Islet Function in Diabetics with Persistent Islet Cell Antibodies

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SUMMARY

Seventeen (14 per cent) of 121 long-term insulin-treated diabetics were found to be positive for islet cell antibodies. Their duration of diabetes ranged between five and 45 years. Thirteen of these 17 patients were tested for the persistence of islet cell function by measurement of C-peptide. There was no detectable C-peptide in 12 patients, confirming that islet function had ceased. The significance of the persistence of islet cell antibodies in diabetes is unknown. DIABETES 27 (Suppl. 1):265-66, 1978.

Islet cell antibodies (ICAs) were first observed in diabetics with polyendocrine and autoimmune disorders.[42,274] They occur almost exclusively in insulin-dependent diabetics and are present in the majority of these patients early in their disease.[250,252] Their presence in diabetics not taking insulin may even presage their need for it.[197] The role of islet cell antibodies in the etiology of diabetes is uncertain, and it is not known whether they cause islet damage or merely reflect it.

Islet cell antibodies rapidly disappear from the serum of insulin-dependent diabetics, and whereas they are present in 60 per cent to 80 per cent of diabetics in the early months after diagnosis, only about 20 per cent are still positive after two to five years.[197a,252] Subsequently, ICAs appear ro persist in 5 per cent to 15 per cent of cases of more than 10 years' duration and have been recorded up to 44 years.

The significance of persistent ICAs is unknown. If islet cell damage provides the antigenic stimulus to ICA production, it is possible that the persistence of ICA could be related to protracted survival of islets that have been damaged but avoided total destruction. By measurement of serum C-peptide levels, Faber and Binder[177] have already shown that in most insulin-dependent diabetics, islet function has completely ceased in less than 10 years, apart from a few patients in whom the presence of C-peptide can be detected for much longer.

The purpose of the present investigation was to discover whether there was evidence of persisting islet function in long-term diabetics positive for ICAs, by measurement of C-peptide levels.

METHODS

Sera were tested for islet cell antibodies by immunofluorescence methods previously described.[250,251,253] The subjects were also tested for thyroid microsomal, gastric-parietal, and adrenal antibodies. C-peptide was determined by the method of Heding.[171] The effective detection limit of the assay is 0.06 nM per liter. Serum C-peptide measurements were made about two hours after breakfast, since Faber and Binder[101] have shown that postprandial levels indicate the presence or absence of islet function and correlate well with the more elaborate method of measurement after intravenous glucagon.

PATIENTS AND RESULTS

One hundred and twenty-one insulin-requiring diabetics with duration of three to 48 years (79 diagnosed before age 20 years, 42 with onset after age 40 years: 46 males and 75 females) selected from the King's College Hospital Diabetic Clinic were examined for the presence of islet cell antibodies. Seventeen (14.0 per cent) were found to be positive, and their relationships to durations of diabetes are shown in table 1. They were all reëxamined on two further occasions during the two years following the initial test and the antibodies were shown to persist. Thirteen patients were available for C-peptide measurement, and full details are shown in table 2. There were 11 women and two men; nine were under 20

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TABLE 1

Presence of islet cell antibodies (ICA) related to duration of diabetes

Duration of diabetes (yr.)	Total patients (no.)	ICA positive (no.)
3-9	19	5
10-19	56	8
20-29	39	2
30-39	5	1
40-49	2	1
Total	121	17

years old at diagnosis of diabetes. Duration of diabetes was five to eight years in four patients and 10 to 45 years in nine. All these patients had been treated with insulin from the onset. Nine patients were positive for HL-A B8 and three for BW15. All 13 patients were examined for thyroid, gastric, and adrenal antibodies: eight showed the presence of autoantibodies, a combination of two being present in three of them. All the patients were fit and healthy and showed no clinical evidence of thyroid disease, Addison's disease, or pernicious anemia.

Postprandial C-peptide was present in only one patient (0.25 nM per liter) aged 49 years: her diabetes, which was of only five years' duration, had presented in ketoacidosis, and she had always taken insulin.

DISCUSSION

There are no special features that distinguish this small group of diabetics in whom islet cell antibodies persisted. The predominance of women is common to other autoimmune disorders.[195] Irvine et al.[197a] have suggested that a relationship exists between the persistence of ICAs and specific HLA types, notably B8, and also with the presence of other autoimmune disorders, an observation supported by Bottazzo (personal communication). The present investigation has demonstrated the absence of residual islet function assessed by C-peptide measurement in 12 of the 13 cases investigated. The cause and consequences of the persistence of islet cell antibodies remain obscure.

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TABLE 2

Patients with persistent islet cell antibodies

Sex	Age at diagnosis (yr.)	Duration (yr)	C-peptide (nm./L.)	HLA antigens	Thyroid anti-bodies	Gastric anti-bodies	Adrenal anti-bodies
F	44	5	0.25	3,10/7,12	–	–	+
F	10	6	–	1,2/8,40	–	–	–
F	11	7	–	1,9/8,40	–	–	–
F	15	8	–	2,-/9,-	+	+	–
F	18	10	–	2,29/40,-	–	–	–
F	19	12	–	2,-/8,15	–	+	+
M	51	15	–	1,11/8,27	–	+	–
F	17	15	–	1,-/8,14	–	–	–
F	59	17	–	2,11/40,-	+	–	–
F	43	19	–	2,3/8,15	+	+	–
F	12	20	–	1,2/8,15	–	weakly +	–
M	41	22	–	2,-/8,40	–	–	–
F	12	45	–	2,32/8,15	–	+	–