Subtype of islet cell antibodies and slowly progressive beta-cell failure

Dear Sir,

A lively controversy has been focused on the possible existence of two distinct types of islet cell antibodies (ICA) [1–3]. One type of antibody is thought to be “whole” or “non-restricted”, reacting with whole islet cells and predictive of subsequent progression to insulin-dependent diabetes mellitus in a high-risk population [1, 2]. The other type of antibody is thought to be “selective” or “restricted”, raised against the beta cell and poorly associated with subsequent progression to insulin-dependent diabetes. Sera containing “restricted” antibodies gave a granular immunofluorescence pattern [3]. The high-risk population in these reports included patients with ICA-positive non-diabetic endocrine autoimmune syndrome [1] and the first-degree relatives of insulin-dependent diabetic patients [2].

We were prompted to examine the predictive value of possible subtypes of ICA for the further progression of beta-cell damage in ICA-positive non-insulin-dependent diabetes mellitus on the basis of the results of our prospective study [4]. Our previous study has shown that some persistently ICA-positive non-insulin-dependent diabetic patients progressed to insulin-dependency over several years. In contrast, the non-insulin-dependent diabetic patients who were initially ICA positive and subsequently became ICA negative did not progress to beta-cell failure [4].

We examined 248 previously obtained serum samples from 49 ICA-positive non-insulin-dependent diabetic patients (mean age: 46 years, sex (male/female): 22/27, mean follow-up period: 67 months, range: 36–120 months). Serum samples had been taken at 6-month intervals during the observation period. Double immunostaining using patient serum and anti-glucagon (A 565, Dakopatts, Glostrup, Denmark) or anti-insulin (A 564, Dakopatts) rabbit sera were applied for detection of ICA subtypes [2]. ICA were assayed by an immunofluorescence method previously described [5]. The quality of our assay was as follows: sensitivity, 90%; specificity, 92%; cut-off value, 5 Juvenile Diabetes Foundation units. Forty-nine ICA-positive non-insulin-dependent diabetic patients were classified into subgroups based on the progression of beta-cell failure during the observation period. The progression group progressed from the non-insulin-dependent state to insulin-dependency over 13–48 months (mean: 27 months, $n = 17$) of observation. The non-progression group comprised non-insulin-dependent diabetic patients who did not progress to insulin dependency during an observation period ranging from 36–120 months ($n = 32$). The group included 11 non-insulin-dependent diabetic patients with persistent ICA positivity, 16 who were initially positive for ICA and became negative during observation, and 5 in whom ICA positivity fluctuated from positive to negative and back to positive.

All ICA-positive samples in the progression group ($n = 112$) and the non-progression group ($n = 135$), except for two samples in one

patient in the non-progression group, showed “whole” or “non-restricted” ICA reacting with whole islet cells. Two samples from a patient treated with sulphonylurea showed a “restricted” or “selective” pattern of reaction only with beta cells. However, the reactivity to beta cells was abolished after absorption of the serum with human insulin-coated sepharose 4B beads. This suggests that the “restricted” pattern was related to the presence of insulin autoantibodies (IAA). The false-positive effect of a high titre of IAA on the ICA assay has already been reported [6].

The present study demonstrated that classical “whole” or “non-restricted” type ICA was detected in non-progressive as well as slowly progressive ICA-positive non-insulin-dependent diabetic patients. The presence of heterogeneous ICA and the clinical value of subclassifying ICA for assessing the risk of progressive beta-cell damage was not confirmed in this study.

Yours sincerely,

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References

1. Genovese S, Bonifacio E, McNally JM et al. (1992) Distinct cytoplasmic islet cell antibodies with different risks for type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 35: 385–388
2. Gianani R, Pugliese A, Bonner-Weir S et al. (1992) Prognostically significant heterogeneity of cytoplasmic islet cell antibodies in relatives of patients with type I diabetes. *Diabetes* 41: 347–353
3. Timsit J, Caillat-Zucman S, Blondel H, Chédin P, Bach JF, Boitard C (1992) Islet cell antibody heterogeneity among type 1 (insulin-dependent) diabetic patients. *Diabetologia* 35: 792–795
4. Kobayashi T, Itoh T, Kosaka K, Sato K, Tsuji K (1987) Time course of islet cell antibodies and B-cell function in non-insulin-dependent stage of type I diabetes. *Diabetes* 36: 510–517
5. Kobayashi T, Sugimoto T, Itoh T et al. (1986) The prevalence of islet cell antibodies in Japanese insulin-dependent and non-insulin-dependent diabetic patients studied by indirect immunofluorescence and by a new method. *Diabetes* 35: 335–340
6. Scott-Morgan L, Keller U, Heitz P et al. (1988) Insulin autoantibodies (IAA) may cause false positive islet cell antibody (ICA) results in the indirect immunofluorescence test. *Diabetes Res* 8: 45–48

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