A Longitudinal Study of GAD65 and ICA512 Autoantibodies During the Progression to Type 1 Diabetes in Diabetes Prevention Trial-Type 1 (DPT-1) Participants

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OBJECTIVE—We examined changes in GAD65 and ICA-512 autoantibodies (GADA and IA-2A) during progression to type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS—Diabetes Prevention Trial–Type 1 (DPT-1) participants were assessed for changes in positivity and titers of GADA and IA-2A during the progression to T1D.

RESULTS—Among 99 progressors to T1D with GADA and IA-2A measurements at baseline and diagnosis (mean interval = 3.3 ± 1.5 years), GADA positivity changed little and GADA titers decreased (P < 0.01). In contrast, both IA-2A positivity and titers increased substantially (P < 0.001). Even among those positive at baseline, IA-2A titers increased from baseline to diagnosis (n = 57; P < 0.001), whereas GADA titers decreased (n = 80; P < 0.01). The same patterns of change were also evident among those positive for both autoantibodies (n = 48) at baseline.

CONCLUSIONS—IA-2A titers increase during the years before the diagnosis of T1D, even among those positive for IA-2A. In contrast, GADA titers tend to decline during those years.

Pancreatic autoantibodies are commonly present years before the diagnosis of type 1 diabetes (T1D) (1–4), and they tend to occur according to a certain sequence (5,6). Yet there is little known about changes in both autoantibody positivity and overall titers as the onset of T1D approaches. In the Diabetes Prevention Trial–Type 1 (DPT-1) (7,8), serial measurements of autoantibodies were obtained before diagnosis. These measurements, together with the large number of participants diagnosed with T1D in DPT-1, provided unique data for studying how autoantibody positivity and titers change over time with progression to T1D.

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Received 25 May 2011 and accepted 2 August 2011.
DOI: 10.2337/dc11-0981
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RESEARCH DESIGN AND METHODS

Subjects
DPT-1 parenteral and oral insulin trial participants (7,8) were all islet cell autoantibody (ICA)-positive relatives of T1D patients. Autoantibodies to GAD65 (GADA) and to ICA512 (IA-2A) were measured along with ICA at baseline. Individuals included in the analyses were selected according to whether they also had autoantibody measurements at the time of diagnosis.

Clinic procedures
Two-hour oral glucose tolerance tests were performed every 6 months for diagnostic surveillance. The majority of individuals were diagnosed with T1D by oral glucose tolerance test criteria (fasting glucose ≥126 mg/dL and/or 2-h glucose ≥200 mg/dL) at a routine study visit. The others were diagnosed clinically. There was no overall effect of the intervention in either trial (7,8).

Laboratory measures
DPT-1 autoantibody procedures have been described previously (9). ICA was determined by an immunofluorescence assay on frozen sections of blood type O human pancreas in the DPT-1 ICA Core Laboratory (Gainesville, FL, February 1994 to September 1997 and January 1999 to October 2003; New Orleans, LA, September 1997 to January 1999). Combined GADA and IA-2A radioassays were performed at the Barbara Davis Center. Positive testing for ICA, GADA, and IA-2A was defined as ≥10 JDF units, ≥0.33, and ≥0.50, respectively. Although quantitative measurements of GADA and IA-2A were based on indexes, for simplicity we have characterized those measurements as “titers.”

Data analysis
Student t tests and χ2 tests were used for comparisons. McNemar tests were used
for intraindividual comparisons of categorical variables. The SAS 9.1.3 version was used for the analyses. All P values are two-sided. A P value < 0.05 was considered statistically significant.

RESULTS—There were 99 progressors (mean ± SD age: 11.5 ± 8.3 years; sex: 65% male) who had measurements of both GADA and IA-2A at baseline (3.3 ± 1.5 years before diagnosis) and at diagnosis. A substantial percentage was positive for GADA at baseline, with a slightly smaller percentage positive at diagnosis (80 of 99 [81%] and 76 of 99 [77%], respectively; P = 0.32). In contrast with GADA, IA-2A positivity increased markedly from baseline to diagnosis (57 of 99 [58%] and 80 of 99 [81%], respectively; P < 0.001).

Figure 1 shows that GADA titers (Fig. 1A) declined (P < 0.01), whereas IA-2A titers (Fig. 1B) increased (P < 0.001) from baseline to diagnosis. When the parenteral (n = 51) and oral (n = 48) trials were analyzed separately for titers, the same difference in directionality was evident (parenteral: P = 0.14 for GADA, P < 0.001 for IA-2A; oral: P < 0.05 for GADA, P < 0.001 for IA-2A).

We also studied changes in autoantibody titers in those positive at baseline. Among the 80 progressors positive for GADA at baseline with measurements at diagnosis, titers fell significantly (medians: 0.33 to 0.20; P < 0.01). Conversely, among the 57 progressors positive for IA-2A at baseline, titers increased from baseline to diagnosis (0.71 to 0.88; P < 0.001). Among those who were positive for both GADA and IA-2A at baseline (n = 48), GADA titers also decreased (0.30 to 0.14; P < 0.001) and IA-2A titers increased (0.73 to 0.88; P < 0.001).

Because DPT-1 participants were ICA positive, we assessed the representativeness of those positive for autoantibodies by examining individuals screened for trial eligibility (n = 92,505). Of the 3,560 GADA positive, 1,353 (38%) were also positive for ICA. Of the 1,484 IA-2A positive, 895 (60%) were also ICA positive. Thus, GADA positivity and IA-2A positivity were frequently associated with ICA positivity at screening.

CONCLUSIONS—This analysis indicates that GADA and IA-2A positivity are both common over 3 years before the diagnosis of T1D. Whereas GADA positivity shows little overall change with progression to T1D, there is a decrease in GADA titers. In contrast, IA-2A positivity and IA-2A titers increase appreciably. Among progressors already positive for autoantibodies, GADA titers decrease and IA-2A titers increase.

There have been no reports of changes in GADA and IA-2A positivity and titer with the approaching onset of T1D, although several prospective studies are currently examining incident autoantibody positivity in children at higher risk for T1D (4, 6). Data from a prior report (5) are consistent with our finding that GADA positivity tended to be higher at baseline than IA-2A positivity.

The data indicate that more information about changes with progression to T1D can be obtained by examining autoantibody titers rather than just positivity. A significant decline in GADA titers was observed, but not in the frequency of positivity. Moreover, even within the positive range, IA-2A titers increased. The latter finding is consistent with prior observations that within the positive range, autoantibody titer can be predictive of T1D (9, 10).
Because the DPT-1 participants were ICA positive, we examined the representa-
tiveness of the data for those GADA positive and those IA-2A positive at baseline. We
found that when individuals are IA-2A positive, ICA positivity is frequently a con-
comitant. ICA positivity is less common among those GADA positive, but it is still
substantial. Thus, the findings are likely to be representative of many who progress to T1D.

The decline in GADA among those positive could have been exaggerated by a
regression toward the mean. However, this would not affect the overall trend.
Moreover, a regression toward the mean would have actually dampened rather than have exaggerated the increase in IA-2A among those positive.

Even though autoantibodies are known predictors of T1D (9–11), and are commonly present at the time of diagnosis (1–4), their relevance to the pathogenesis of T1D is still unclear. The differing patterns of change between GADA and IA-2A in the years before diagnosis could be related to pathogenetic processes that are occurring during the progression to T1D.

Acknowledgments — The sponsor of the study was the Type 1 Diabetes TrialNet Study Group. Type 1 Diabetes TrialNet Study Group is a clinical trials network funded by the National Institutes of Health through the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, through the cooperative agreements U01 DK061010, U01 DK061016, U01 DK061034, U01 DK061036, U01 DK061040, U01 DK061041, U01 DK061042, U01 DK061055, U01 DK061058, U01 DK084565, U01 DK085453, U01 DK085461, U01 DK085463, U01 DK085466, U01 DK085499, U01 DK085505, U01 DK085509, and a contract HHSN267200800019C, the National Center for Research Resources, through Clinical Translational Science Awards UL1 RR024131, UL1 RR024139, UL1 RR024153, UL1 RR024975, UL1 RR024982, UL1 RR025744, UL1 RR025761, UL1 RR025780, UL1 RR029890, UL1 RR031986, and General Clinical Research Center Award M01 RR00400; the Juvenile Diabetes Research Foundation International; and the American Diabetes Association.

No potential conflicts of interest relevant to this article were reported.

J.M.S. analyzed data and wrote the manu-
script. J.S.S. conducted the study and re-
viewed the manuscript. J.P.P. conducted the study, reviewed the manuscript, and assisted in writing the manuscript. J.P.K. conducted the study and reviewed the manuscript. D.C. programmed the study for the review of the manuscript. L.Y. reviewed the manuscript. D.A.S., T.O., and G.E. conducted the study and reviewed the manuscript.

Parts of this study were presented in abstract form at the 70th Scientific Sessions of the American Diabetes Association, Orlando, Florida, 25–29 June 2010.

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