Published in final edited form as:
Nat Rev Endocrinol. ; 8(1): 5–8. doi:10.1038/nrendo.2011.193.

Celiac disease in T1DM—the need to look long term

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Abstract

Does untreated celiac disease associated with type 1 diabetes mellitus worsen microvascular outcomes? Previous studies have concluded that a gluten-free diet offers no major benefit for glycemic control, whereas Leeds and colleagues provide preliminary data to the contrary. The question awaits a long-term prospective study or a clinical trial.

Data are lacking concerning the effect of celiac disease on diabetes-related complications among adults with type 1 diabetes mellitus (T1DM). A recent study by Leeds *et al.*[1] attempted to partially fill this gap and add a provocative twist to the picture by suggesting that adults with undetected celiac disease and T1DM have worse glycemic control and an increased prevalence of retinopathy and nephropathy.

Celiac disease prevalence and associated mortality have increased dramatically in the USA during the past 50 years.[2] Evidence is growing that diagnosis is delayed by years or even decades in a large proportion of patients with this disease, despite the availability of a highly sensitive and specific test, which involves the detection of transglutaminase autoantibodies.[3] Untreated celiac disease is associated with increased morbidity and mortality.[4] By contrast, early initiation of a gluten-free diet prolongs life and saves health-care expenditures.[5]

Celiac disease affects at least 10% of patients with T1DM at some point in their lives.[6] The increased prevalence of celiac disease in patients with T1DM is due to an overlap in the genetic susceptibility to both diseases conferred by the human leukocyte antigen (HLA) haplotype *HLA-DR3/DQ2*. This haplotype is present in over 90% of patients with celiac disease and 55% of those with T1DM, compared with only 20–25% of the general population of European ancestry. The second *HLA* class II allele important for celiac disease (*DQ8*) also confers risk of T1DM. Several shared non-*HLA* susceptibility genes (which have a much smaller effect compared with *HLA* loci for both celiac disease and T1DM) have also been confirmed. Hypotheses proposing common environmental roots of these two autoimmune diseases have not been supported by recent investigations.[7]

Guidelines from professional societies recommend screening patients with T1DM for celiac disease using transglutaminase autoantibodies. Children with T1DM who have symptomatic celiac disease have been shown to benefit from a gluten-free diet;[8] in asymptomatic cases, the benefit appears to be limited to growth and bone mineralization.[9] Additional reasons to screen patients with T1DM for celiac disease include anecdotal reports of an increased risk of hypoglycemia and higher HbA_{1c} levels in untreated children,[6] but these findings were

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Competing interests
The authors declare no competing interests.

unconfirmed in prospective follow-up studies.[9] On the other hand, a gluten-free diet often requires an increase in insulin dose and can lead to excessive weight gain.

Leeds *et al*. screened 1,000 consecutive patients with a clinical diagnosis of T1DM, who attended a secondary-care clinic, for IgA deficiency, transglutaminase autoantibodies and endomysial autoantibodies (a positive result for endomysial autoantibodies simply corresponds to high-titer transglutaminase autoantibodies). Of the 1,000 patients, 21 had known celiac disease and an additional 82 had either IgA deficiency or elevated levels of endomysial or transglutaminase autoantibodies. Duodenal biopsy was performed in 78 of these 82 patients, which confirmed celiac disease (Marsh grade 3 mucosal atrophy) in 12 individuals. Characteristics of the 12 patients with newly diagnosed celiac disease and 24 control individuals with T1DM who screened negative for celiac disease were compared at baseline, and also at 1 year when the group with celiac disease had received a gluten-free diet for 12 months.

Despite a very small sample size, the authors reported that, at baseline, the patients with newly diagnosed celiac disease had higher HbA_{1c} levels, lower total and HDL cholesterol levels and a higher prevalence of advanced diabetic nephropathy and retinopathy compared with patients without celiac disease. Advanced nephropathy and retinopathy were not clearly defined. HbA_{1c} was apparently measured using two different methods during the study period, and the control group, although reported as ‘matched’ for duration of T1DM, had a 6-year longer mean duration than the celiac disease group. No comparison of diabetes-related outcomes was provided between the 12 newly diagnosed cases of celiac disease and the 21 patients with known celiac disease. Such a comparison could have shed light on why the newly diagnosed group had not previously been diagnosed, despite the fact that many had gastrointestinal symptoms or anemia. Limited contact with diabetes care providers or low socioeconomical status could have been unmeasured confounders associated with both delayed diagnosis of celiac disease and high HbA_{1c} levels and microvascular complications.

The inspection of results of the reported 1-year follow-up of cases and controls makes us wonder about the quality of the data. After being newly diagnosed with celiac disease, a gluten-free diet was recommended for the 12 patients and nine complied, as judged by the decreased levels of transglutaminase or endomysial autoantibodies that were found at follow-up after 1 year. The control patients, who had a normal diet, were also followed for 1 year. Most parameters did not change during the follow-up. However, some of the reported changes appear illogical and so should have been explained in the discussion. For example, the estimated glomerular filtration rate worsened during the year among the 12 patients with celiac disease, from 96 ml/min/1.73 m^2 to 84 ml/min/1.73 m^2, but the number of individuals classified as having ‘nephropathy stage >3′ decreased from five to two. Curiously, although weight did not change in the patients with celiac disease, the control individuals gained an average of 5.2 kg and their HbA_{1c} level worsened from 7.5% to 8.5%, triglycerides improved from 0.75 mmol/l to 0.65 mmol/l, but insulin dose did not change. The HbA_{1c} levels in control individuals at 1 year (8.5%) were slightly higher than those in the patients with celiac disease at baseline (8.2%), which negates the main conclusion of this study that adults with undetected celiac disease and T1DM have worse glycemic control than patients with T1DM without celiac disease.

Is it time to draw the curtain on the main hypothesis of this study? Certainly not, but the article by Leeds *et al* suffers from too many limitations to draw any firm conclusions. The question would be better addressed in long-term, prospective studies. For instance, the Diabetes Control and Complications trial (DCCT) and its observational extension, the Epidemiology of Diabetes Interventions and Complications Study (EDIC),[10] have followed a well-characterized cohort of 1,441 individuals with T1DM for more than 20 years, with

outstanding completeness of assessment for development of diabetic complications. Serial serum samples from the DCCT/EDIC study participants are available for transglutaminase autoantibody testing, if anyone wishes to take a long-term look at the vascular consequences of treated or untreated celiac disease in patients with T1DM.

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