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Letters to the editor

Islet autoimmunity before and after pancreas transplantation in patients with Type I diabetes mellitus

Dear Sir,

Insulitis, leading to relapse of Type I (insulin-dependent) diabetes mellitus after pancreatic transplantation, is associated with seroconversion (negative to positive) of islet cell antibodies (ICA) and glutamic acid decarboxylase 65 antibodies (GADA) [1]. This study was aimed to further explore the interaction between putative diabetogenic antigens in the transplanted pancreas and islet autoimmunity before and after pancreas transplantation in Type I diabetic patients.

We followed 16 consecutive Type I diabetic patients (recruited during a 2 year period) up to 24 weeks after successful pancreas transplantation. Immunosuppressive therapy was given to all patients. Autoantibodies to the intracytoplasmic domain of protein tyrosine phosphatase-like protein IA2 antibodies (IA-2 ab) and GAD 65 (GADA) were determined using ^{35}S-methionine RIA:s (GADA assay: specificity 89 %, sensitivity 76 %, intra- and inter- assay coefficients of variation less than 5 and 10 %, respectively; IA2-ab assay: specificity 92 %, sensitivity 54 %, intra- and inter assay coefficients of variation less than 4 and 8 %, respectively). Antibody levels were expressed as index values (values > 0.10 abnormal, i.e. > Means + 4 SD of 100 healthy control subjects). Islet cell antibodies were measured by an immunofluorescence assay [2] (sensitivity 100 %, specificity 100 %; abnormal ≥ 7 Juvenile Diabetes Foundation Units).

Before pancreas transplantation, 8 of 16 patients were IA2-ab positive (6/8 also GADA positive), 13/16 GADA positive, and 3/16 ICA positive (all 3 positive for both IA2-ab and GADA). Ten patients had preserved islet endocrine function 24 weeks after pancreas transplantation. Amongst IA2-ab positive patients, there were no changes in IA2-ab index levels after transplantation whereas, amongst IA2-ab negative, there was an increase ($p = 0.043$) increase from 0.02 ± 0.01 (Means ± SEM) before to 0.09 ± 0.03 2 weeks after pancreas transplantation; 4/8 IA2-ab negative became positive after pancreas transplantation. The IA2-ab index, however, decreased ($p = 0.0277$) in all patients 24 weeks after pancreas transplantation (from 0.25 ± 0.10 to 0.18 ± 0.10) and all seroconverters were again IA2-ab negative. Amongst GADA positive patients, there was an increase ($p = 0.0406$) in GADA concentrations 5 weeks after pancreas transplantation (0.66 ± 0.03 compared with 0.45 ± 0.10 before transplantation). In addition, all GADA negative patients became GADA positive 1 week after pancreas transplantation. The GADA index, however, had decreased ($p = 0.0277$) in those primary GADA positive 24 weeks after pancreas transplantation and all GADA con-

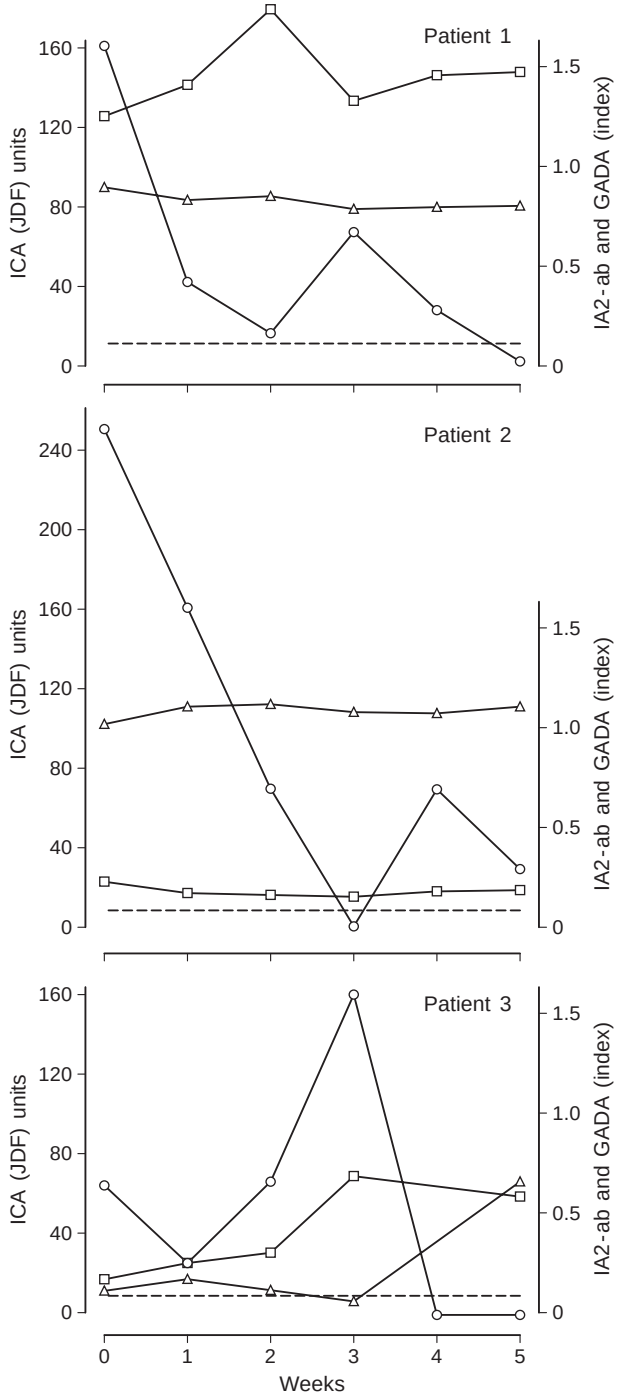

Fig. 1. Concentrations of islet cell antibodies (ICA; ◯), protein tyrosine phosphatase-like protein IA2 antibodies (IA2-ab; △), and glutamic acid decarboxylase 65 antibodies (GADA; □) before and after transplantation in three initially ICA positive patients. JDF, Juvenile Diabetes Foundation

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verters were again GADA negative. In contrast to IA2-ab and GADA negative patients, ICA negative patients continued to be negative after pancreas transplantation. Moreover, ICA concentrations decreased in all 3 ICA positive patients after pancreas transplantation; 2/3 ICA positive patients became ICA negative. In patient 1 (Fig. 1), although IA2-ab and GADA indices were clearly elevated, ICA disappeared after pancreas transplantation. In patient 2, although IA2-ab and GADA indices were unchanged, the ICA diminished and disappeared completely 3 weeks after pancreas transplantation (ICA later reappeared at low concentrations). In patient 3, although IA2-ab and GADA increased, ICA disappeared after pancreas transplantation.

The GAD65 are regarded as major antigens involved in the pathogenesis of Type I diabetes. In keeping with this, our patients showed a clear increase in GADA concentrations during the first weeks after pancreatic transplantation. Hence, the provision of GAD65 in the transplanted pancreatic graft had stimulated an autoimmune re-activation against GAD65. In addition, IA2-ab negative patients also increased their IA2-ab indices during the first weeks after pancreas transplantation. Protein tyrosine phosphatase-like protein (identified as the antigen related to the 37/40 kDa tryptic fragments of a non GAD 65 islet antigen [3]) in the transplanted pancreas graft had therefore induced an autoimmune reaction in IA2-ab negative patients. Patients converting to IA2-ab and GADA positivity later converted back to negativity, perhaps as a consequence of immunosuppression or loss of islet antigens or both.

Protein tyrosine phosphatase-like protein together with GAD 65 are considered as the main antigens behind ICA [4]. Despite the high frequency of GADA and IA2-ab, however, only three patients showed ICA before pancreas transplantation. This could reflect differences in sensitivity for autoimmunity between the antigen specific assays compared with the ICA assay as the findings in kidney transplanted diabetic patients also show that ICA and not GADA disappear during immunosuppressive therapy [5]. Nevertheless, in contrast to IA2-ab and GADA, ICA diminished or disappeared in our ICA positive patients during the first 5 weeks after pancreas transplantation. Hence, autoimmunity against the two major antigens (IA2 and GAD65) involved in the pathogenesis of Type I diabetes seems to be resistant to immunosuppressive therapy. The discrepancy in ICA compared with IA2-ab and GADA favour principle differences in the antigen-antibody reaction between ICA compared with IA2-ab and GADA. Islet cell antibodies may recognise a subset of epitopes on the IA2 or GAD 65 molecules or both that disappears more easily than other epitopes of the IA2/GAD65 proteins.

In conclusion, despite immunosuppression, pancreas transplantation activates autoimmunity against IA2 and GAD 65; islet antigens believed to be of major importance for the development of Type I diabetes.

Yours sincerely,
G. Sundkvist, G. Tydén, F. A. Karlsson, J. Bolinder

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Trp64Arg mutation of β_3-adrenoceptor gene is associated with diabetic nephropathy in Type II diabetes mellitus

Dear Sir,

Diabetic nephropathy develops in 15–60 % of patients with Type II (non-insulin dependent) diabetes mellitus depending of their ethnic origin. European patients tend to have the lowest frequency, whereas the highest cumulative incidence of 50–60 % after 20 years of diabetes was reported among Pima Indians and Japanese subjects [1]. Pima Indians have a high frequency of the missense mutation of β_3-adrenoceptor gene (Trp64Arg), and those with the mutation have early onset of Type II diabetes. This mutation is associated with abdominal obesity and resistance to insulin in Finns, and an increased capacity to gain weight in the French [2]. Its frequency among the Japanese is higher than that among whites from the United States of America and Finns but lower than that in Pima Indians. The mutation is assocated with diabetic retinopathy and coronary heart disease [2, 3] but its relation with diabetic nephropathy is unclear.

The association of this mutation with diabetic nephropathy was therefore examined in 328 Japanese patients with Type II diabetes and a history of 8 years or more of diabetes (181 men and 147 women, age: 56.8 ± 9.6 years, duration of diabetes: 15.4 ± 5.7 years, body mass index (BMI) 22.1 ± 3.4 kg/m^2; means ± SD), 14 Trp64Arg homozygotes, 106 Trp64Arg heterozygotes, 208 normal homozygotes. The Trp64Arg mutation was determined by polymerase chain reaction-restriction fragment length polymorphism analysis according to the method described previously [3]. Urinary albumin concentration (UAC) was determined by radioimmunoassay. Diabetic nephropathy was defined by a UAC of 300 μg/ml or more or end-stage renal failure with retinopathy and without clinical or laboratory evidence of any other kidney disease. Microalbuminuria was defined by a UAC of 30–299 μg/ml, and normoalbuminuria was defined by a UAC of 30 μg/ml or less.

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