# Type 1 Diabetes and Celiac Disease: Can (and Should) We Raise the Cut-off of Tissue Transglutaminase Immunoglobulin A to Decide Whether to Biopsy?

Celiac disease prevalence is high and increasing worldwide, albeit with wide regional variations around the globe.[1,2] The prevalence seems to be significantly greater in children than in adults (0.9% vs 0.5%; $P < .001$).[2] In addition, there is a well-known association with other autoimmune diseases, with which celiac disease shares common HLA-associated genes.[3] Perhaps the best known association is with type 1 diabetes (T1DM). In fact, patients with T1DM have a high prevalence of a number of other autoimmune diseases, including autoimmune thyroid disease, gastric autoimmunity with pernicious anemia, vitiligo, and adrenal gland insufficiency.[4] First described in a small series of children with diabetes and "malabsorption" in 1968 by Hooft et al, the association of T1DM with celiac disease was then reported from Australia in a 5-year-old girl in1969 by Walker-Smith and Grigor, who wrote: "This is an association we have not previously observed, and the relationship between the two conditions, if any, is uncertain. However, in the light of this experience, it is suggested that all diabetic children in whom malabsorption is demonstrated should have a diagnostic small-bowel biopsy."[5,6] Subsequently, multiple studies from various parts of the world have confirmed the strong association, with prevalence rates varying between 1.6% and 16.4%.

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Because of this association, and the long list of complications associated with untreated celiac disease, there is general agreement that patients with T1DM should be screened for celiac disease at the time of T1DM diagnosis using tissue transglutaminase IgA (TTG).[7] This recommendation is shared by the American Diabetes Association, the International Society for Pediatric and Adolescent Diabetes, the British Society of Paediatric Gastroenterology, Hepatology and Nutrition, the European Society for Pediatric Gastroenterology, Hepatology and Nutrition in their 2012 as well as 2020 guidelines, and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.[8-13] Furthermore, given that celiac disease may develop in a small number of cases some years after the diagnosis of T1DM, it is recommended that repeat testing occur periodically in those who initially have a negative test.

All is settled then? Case closed? Not so fast…. There is in fact a problem plaguing this approach: these autoantibodies, when present, are known to fluctuate and even normalize spontaneously in a large number (about one-third) of patients with T1DM who remain on gluten.[14,15] In addition, even persistently positive TTGs (especially in low titers) are frequently found in patients with T1DM who have normal intestinal histology after endoscopy and biopsies as recommended by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition criteria. These cases are quite common and end up by being either considered a "false positive" TTG or are given the dubious diagnosis of potential celiac disease.

This issue is precisely what the article published in this volume of *The Journal* by Wessels et al aims to clarify.[16] By following the European Society for Pediatric Gastroenterology, Hepatology and Nutrition guidelines that recommend endoscopy with biopsies in those patients with T1DM who have a TTG >3 times the upper limit of normal (ULN), they hypothesize an excessive number of patients will be subject to an unnecessary invasive procedure.[11] Their aim was, therefore, to determine a TTG cut-off level that would optimize specificity while minimizing loss of sensitivity. To this purpose, they analyzed retrospectively the experience of 13 centers in the Netherlands over a span of 13 years, and identified a total of 63 children with T1DM (two-thirds of them asymptomatic) with a TTG >3 times ULN who subsequently underwent endoscopy with duodenal biopsies to confirm or rule out celiac disease. Unfortunately, the centers did not use the same methodology to test for TTG (6 different manufacturers), so the individual values had to be adjusted in terms of increments above the ULN to be compared. Furthermore, values that were particularly high were reported as being above a certain threshold, varying within the laboratories, thus introducing an additional, although probably minor, element of ambiguity. That said, the data were rigorously analyzed and a receiver operating characteristic curve for TTG vs the eventual diagnosis of celiac disease was generated. From this analysis, the authors conclude that to substantially decrease the number of unnecessary procedures (hence increasing the specificity), the actual threshold for subjecting a child or adolescent with T1DM to an endoscopy with biopsies is a TTG of >11 ULN. Using this cut-off level would have resulted in an increase in specificity from 36% (using the recommended cut-off of >3 ULN) to 73%.

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| EMA | Endomysium antibodies |
| GFD | Gluten-free diet |
| IgA | Immunoglobulin A |
| T1DM | Type 1 diabetes |
| TTG | Tissue transglutaminase IgA |
| ULN | Upper limit of normal |

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Could addition of anti-endomysium antibodies (EMA), a test known to be highly specific for celiac disease, have added value in identifying those patients who are more likely to have celiac disease and hence need a biopsy? A previous large meta-analysis conducted in 2004 by Dretzke et al on patients with T1DM and celiac disease concluded: "In terms of test accuracy in testing for coeliac disease, immunoglobulin A (IgA) antiendomysium is the most accurate test."[17] In fact, in a recent large series of patients with T1DM and celiac disease, 83% of those who had a positive TTG—at any titer—and a positive EMA were confirmed to have celiac disease.[18] In the series from Wessels et al, however, surprisingly "50% of EMA positive patients had normal duodenal histology."[16] One wonders in how many of these patients a search for intestinal deposits of anti-TTG IgA might have identified them as having celiac disease, because these antibodies are considered "a constant presence and appear very early in the natural history of disease."[19]

This report focuses on the value of TTG only. Although the higher cut-off level increased the specificity as expected, the sensitivity decreased from 96% to 87% (hence 13% of patients with celiac disease would have been left undiagnosed). As for predictive values, the positive predictive value in this series increased from 88% to 94%, and the negative predictive value decreased from 67% to 53%. In lay terms, almost one-half of the patients with T1DM in this particular series with a TTG of <11 ULN had celiac disease and would have been left undiagnosed if this level was used in the decision making process.

Are we ready to accept this recommendation? Is the saving of cost and of unnecessary endoscopies worth missing so many patients with true celiac disease and deny them the long-term benefits of the gluten-free diet (GFD)? We should consider that it may not be entirely accurate to assume that most children and teenagers with T1DM and celiac disease have no or minimal symptoms: in fact, they may well have mild or under-reported symptoms, not unlike those of patients with celiac disease alone.[20] Additionally, a GFD does not seem to negatively influence the quality of life and may be beneficial to patients with T1DM and celiac disease, regardless of symptoms.[21] A study in a large series of such patients showed that those who achieved normalization of their TTG titers had better control of their glycated hemoglobin and growth. In the same vein, recent data from the first prospective randomized clinical trial in this regard concluded there could be a decrease in hypoglycemic episodes and better glycemic control in patients with T1DM with minimally symptomatic celiac disease following a GFD.[22,23] A recent interventional trial also suggests that there might be a beneficial effect of GFD in patients with T1DM, even if they do not have celiac disease.[24]

Be that as it may, in my view the issue boils down to the following: There is solid evidence that celiac disease is quite common in children and adolescents with T1DM. All involved medical societies and academic bodies recommend testing for celiac disease in patients with T1DM at the time of diabetes diagnosis, and subsequently thereafter if initially negative. Although there are no universally accepted recommendations on how frequently repeat testing should be performed, it seems logical to do this annually at the time of a diabetes check-up. The recommended screening test is with TTG-IgA, acknowledging the fact that in T1DM this test may be positive, especially in low titers, in the absence of celiac disease. How high should the TTG level be to proceed with EMA and confirmatory biopsy? Clearly, titers >11 times the ULN demand a confirmatory diagnosis, but for lower titers the physician will have to apply his or her knowledge and conscience in each individual case. I personally believe we must always be mindful of the serious risk of missing too many patients with celiac disease by applying a high threshold, a risk probably outweighing that of an unnecessary biopsy. Finally, the GFD (and regular follow-up) is to be recommended after celiac disease is confirmed in all cases, regardless of symptoms; fears of negative impacts on quality of life should not hamper this recommendation. Otherwise, why bother testing in the first place? ■

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# Neonatal Hypoglycemia: GLOW at the End of the Tunnel?

Nearly 50 years ago, *The Journal* published a landmark review of hypoglycemia in children by Pagliara, Karl, Haymond, and Kipnis from St. Louis Children's Hospital.[1] This 2-part review focused on recent advances in the physiology of fuel homeostasis during fasting as the foundation for diagnosis and treatment of the many metabolic and endocrine hypoglycemia disorders of childhood. In a short section devoted to neonatal hypoglycemia, the authors noted that fetal glucose is provided by placental transfer from the maternal circulation so that ambient glucose concentrations in the fetus are similar to maternal levels. After delivery, glucose levels decrease to values that would be considered hypoglycemia in older infants and children and remain low for the first few days of life. Pagliara et al considered it unlikely that tissue glucose requirements were different during this brief period of transitional neonatal hypoglycemia and concluded that it was appropriate to use the same glucose standards for treatment of hypoglycemia in newborns as for older infants and children. Their suggestion generated heated letters to the editor from neonatology experts arguing that statistical definitions of "clinically significant" neonatal hypoglycemia (mean – 2 SDs) had been established a decade earlier as a blood glucose of <30 mg/dL for normal birth-weight infants and <20 mg/dL for low-birth-weight infants.[2-4] This controversy rages on down to the present day, owing to our many gaps in knowledge about the mechanism of transitional neonatal hypoglycemia and is reflected by the differences in guidelines from several neonatology and pediatric organizations and by the recommendations published in *The Journal* from the Pediatric Endocrine Society, on which the authors of this editorial were co-authors.[5-8]

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At the time Pagliara et al wrote their review, they believed that the mechanism of transitional neonatal hypoglycemia might reflect delays in development of one or more of the steps in hepatic gluconeogenesis. Attention has recently focused more on insulin as the culprit: evidence in human newborns indicates that the glucose threshold for suppressing insulin release from pancreatic beta-cells is lower in the fetus and early newborn period.[9] This low glucose threshold could be important for maintaining insulin secretion to permit normal fetal growth; it could also explain the stability of low glucose levels during normal newborn transitional neonatal hypoglycemia and its resemblance to hyperinsulinemic hypoglycemia caused by gain-of-function mutations of glucokinase, the beta-cell glucose sensor.[10] Consistent with this finding, islets from fetal and newborn laboratory rodents have been shown to have a lower glucose threshold for insulin release.[11] The mechanism responsible for the low glucose

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