newly identified CD patients had micronutrients, such as vitamin B_{12} and folic acid, measured, which were normal. One previous study examined the prevalence of positive tTG antibodies in patients with type 1 diabetes with and without autonomic neuropathy (judged by cardiac reflex testing and gastric scintigraphy). They found no difference in the prevalence of positive tTG antibodies in those with and without autonomic neuropathy. This study has limitations in that it is unclear whether the two groups were matched for similar clinical characteristics; only one individual had a duodenal biopsy confirming CD, and longitudinal follow-up is only described in this patient (14). In our study, there was no difference in the prevalence of autonomic neuropathy in those with and without CD. Changes in blood glucose levels may be secondary to gastrointestinal motor dysfunction, as occurs in diabetic gastroparesis, which may be compounded by similar findings described in CD. No study has compared the rate of the development of autonomic neuropathy in patients with type 1 diabetes and CD compared with those with type 1 diabetes alone.

The mechanism by which CD increases the risk of microvascular disease is unclear and is likely to be multifactorial. Unrecognized CD is associated with raised homocysteine levels, which is probably a result of deficiency in folic acid and other B vitamins, which is a risk factor for endothelial dysfunction (24). A recent study showed that supplementation of vitamin B in CD was associated with significantly lower homocysteine levels, potentially reducing the risk of vascular disease (25). In the current study, the combination of higher HbA_{1c} and lower HDL cholesterol, possibly secondary to underlying chronic inflammation, may be the mechanism. Improvement of these parameters after 1 year on a GFD is encouraging and similar to that seen in newly diagnosed CD without diabetes.

Additional studies are required to determine whether early detection of CD in type 1 diabetes and treatment with a GFD affects the development of microvascular complications. Follow-up of the current study group over several years also may provide additional insight into the interplay between type 1 diabetes and CD. Such investigations are likely to be more informative if conducted in a multicenter fashion with a larger study population and corresponding control group.

In summary, this is the first study to assess the effects of undetected CD in adult patients with type 1 diabetes. These individuals have worse glycemic control and a higher prevalence of retinopathy and nephropathy. Treatment with a GFD is safe and does not impact quality of life.

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