Type 1 Diabetes and Celiac Disease: Causal Association or True, True, Unrelated?

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Celiac disease (CD) and type 1 diabetes (T1D) are T-cell mediated autoimmune diseases that have several overlapping features. Both diseases typically originate in childhood, with asymptomatic preclinical stages and autoantibody development before disease onset. The etiology of CD and T1D include a combination of genetic and environmental factors; most notably, shared HLA antigen loci are important risk factors for both diseases.[1]

In the past 3 decades, there has been a global rise in the incidence of T1D and CD.[2–4] CD occurs in ∼5% to 8% of individuals with T1D,[5] raising the question of whether 1 disease predisposes to the development of the other, or if simply common genetic and environmental risk factors drive disease co-occurrence without a causal link. A better understanding of the pathophysiology leading to autoimmunity and disease onset in CD and T1D may result in more effective treatment strategies for both conditions, and may suggest novel targets for intervention before disease onset.

Previous studies to determine a causal association between T1D and CD are limited to explorations of individuals with preexisting disease, without investigation of asymptomatic stages of disease in which autoimmunity begins.[6–8] Risk factors for development and co-occurrence of autoimmunity in T1D and CD therefore remain largely unexplored. The Environmental Determinants of Diabetes in the Young (TEDDY) study is a prospective cohort of infants genetically at risk for developing T1D.[9] This cohort allows a unique opportunity to study risk factors for onset of T1D and CD autoimmunity, providing insight into the preclinical stages of disease, and the possible relationship between the 2 conditions.

In this issue, Hagopian et al[10] find that the co-occurrence of T1D autoimmunity and CD autoimmunity is higher than would be expected in the general population. In a cross-sectional analysis, individuals with autoantibodies to 1 disease had increased prevalence of antibodies to the other disease. The authors further describe T1D autoimmunity proceeding CD autoimmunity, and suggest that T1D autoimmunity is a risk factor for CD autoimmunity and subsequent disease development. CD autoimmunity was not a significant risk factor for T1D autoimmunity, but the small sample size may limit the power to detect this influence. Finally, the influence of genetic and demographic risk factors for co-occurrence of CD and T1D autoimmunity are explored, with first-degree relatives with T1D identified as a significant contributor.

Although the results from the TEDDY study are hypothesis-generating, they do not directly establish causality. It is important to note that for both diseases, the autoantibodies are useful markers to follow in the onset and progression toward clinical disease development, but they are considered

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epiphenomenon and not causative of end organ damage, which is primarily a T-cell mediated process in both diseases.[11,12] To establish causality, one could conduct randomized clinical trials to see if blocking the development of 1 disease influences the appearance of the other, which is of course difficult to accomplish.

There are preclinical studies demonstrating that a gluten-free diet prevents or delays diabetes onset in nonobese diabetic mice,[13] and changes the composition of the innate immune system,[14] which is in contrast to results reported by Hagopian et al[10] in which autoimmunity to CD was not significantly associated with development of T1D autoimmunity. Two clinical trials have been conducted to evaluate the relationship between gluten exposure and T1D. Pastore et al[15] demonstrated that gluten removal for 6 months in antibody positive nondiabetic first degree relatives at risk for T1D did not reduce titers of diabetes-related autoantibodies. The largest trial to date was performed by Ziegler and co-workers,[16] demonstrating that late versus early introduction of gluten did not alter the timing of diabetes autoantibody development. Results from these trials support the findings in this TEDDY study, but both trials have significant limitations, because by their nature they cannot be conducted in blinded fashion.

Determining the converse relationship (ie, the impact of T1D autoantibodies on development of CD autoimmunity) is even more challenging. Despite significant efforts to use T1D antigens such as insulin and glutamic acid decarboxylase to prevent autoimmunity, there are currently no means to prevent development of T1D, and thus investigators are unable to determine if prevention of T1D autoimmunity ameliorates progression to CD autoimmunity and disease. It would be interesting to expand this study by investigating the development of other autoimmune diseases that occur with T1D, particularly thyroid autoantibodies and the development of Hashimoto thyroiditis or Graves' disease.

The current TEDDY study contributes to the hypothesis that that initial autoimmunity triggered against 1 organ may potentiate additional autoimmune diseases. Future studies directed to understand the risk factors and mechanism for the initial autoimmune hit may pinpoint modifiable novel drug targets with the potential to prevent 1 or more autoimmune diseases.

ABBREVIATIONS

CD: celiac disease
T1D: type 1 diabetes
TEDDY: The Environmental Determinants of Diabetes in the Young

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