Frequency of islet autoantibodies in relatives of patients with Type II diabetes or gestational diabetes

Dear Sir,

Despite differences in aetiology and genetic background several studies have suggested an association between Type I (insulin-dependent) and Type II (non-insulin-dependent) diabetes mellitus and have reported an increased risk of developing Type I diabetes for subjects having a parent with Type II diabetes [1–3]. To address whether Type I diabetes-associated islet autoimmunity is also frequent in relatives of patients with Type II diabetes and to clarify whether it could be useful to screen for Type I diabetes-associated autoimmunity in descendants of Type II diabetic patients, we measured autoantibodies to insulin (IAA), glutamic acid decarboxylase (GADA), the protein tyrosine phosphatase IA-2 (IA2A) and islet cells (ICA [4, 5]) in sera from 737 offspring or grandchildren of patients with Type II or gestational diabetes (median screening age 6.0 years, range 1 to 30 years, 340 female). These included 142 offspring and 190 grandchildren of probands with Type II diabetes and 405 offspring from women with gestational diabetes. Diabetes treatment in patients with Type II diabetes consisted of diet in 17, oral agents in 85, insulin in 71 patients and was not specified in the remainder. Of probands with gestational diabetes (GDM), 103 were treated with insulin during pregnancy and at the time of offspring screening, 75 had developed diabetes postpartum. The distribution of antibody titers in offspring and grandchildren of patients with Type II or gestational diabetes was similar to that found in control cohorts and in antibody negative relatives of patients with Type I diabetes by Q-Q plot and histogram [5, 6]. Of the relatives six (1.5%) had islet antibody titers outside the normal distribution and above the previously determined 99th centile of antibody titers in our control group (Table 1) [4, 6]. Antibody positivity was confirmed in follow-up samples 0.1 to 6.7 years after the first screening in three of six relatives and one relative had raised IAA in two consecutive samples but became negative on further follow-up. There were three relatives who had HLA DR3, DQB1*0201 or DR4, DQB1*0302 haplotypes associated with Type I diabetes and the one relative who had both, DR3 and DR4, developed Type I diabetes at the age of 6 years. Oral glucose tolerance tests were normal in the remaining five. The islet autoantibody prevalence of 0% (0/142; 95% CI 0–3) in offspring and 0.5% (1/190; 95% CI 0–3) in grandchildren of patients with Type II diabetes and of 1.2% (5/405; 95% CI 0–3) in offspring of mothers with gestational diabetes is similar to that reported for children from a general population [7] and signifi-

cantly lower ($p < 10^{-5}$) than that found in relatives of patients with Type I diabetes [5, 8]. We conclude that Type II diabetes in Germany is not associated with an increased risk for islet autoimmunity in descendants and that screening for markers of Type I diabetes in Type II families will have a similar cost-benefit ratio to that of screening in the general population and is therefore warranted only in the context of research or intervention trials aiming at studying or preventing the natural course of the Type I diabetes in non-familial cases.

Yours sincerely,

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Table 1. Relatives with raised islet autoantibodies from 737 patients with Type II diabetes or gestational diabetes

Proband				Relative				
Proband ^a	Current therapy	Antibody status	BMI	Screening age (year)	Antibody status ^c	Age at last follow-up (year)	HLA DR	HLA-DQB1
grandmother	oral agents	n. a.	n. a.	28.2	IAA (9.3U)	29.7	11,15	0301,0602
mother GDM-B	none ^b	negative	32.8	1.1	IAA (5.3U) ^d	6.8	01,11	0501,0301
mother GDM-B	insulin	negative	27.3	3.2	GADA (26U)	3.5	01,4	0501,0302
mother GDM-B	insulin	GADA	31.5	6.7	GADA (108U), ICA (20JDFU)	13.4	07,13	02,0604
mother GDM-A	none	negative	24.1	3.0	GADA (41U)	3.1	01,03	0501,02
mother GDM-A	none	negative	26.3	3.0	IAA (23U), GADA (112U), IA2A (39U), ICA (40JDFU)	6.0 DM	03,0401	02,0302

^a GDM-A: treated with diet during pregnancy, GDM-B treated with insulin during pregnancy, ^b none: no diabetes postpartum; ^c arbitrarily defined units; threshold for positivity (99th centile of control subjects) corresponds to 4U for IAA, 13U

for GADA, 5U for IA2A, and 5 Juvenile Diabetes Foundation units (JDFU) for ICA (ref. 4,6); ^d transient positive; n. a. = not available

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