# Screening and Treatment Outcomes in Adults and Children With Type 1 Diabetes and Asymptomatic Celiac Disease: The CD-DIET Study

Farid H. Mahmud,[1] Antoine B.M. Clarke,[1] Kariym C. Joachim,[1] Esther Assor,[1] Charlotte McDonald,[2] Fred Saibil,[3] Heather A. Lochnan,[4] Zubin Punthakee,[5] Amish Parikh,[6] Andrew Advani,[7] Baiju R. Shah,[8] Bruce A. Perkins,[9] Caroline S. Zuijdwijk,[10] David R. Mack,[11] Dror Koltin,[6] Emilia N. De Melo,[1] Eugene Hsieh,[12] Geetha Mukerji,[13] Jeremy Gilbert,[8] Kevin Bax,[14] Margaret L. Lawson,[10] Maria Cino,[15] Melanie D. Beaton,[16] Navaaz A. Saloojee,[17] Olivia Lou,[18] Patricia H. Gallego,[19] Premysl Bercik,[20] Robyn L. Houlden,[21] Ronnie Aronson,[22] Susan E. Kirsch,[23] William G. Paterson,[24] and Margaret A. Marcon[25]

## OBJECTIVE

To describe celiac disease (CD) screening rates and glycemic outcomes of a gluten-free diet (GFD) in patients with type 1 diabetes who are asymptomatic for CD.

## RESEARCH DESIGN AND METHODS

Asymptomatic patients (8–45 years) were screened for CD. Biopsy-confirmed CD participants were randomized to GFD or gluten-containing diet (GCD) to assess changes in $HbA_{1c}$ and continuous glucose monitoring over 12 months.

## RESULTS

Adults had higher CD-seropositivity rates than children (6.8% [95% CI 4.9–8.2%, $N$ = 1,298] vs. 4.7% [95% CI 3.4–5.9%, $N$ = 1,089], $P$ = 0.035) with lower rates of prior CD screening (6.9% vs. 44.2%, $P$ < 0.0001). Fifty-one participants were randomized to a GFD ($N$ = 27) or GCD ($N$ = 24). No $HbA_{1c}$ differences were seen between the groups (+0.14%, 1.5 mmol/mol; 95% CI −0.79 to 1.08; $P$ = 0.76), although greater postprandial glucose increases (4-h +1.5 mmol/L; 95% CI 0.4–2.7; $P$ = 0.014) emerged with a GFD.

## CONCLUSIONS

CD is frequently observed in asymptomatic patients with type 1 diabetes, and clinical vigilance is warranted with initiation of a GFD.

Celiac disease (CD) is an immune reaction–mediated condition triggered by gluten, a protein found in wheat, barley, and rye. CD risk is increased in patients with type 1 diabetes and is characterized by a broad spectrum of presentations, including gastrointestinal symptoms, growth alterations, and anemia, but many patients are asymptomatic (1–4).

Serologic screening for CD has high sensitivity and specificity, but few reports have evaluated CD rates and the impact of treatment with a gluten-free diet (GFD) in asymptomatic CD (aCD) patients with type 1 diabetes. The Celiac Disease and Diabetes-Dietary Intervention and Evaluation Trial (CD-DIET) prospectively screened a large cohort of patients aged 8–45 years with subsequent engagement in a randomized, dietary treatment trial to evaluate changes in $HbA_{1c}$ and glycemic variability.

[1]Division of Endocrinology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
[2]Division of Endocrinology and Metabolism, St. Joseph's Health Care, London Health Sciences Centre, Western University, London, Ontario, Canada
[3]Division of Gastroenterology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
[4]Department of Endocrinology, The Ottawa Hospital, Ottawa, Ontario, Canada
[5]Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[6]Division of Endocrinology, Trillium Health Partners, Toronto, Ontario, Canada
[7]Division of Endocrinology, St. Michael's Hospital, Toronto, Ontario, Canada
[8]Division of Endocrinology and Metabolism, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[9]Division of Endocrinology and Metabolism, University Health Network, University of Toronto, Toronto, Ontario, Canada
[10]Division of Endocrinology and Metabolism, University of Ottawa, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada
[11]Division of Gastroenterology, Hepatology and Nutrition, University of Ottawa, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada
[12]Department of Pathology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[13]Division of Endocrinology, Women's College Hospital, Toronto, Ontario, Canada
[14]Pediatric Gastroenterology, Department of Pediatrics, Children's Hospital, London Health Sciences Centre, Western University, London, Ontario, Canada
[15]Division of Gastroenterology, University Health Network, University of Toronto, Toronto, Ontario, Canada
[16]Division of Gastroenterology, London Health Sciences Centre, London, Ontario, Canada

## RESEARCH DESIGN AND METHODS

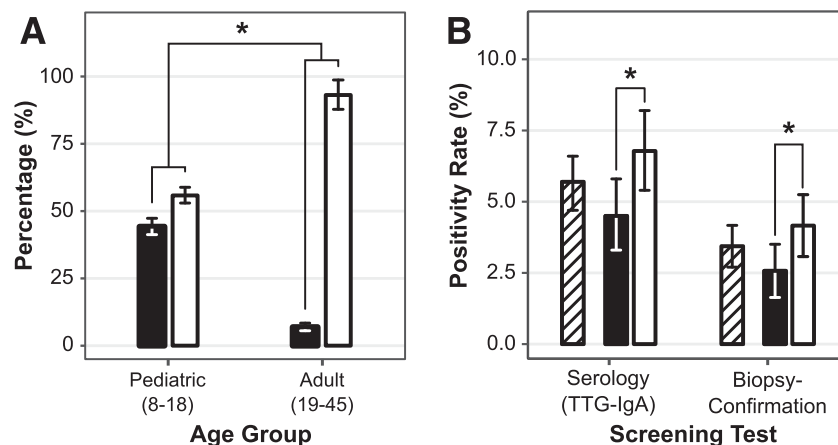### Recruitment of Participants

Patients aged 8–45 years with type 1 diabetes (≥1 year duration) were approached to undergo CD testing at 22 diabetes centers in Ontario, Canada, as part of the CD-DIET study (clinicaltrials.gov, NCT01566110) (5). Exclusion criteria included CD symptoms (gastrointestinal symptomology or evidence of growth impairment, anemia, or osteoporosis), a previous CD diagnosis, and pregnancy.

### CD Screening

Eligible participants (Supplementary Fig. 1) were screened using tissue transglutaminase IgA (TTG-IgA; Inova Diagnostics). CD-seropositive participants (TTG-IgA ≥30 chemiluminescent units [CU]) progressed to a gastroenterology consultation with centralized biopsy confirmation (Marsh score ≥2).

### Dietary Intervention Study

Interested participants with biopsy-confirmed CD were randomized in a 1:1 ratio to a GFD or a gluten-containing diet (GCD) and followed for 1 year. Study visits with a dietitian occurred every 3 months using a standardized educational curriculum. Dietary adherence was also evaluated through quantification of dietary gluten intake and repeat TTG-IgA testing. Safety laboratory tests were evaluated (see Supplementary Material) with monitoring of growth, symptomology, and pregnancy. GCD participants who became symptomatic were transitioned to a GFD with the completion of outcome measures. A Data Safety Monitoring Committee evaluated adverse events. The primary outcome of CD-DIET was the change in $HbA_{1c}$ from baseline to 12 months. $HbA_{1c}$ was assessed centrally at baseline and at 6 and 12 months, with additional testing by local laboratories. Continuous glucose monitoring (CGM)

was conducted using the iPro2 CGM system (Medtronic, Inc.) for blinded assessment.

Analysis was by intention to treat. Longitudinal differences in $HbA_{1c}$ between groups were analyzed using the difference in differences approach and confirmed using linear mixed-effects regression. CGM results were summarized using standard parametric methods, while paired $t$ tests were used to assess within-group differences in $HbA_{1c}$ and postprandial glucose levels. All analyses were completed using R Statistics 3.5.1.

A sample size of $n = 60$ (30 patients per arm) was determined to be sufficient for our between-group analysis to reach 80% power at a 5% significance level under two-sided conditions. Paired analysis of $HbA_{1c}$ in the GFD arm, a sample size of $n = 25$ before versus after pairs, reached a power above 80% using a two-sided paired $t$ test with significance set at $P = 0.05$.



**Figure 1**—The results from the CD-DIET screening of asymptomatic patients with type 1 diabetes. A: The percentage of participants previously (black bars) and nonpreviously (white bars) screened for CD by age-group showing lower screening rates in adults (6.9% vs. 44.2%, $P < 0.0001$). B: CD serology– (TTG-IgA) and CD biopsy–confirmed rates of CD among the 2,387 subjects screened. Hatched bars indicate combined rates of CD serology and biopsy positivity, black bars illustrate pediatric data (8–18 years, $N = 1,089$), and white bars show adult rates (19–44 years, $N = 1,298$). Error bars represent 95% CIs. *Significant differences, $P < 0.05$.

## RESULTS

### Recruitment and CD Screening

Overall, 2,585 patients consented and 2,387 subjects completed CD screening, including 1,298 adults (54.4%, 19–45 years) and 1,089 children (45.6%, 8–18 years) (see Supplementary Material). Higher rates of any prior CD serologic screening were seen in pediatric participants ($n = 475$, 43.6%, 95% CI 40.7–46.5%) as compared with adult participants ($n = 89$, 6.9%, 95% CI 5.5–8.3%) (odds ratio [OR] 10.5, $P < 0.0001$) (Fig. 1A). Adults had higher CD seropositivity rates ($n = 88$, 6.8%; 95% CI 5.4–8.2%) compared with children ($n = 51$; 4.7%; OR 1.48, 95% CI 3.4–5.9%, $P = 0.035$), but rates did not differ within each age-group on the basis of previous CD screening status. Biopsies were completed in 104 participants, and 82 were confirmed by biopsy with CD positivity rates of 4.2% ($n = 54$; 95% CI 3.1–5.3%) and 2.6% ($n = 28$; 95% CI 1.6–

[17]Department of Gastroenterology, The Ottawa Hospital, Ottawa, Ontario, Canada
[18]JDRF, New York, NY
[19]Division of Endocrinology, Children's Hospital, London Health Sciences Centre, Western University, London, Ontario, Canada
[20]Department of Gastroenterology, McMaster University, Hamilton, Ontario, Canada
[21]Department of Endocrinology, Kingston General Hospital, Kingston, Ontario, Canada
[22]LMC Diabetes & Endocrinology, Toronto, Ontario, Canada

[23]Division of Endocrinology, Markham-Stouffville Hospital, Markham, Ontario, Canada
[24]Department of Gastroenterology, Kingston General Hospital, Kingston, Ontario, Canada
[25]Division of Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Corresponding author: Farid H. Mahmud, farid .mahmud@sickkids.ca

3.5%) for adult and pediatric participants, respectively (OR 1.64, $P = 0.042$) (Fig. 1B).

## Dietary Intervention Study

The 51 participants were randomized into the intervention phase, with 27 to the GFD group and 24 to the GCD group. Adherence to the assigned diet, as assessed by serial measures of gluten intake and TTG antibody titers, was deemed excellent (Fig. 2A). Ultimately, we observed no longitudinal difference in $HbA_{1c}$ between the GFD group and GCD group (+0.14% [1.5 mmol/mol], 95% CI −0.79 to 1.08, $P = 0.76$). Within the GFD group, an increase in $HbA_{1c}$ of +0.30% (3.3 mmol/mol) was observed over 12 months (95% CI 0.04–0.57%, $P = 0.028$) (Fig. 2B).

Using blinded CGM, no differences were seen in the percentage of time spent in hypoglycemic, euglycemic, or hyperglycemic ranges at 12 months. Despite this, postprandial glycemia was higher with the GFD relative to premeal levels at both the 2-h (+1.6 mmol/L, 95% CI 0.7–2.6, $P = 0.0015$) and 4-h (+1.5 mmol/L, 95% CI 0.4–2.7, $P = 0.014$) time points, while glucose levels of the GCD arm returned to premeal levels ($\Delta = 0.1$ mmol/L after 4 h; 95% CI −0.8 to 1.0) (Fig. 2C). No differences were observed between groups in growth parameters (including height, weight, or BMI in children and adults; Supplementary Figs. 2 and 3), total daily insulin dose, or total daily insulin dose per kilogram.

Hypoglycemic adverse events that were nonsevere were reported with the GCD group ($N = 3$, 12.5%), with none reported with the GFD group ($P = 0.097$).

## CONCLUSIONS

This study describes screening and treatment outcomes from a large prospective assessment of adult and pediatric patients with type 1 diabetes with aCD. We observed high rates of aCD with 1.5-fold higher rates in adults as compared with children. This result is consistent with increasing rates of CD in adults (6) and changes in the symptom profile toward a more subtle and less classical malabsorptive presentation with increasing age (7). In addition, age-related increases in autoimmune comorbidities are also well recognized, with recent T1D Exchange clinic registry data confirming rising rates of autoimmune comorbidities from adolescence into adulthood (8,9).

Adult participants in our study were also less likely to be screened for CD than children. This may reflect a lack of clarity about CD screening recommendations in adults and the absence of outcome studies in this population. Current North American diabetes guidelines advise consideration of screening patients with type 1 diabetes for CD, but actual details regarding screening tests, timing, and intervals are only explicitly described for children (10,11).

Dietary intervention with a GFD did not result in a difference in $HbA_{1c}$ between randomized groups but led to greater postprandial glucose excursions relative to a GCD. These changes are consistent with mucosal recovery, which can be prolonged (1–3 years), with subsequent improvements in absorption (2,12). Nonetheless, transition to a GFD was safe with no significant differences observed in hypoglycemic time or adverse events.

Strengths of this report include the large number of patients screened and the rigor in delineating an asymptomatic cohort. In addition, participants in the intervention phase, who were provided with frequent dietitian-based support, exhibited clear differences in gluten intake and follow-up TTG serology. Limitations of this study include a small sample size and the heterogeneity of participant characteristics that limits generalization of these findings. In addition, our data do not represent the prevalence rates, as we were challenged by enumeration of the complete population at risk in the clinics where screening was completed. It was also our experience that despite facilitated and no-cost access to care, many asymptomatic participants were overwhelmed by the diagnostic process and by the prospect of managing these two conditions, each with significant lifestyle implications.

In summary, diabetes clinicians should be aware of CD as an important autoimmune comorbidity of type 1 diabetes that is frequently asymptomatic. In addition, clinical vigilance is warranted during dietary transition, as GFD treatment
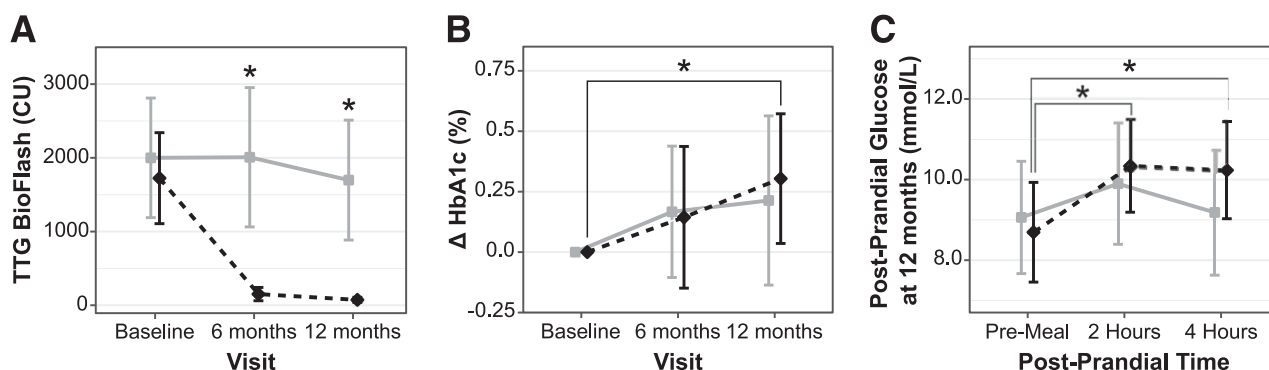
**Figure 2**—The results from CD-DIET. Data from the GFD arm shown in black with a dashed line, while data from the GCD are shown with solid gray line. A: Dietary adherence to the assigned group was assessed using serial serologic testing. TTG-IgA antibody titers were similar in the GCD and the GFD groups at baseline. They appropriately decreased in the GFD arm by 6 months and continued to drop among GFDs, resulting in a significant difference between GCDs (1,698.0 ± 1,834.0 CU) and GFDs (73.4 ± 83.9 CU) at 12 months ($P < 0.0001$). B: The change in $HbA_{1c}$ between study groups. No difference in $HbA_{1c}$ was seen between the GFD group relative to those on a GCD over the 12 months (+0.14% [1.5 mmol/mol], $P = 0.76$); however, within the GFD group, $HbA_{1c}$ increased (+0.30% [3.3 mmol/mol], 95% CI 0.04–0.57%, $P = 0.028$). C: Changes in postprandial glucose assessed by CGM. Postprandial glycemia in the GFD was higher compared with premeal levels at both the 2-h time point (+1.6 mmol/L [29 mg/dL]; $P = 0.0015$) and 4-h time point (+1.5 mmol/L [27 mg/dL]; $P = 0.014$), while glucose levels of the GCD arm returned to premeal levels ($\Delta = 0.1$ mmol/L [1.8 mg/dL]). Error bars represent 95% CIs. *Significant differences, $P < 0.05$.

may impact short-term glycemic variability. Given the additional risks for CD-related microvascular and bone complications, longitudinal studies are also needed to assess the clinical impact of this double diagnosis across the patient's life span (13–15).

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