COMMENTS AND RESPONSES

High Titer of Autoantibodies to GAD Identifies a Specific Phenotype of Adult-Onset Autoimmune Diabetes

Response to Kobayashi et al.

In our article (1) on adult-onset autoimmune diabetes, titers of antibodies to GAD (GADA) are reported in arbitrary units, i.e., they are elaborated in-house; therefore, they are unsuitable for comparison with other studies. However, as anticipated by Kobayashi et al. (2), the participation in the Diabetes Antibody Standardization Program (3) allows us to convert these measurements into World Health Organization (WHO) units. The value of 32 units, which in our study indicates the threshold separating patients having low from those having high GADA titers, corresponds to 300 WHO units. With regard to thyroid autoimmunity, the finding of the preferential association of thyroid peroxidase (TPO) antibodies in patients with high GADA titers is only one of the several traits indicating that high GADA titers identify a subgroup of patients having, as a whole, more prominent characteristics of insulin deficiency (e.g., higher A1C, lower BMI, a lower prevalence of metabolic syndrome and its components) and a profile of more severe and extended autoimmunity (1). Furthermore, the corresponding genetic heterogeneity shown in our study suggests that some differences between high and low GADA titer subjects may in fact exist (not only higher prevalence of DRB1*03-DQB1*0201 but also a decreasing frequency of DQB1*0602 and DRB1*0403 from type 2 diabetes to low and high GADA titer autoimmune diabetes). The classification of patients with adult-onset autoimmune diabetes according to the presence or absence of TPO antibodies drawn from the study clearly shows and further emphasizes this difference (TPO positive, $n = 51$: high GADA, $n = 35$ [68.6%], and low GADA, $n = 16$ [31.4%]; and TPO negative, $n = 140$: high GADA, $n = 59$ [42.2%]; low GADA, $n = 81$ [57.8%]; $P < 0.002$). If we consider this distribution, we can see that a considerable percentage of subjects (42%), despite having high GADA titer, are TPO antibody negative, showing that in this case, the Th2-dominant state is not able to enhance the titer of GADA. On the other hand, human autoimmune diseases rarely fall into exclusive pro-Th1 or -Th2 patterns (4). Nevertheless, we agree that the pathogenetic implications of this association remain to be clarified, and further studies are requested.

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