GAD Antibody Positivity Predicts Type 2 Diabetes in an Adult Population

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OBJECTIVE—To evaluate the significance of GAD antibodies (GADAs) and family history for type 1 diabetes (FH1T) or type 2 diabetes (FH2T) in nondiabetic subjects.

RESEARCH DESIGN AND METHODS—GADAs were analyzed in 4,976 nondiabetic relatives of type 2 diabetic patients or control subjects from Finland. Altogether, 289 (5.9%) were GADA+—a total of 253 GADA+ and 2,511 GADA- subjects participated in repeated oral glucose tolerance tests during a median time of 8.1 years. The risk of progression to diabetes was assessed using Cox regression analysis.

RESULTS—Subjects within the highest quartile of GADA+ (GADA high) had more often first-degree FH1T (29.2 vs. 7.9%, P < 0.00001) and GADA+ type 2 diabetic (21.3 vs. 13.7%, P = 0.002) or nondiabetic (26.4 vs. 13.3%, P = 0.010) relatives than GADA- subjects. During the follow-up, the GADA+ subjects developed diabetes significantly more often than the GADA- subjects (36/253 [14.2%] vs. 134/2,511 [5.3%], P < 0.00001). GADA+ conferred a 4.9-fold increased risk of diabetes (95% CI 2.8–8.5) compared with GADA- —seroconversion to positive during the follow-up was associated with 6.5-fold (2.8–15.2) and first-degree FH1T, with 2.2-fold (1.2–4.1) risk of diabetes. Only three subjects developed type 1 diabetes, and others had a non–insulin-dependent phenotype 1 year after diagnosis. GADA+ and GADA- subjects did not clinically differ at baseline, but they were leaner and less insulin resistant after the diagnosis of diabetes.

CONCLUSIONS—GADA positivity clusters in families with type 1 diabetes or latent autoimmune diabetes in adults. GADA positivity predicts diabetes independently of family history of diabetes, and this risk was further increased with high GADA concentrations. Diabetes 59:416–422, 2010

Latent autoimmune diabetes in adults (LADA) was introduced nearly 2 decades ago to separate a GAD antibody (GADA)-positive subgroup of adult patients initially diagnosed with type 2 diabetes (1,2). Using this definition with the add-on criteria of no exogenous insulin during the first 6–12 months, the prevalence of LADA among unselected “type 2 diabetic patients” is ~25% in subjects younger than 35 years and between 4 and 13% in subjects older than 35 years at diagnosis in populations of European origin (3–9). In follow-up studies, a progressive defect in insulin secretion was observed in ~50–60% of LADA patients within 6–10 years (3,10), which led to the inclusion of these patients as a slowly progressing form of type 1 diabetes in the last World Health Organization (WHO) classification of diabetes (11). However, both the existence of LADA as a distinct subgroup of diabetes and the criteria that should be used to diagnose it have been challenged (e.g., (12,13). The LADA group is heterogeneous, and most studies have been cross-sectional, whereas prospective studies including patients at or before diagnosis and population-based studies are few (3,4,14–16). Genetic background, especially for type 1 diabetes, may be a confounding factor, and we have shown that LADA was more frequent in families with both type 1 and type 2 diabetes than in families with type 2 diabetes only (17). Moreover, some data support that type 1 and type 2 diabetes cluster in same families (17–20), although this has been contradicted in a large U.K. study on parents of type 1 diabetic patients (21).

In children, progression to diabetes has been associated with high antibody levels and early development of multiple autoantibodies, whereas subjects with a later appearance of antibodies had a slower progression (22–25). We have previously hypothesized that GADAs would be a marker of a subclinical autoimmune process and showed that GADA positivity was associated with a decrease in maximal insulin secretory capacity in nondiabetic subjects (26). If that is the case, GADAs should also be a predictor of future diabetes in adults. This was not supported by two studies on the general population (16,27), but a Swedish study reported a sixfold increased risk for diabetes in GADA+ subjects (15).

In a prospective follow-up study of a large cohort of relatives of type 2 diabetic patients and population control subjects from Finland, we have now evaluated the predictive value of GADAs and family history for type 1 or type 2 diabetes in conjunction with the traditional risk factors for diabetes.
of the 2,511 GADA resistance (insulinogenic index/HOMAIR). The disposition index was used to adjust insulin secretion for the degree of insulin secretion during the first 30 min of the OGTT (also called the insulinogenic index). The correlation coefficient between RIA and EIA as well as FIA and EIA was 0.98 (P < 0.0001). Serum total cholesterol, HDL cholesterol, and triglyceride concentrations were measured on a Cobas Mira analyzer (Hoffman-LaRoche, Basel, Switzerland), and LDL cholesterol concentration was calculated using the Friedewald formula.

Statistical analysis. All statistical analyses were performed using SPSS statistical software version 13 (SPSS, Chicago, IL). Data are expressed as frequencies, mean ± SD, or median (IQR) in the case of non-normally distributed values. The Mann-Whitney test was used to compare group means and the χ² test (Pearson) was used to compare group frequencies. The insulin data were logarithmically transformed and a linear mixed-effects model was used to compare group differences adjusted for age, sex, and BMI while accounting for the underlying correlation between subjects from the same family. Cumulative risk for diabetes was analyzed with the Cox proportional hazards model. Variables that were found to be significant in univariate analyses were included in the multivariate model, and GADA positivity was used as a time-dependent variable, since some subjects became positive during the follow-up. Two-sided P values <0.05 were considered statistically significant.

RESULTS

Altogether, 236 (4.7%) nondiabetic subjects were GADA⁺ at the baseline visit and 53 converted to positive during the follow-up (Fig. 1). A total of 3.9% (11/281) of the GADA⁺ subjects were also IA2ab⁺ compared with only one of the GADA⁻ subjects (P < 0.0001). The GADA⁺ and GADA⁻ groups had similar age [50.6 (22.0) versus 48.2 (23.3) years] and sex distribution, with women predominating (55 vs. 54%). The majority of the subjects in both groups had normal glucose tolerance (69.6 vs. 71.9%), and about one-third had impaired glucose tolerance or impaired fasting glucose (30.4 vs. 28.1%). A total of 15.7 and 15.4% of the GADA⁺ and GADA⁻ subjects who participated in the follow-up had the highest median antibody concentrations of these three groups overlapped, and individuals having GADA concentrations stratified into quartiles, and individuals having GADA positivity and type 1 diabetes clustered in fami-
lies (Fig. 2). Compared with the GADA^- subjects, particularly the GADA^high subjects had first-degree relatives with type 1 diabetes significantly more often (29.2 vs. 7.9%, \( P < 0.00001 \) as well as GADA^- subjects (50 vs. 23%, \( P < 0.00001 \)); both nondiabetic GADA^- relatives (26.4 vs. 13.3%, \( P = 0.010 \)) and GADA^- relatives diagnosed with type 2 diabetes (LADA; 21.3 vs. 13.7%, \( P = 0.002 \)) (Fig. 2). The subjects with low or medium GADA concentrations did not differ from the GADA^- subjects with respect to family history for type 1 diabetes, but the GADA^low/med group had GADA^- relatives more often (33 vs. 23%, \( P = 0.002 \)).

Overall, the clinical characteristics of the GADA^+ and GADA^- subjects did not differ much at baseline, but the GADA^- subjects were a bit younger (Table 1). However, GADA^high subjects were younger and had a blunted insulin response during OGTT (i.e., lower insulinogenic and disposition indexes) than subjects with lower GADA concentrations or no GADAs (Table 1).

**Development of diabetes.** The GADA^+ subjects developed diabetes significantly more often than the GADA^- subjects (36/253 [14.2%] vs. 134/2,511 [5.3%, \( P < 0.00001 \)) and higher GADA concentrations were associated with a higher risk (Fig. 3). Surprisingly, type 1 diabetes was diagnosed in only three male subjects aged 31–44 years. Two had been highly GADA^+ 4.0 and 5.2 years earlier and the third was IA2ab^- and IA2ab^- at diagnosis. Altogether, 5 of the 11 (45.5%) IA2ab^- subjects developed diabetes. Except for these three type 1 diabetic patients, all the other 167 patients were diagnosed with type 2 diabetes, and they were not treated with insulin during the first year.

At the baseline visit, there was no difference between the GADA^+ and GADA^- subjects who were later to develop diabetes (data not shown), except that the GADA^- pre-diabetic subjects had a reduced waist circumference (92.2 vs. 97.6 cm, \( P = 0.019 \)) and lower BMI (27.4 vs. 28.9 kg/m^2, \( P = 0.059 \)). We have previously shown that both fasting plasma glucose and BMI were strong predictors of diabetes (29), and this applied also to the GADA^+ group (data not shown).

As shown in Table 2, after the diagnosis of diabetes, GADA^- patients were leaner than GADA^- patients [BMI 27.75 ± 2.7 vs. 30.06 ± 5.3 kg/m^2; \( P = 0.023 \)], but the groups had had similar weight gain. GADA^- patients also had less evidence of insulin resistance, as reflected by a lower fasting insulin concentration [7.24 (7.9) vs. 13.13 (11.4) IU/ml, \( P = 0.008 \)] and lower HOMA_index [2.09 (2.6) vs. 4.04 (3.9), \( P = 0.008 \)], despite similar fasting plasma glucose (Table 2). GADA^high subjects developed diabetes at a significantly younger age than GADA^- subjects [45.8 (13) vs. 63.1 (13.5) vs. 62 (19.4) years, \( P = 0.00014 \)]. At diagnosis, the GADA^- diabetic patients were comparable to other type 2 diabetic patients included in the Botnia study, except for higher C-peptide and lower fasting plasma glucose concentrations.

Subjects with family history for type 1 or type 2 diabetes developed diabetes more often (143/2062, 6.9% vs. 17/420, 4.0%; \( P = 0.028 \)) and at a younger age [59.7 (12.7) vs. 71.8 (7.8) years, \( P = 0.0001 \)] than subjects without any family history. There was no significant difference between individuals with FH_T1 (7.9%) and FH_T2 (6.2%). However, the majority of subjects with FH_T1 also had type 2 diabetic relatives, so we could not analyze the effect of pure type 1 diabetes family history. At diagnosis of diabetes,
TABLE 1
Clinical characteristics of the nondiabetic subjects at baseline according to the strength of GADA positivity

|                      | GADA− | P     | GADA+ (low/med) | P    | GADA+ (high) | P (high vs. negative) |
|----------------------|--------|-------|-----------------|------|-------------|----------------------|
| n (male/female)      | 4,687  | 216   | 73              |      |             |                      |
| NGT/IGT (%)          | 72/28  | 0.036 | 53.8 (21.4)     | 0.014| 43.9 (17.5) |                      |
| Age at baseline (years) | 48.2 (23.2) |      | 6.1 ± 1.6       | 0.04 | 6.4 ± 1.8   |                      |
| FPG (mmol/l)         | 5.5 ± 0.6 |      | 5.4 ± 0.7       | 0.7  |            |                      |
| Plasma glucose 30 min (mU/l) | 8.5 ± 1.6 |      | 8.6 ± 1.7       | 0.8  |            |                      |
| Plasma glucose 120 min (mU/l) | 6.3 ± 1.5 |      | 6.1 ± 1.6       | 0.4  |            |                      |
| Fasting serum insulin (mU/l) | 47 (4) |      | 4.7 (3.5)       | 0.5  |            |                      |
| Serum insulin 30 min (mU/l) | 35.9 (37.8) |      | 41.7 (35.5)     | 0.053| 31.9 (31.9) | 0.04                |
| Serum insulin 120 min (mU/l) | 26.7 (33.2) |      | 26.0 (31.0)     |      | 23.7 (16.7) |                    |
| Fasting serum C-peptide (nmol/l) | 0.5 ± 0.3 |      | 0.5 ± 0.3       | 0.3  |            |                      |
| Insulinogetic index   | 12.4 (14.6) |      | 13.5 (16)       | 0.032| 11 (7.3)    | 0.013               |
| HOMA                  | 1.1 (1.0) |      | 1.1 (0.9)       | 0.9  |            | 1.1 (1.2)           |
| Disposition index     | 10.2 (12.7) |     | 10.3 (13.3)     | 0.042| 7.8 (11.1)  | 0.019               |
| BMI (kg/m²)           | 26.1 ± 4.1 |      | 26.3 ± 3.8      | 0.7  |            |                      |
| Systolic blood pressure (mmHg) | 130.2 ± 18.6 |     | 134.5 ± 20.2    |      | 127.4 ± 19.8 |                    |
| Diastolic blood pressure (mmHg) | 79 ± 10.4 |      | 80.4 ± 10.7     |      | 78.6 ± 10.4 |                    |
| A1C (%)               | 5.3 ± 0.5 |      | 5.4 ± 0.5       | 0.7  |            |                      |
| LDL cholesterol (mmol/l) | 3.6 ± 1.0 |      | 3.6 ± 1.1       | 1.0  |            |                      |
| HDL cholesterol (mmol/l) | 1.4 ± 0.4 |      | 1.4 ± 0.3       | 0.4  |            |                      |
| Triglycerides (mmol/l) | 1.4 ± 0.9 |      | 1.3 ± 0.7       | 0.6  |            |                      |
| Control subjects (GADA−) | 216 | 0.036 | 53.8 (21.4)     | 0.014| 43.9 (17.5) |                      |
| Data are means ± SD or median (IQR). GADA−, no GADAs; GADA+ (low/med), GADAs within the three lower quartiles of positivity; GADA+ (high), GADAs within the highest quartile. In the statistical analyses, a linear mixed-effects model was used to compare group differences adjusted for age, sex, and BMI while accounting for the underlying correlation between subjects from the same family when appropriate.

Thus, patients with first-degree FH1 were markedly younger [43.2 (12.7) years] than individuals without any family history for diabetes [71.8 (13.2) years] (P < 0.005, FH− versus all other groups).

DISCUSSION
In this large population-based family study from Finland, we have shown that in addition to the traditional risk factors for type 2 diabetes, GADA positivity significantly increased the risk of diabetes. The incidence of diabetes
was highest in individuals with GADAs in the highest quartile of positivity (23.3%; HR 4.9, 95% CI 2.80–8.51), intermediate in individuals having GADAs within the three lower quartiles (13.0%), and lowest in GADA− subjects (5.6%). The younger age of the GADA+high group and the shorter follow-up of the GADA+ subjects reflects their increased rate of progression to diabetes, since the follow-up was terminated at diagnosis of diabetes. Although the increased risk was clearly associated with strength of GADA reactivity, we could not distinguish a GADA cutoff, under which diabetes would be less likely, and we observed no bimodality in the GADA distribution, as has been suggested (9). Also, seroconversion from GADA− to GADA+ during the follow-up conferred an increased risk of diabetes, but IA2abs were too rare in this population to have a high impact. GADA concentrations have been associated with lower C-peptide concentration in cross-sectional studies of LADA (4,30,31) as well as development of complete β-cell failure in adults with newly diagnosed diabetes of any type (32), although data from the U.K. Prospective Diabetes Study did not support an association between GADA level and need of insulin (33). Phenotypically, only three of our patients who developed diabetes had type 1 diabetes, whereas all other GADA+ patients had type 2 diabetes. We could not see a decreased insulin response to glucose, but the GADA+ diabetic patients were less insulin resistant than the GADA− patients, which indirectly supports the hypothesis that GADAs might be associated with a defect in insulin secretion. We have previously shown in nondiabetic subjects with thyroiditis that GADA+ subjects had a decreased maximal insulin secretory capacity, as estimated with an intravenous glucose-arginine test compared with GADA− subjects (26). Apparently, the insulin secretory defect associated with GADAs is mild and can only be seen with a test that stresses the β-cells maximally.

GADA positivity and type 1 diabetes clustered in families. In concert with the high prevalence of type 1 diabetes in Finland (34), FH1 was found in ~8% of GADA− and GADA+low/med subjects, whereas almost one-third (29%) of the GADA+ high group had type 1 diabetic relatives. Moreover, 50% in the GADA+ high and 30% of the GADA+low/med groups had GADA+ relatives. It would be important to study how much the known type 1 diabetes susceptibility genes, such as HLA and PTPN22, explain of this clustering. With this background, the high frequency of GADAs (4.7%) among the nondiabetic relatives and even control subjects without any family history for diabetes was not that surprising. In a 6-year follow-up study of this population, family history for type 2 diabetes together with BMI >30 kg/m² and fasting plasma glucose >5.5 mmol/l conferred a 3.7-fold risk of diabetes (29). We now hypothesized that FH1 would increase the risk of type 2 diabetes (or LADA) through an effect on insulin secretory capacity. We were reassured to find that in conjunction with the other risk factors, FH1 doubled the risk of diabetes (HR 2.2, CI 1.23–4.01). However, even when FH1 was in the model, high GADAs implied an even stronger risk (HR 4.9, CI 2.8–8.5). Further, there seemed to be a difference in incidence rates between the population control subjects without any family history for diabetes, in whom high GADAs only affected diabetes risk, and subjects with family history for type 1 or type 2 diabetes, whose diabetes risk was doubled also with low or medium-high GADAs. Mild autoimmunity might not be sufficient to cause diabetes in the absence of other factors decreasing insulin secretion or increasing insulin resistance. One such factor could be having inherited the risk allele of the gene with

### Table 2

Clinical characteristics of the GADA− and GADA+ subjects at follow-up according to progression to diabetes (DM+)

|                | DM−       | DM+       | DM−       | DM+       | P*       |
|----------------|-----------|-----------|-----------|-----------|----------|
| n              | 2,377     | 134       | 216       | 36        |          |
| Age (years)    | 54.6 (20.6)| <0.0001   | 61.9 (19.4)| <0.0001   | 60.1 (19) | 0.039    |
| Follow-up time (years)† | 8.0 (5.6)     | 7.7 (5.4)  | 9.6 (5.4)  | 0.001     | 6.3 (4.9) | 0.004    |
| AIC (%)        | 5.5 ± 0.5 | <0.0001   | 6.3 ± 0.6 | <0.0001   | 5.7 ± 0.4 | <0.0001  | 6.7 ± 1.1 | 0.004    |
| FPG (mmol/l)   | 5.3 ± 0.6 | <0.0001   | 6.9 ± 1.0 | <0.0001   | 5.3 ± 0.6 | <0.0001  | 6.9 ± 0.9 |          |
| Plasma glucose 30 min (mmol/l) | 8.5 ± 1.8 | <0.0001 | 11.5 ± 2.2 | <0.0001 | 8.4 ± 1.7 | <0.0001 | 11.5 ± 1.4 |          |
| Plasma glucose 120 min (mmol/l) | 5.9 ± 1.7 | <0.0001 | 11.3 ± 2.9 | <0.0001 | 5.8 ± 1.7 | <0.0001 | 10.5 ± 2.8 |          |
| Fasting insulin (mU/l) | 7.3 (6.5) | <0.0001 | 13.1 (11.4) | <0.0001 | 7.0 (7.1) | <0.0001 | 7.2 (7.9) | 0.008    |
| Serum insulin 30 min (mU/l) | 53.5 (43.5) | 0.0003 | 50.5 (46.6) | <0.0001 | 53.4 (38.0) | 0.006 | 36.8 (37.1) |          |
| Serum insulin 120 min (mU/l) | 30.9 (37.2) | <0.0001 | 74.6 (91.9) | <0.0001 | 29.3 (33.8) | 0.009 | 61.2 (74.7) |          |
| Fasting serum C-peptide (nmol/l) | 0.5 ± 0.3 | <0.0001 | 0.9 ± 0.5 | <0.0001 | 0.5 ± 0.3 | 0.073 | 0.7 ± 0.4 |          |
| Insulinogenic index | 14.6 (16.2) | <0.0001 | 8.1 (10.9) | <0.0001 | 15.6 (13.2) | <0.0001 | 6.4 (7.3) |          |
| HOMA            | 1.7 (1.6) | <0.0001   | 4.0 (3.9) | <0.0001   | 1.7 (1.7) | 0.036 | 2.1 (2.6) | 0.005    |
| Disposition index | 8.8 (11.2) | <0.0001 | 2.3 (1.9) | <0.0001 | 8.8 (10.2) | <0.0001 | 2.9 (2.5) |          |
| Waist (cm)      | 91.8 ± 12.5| <0.0001 | 102.9 ± 12.6 | 0.026 | 91.1 ± 11.5 | 0.026 | 88.0 ± 9.6 |          |
| BMI (kg/m²)     | 26.7 ± 4.2 | <0.0001 | 30.1 ± 5.3 | <0.0001 | 26.6 ± 4.3 | <0.0001 | 27.8 ± 2.7 | 0.023    |
| Fat %           | 28.3 ± 7.3 | <0.0001 | 30.2 ± 6.4 | <0.0001 | 28.8 ± 9.3 | <0.0001 | 30.0 ± 6.2 |          |
| Systolic blood pressure (mmHg) | 133.5 ± 19.6 | <0.0001 | 145.3 ± 22.2 | <0.0001 | 135.0 ± 19.2 | 0.055 | 146.6 ± 37.4 |          |
| Diastolic blood pressure (mmHg) | 81.4 ± 9.9 | <0.0001 | 85.7 ± 10.2 | <0.0001 | 82.0 ± 9.3 | <0.0001 | 83.6 ± 9.7 |          |
| HDL cholesterol (mmol/l) | 1.3 ± 0.4 | <0.0001 | 1.1 ± 0.3 | 0.044 | 1.4 ± 0.4 | 1.3 ± 0.4 |          |
| Triglycerides (mmol/l) | 1.4 ± 0.8 | <0.0001 | 1.8 ± 1.0 | <0.0001 | 1.4 ± 0.8 | 1.8 ± 0.9 |          |
| LDL cholesterol (mmol/l) | 3.4 ± 1.0 | <0.0001 | 3.5 ± 1.1 | <0.0001 | 3.2 ± 0.8 | 3.4 ± 1.0 |          |

Data are means ± SD or median (IQR). In the statistical analyses, a linear mixed-effects model was used to compare group differences adjusted for age, sex, and BMI while accounting for the underlying correlation between subjects from the same family. BMI was adjusted for age and sex. OGTT data were available for 60% of the GADA+ subjects and 87% of the GADA− subjects who developed diabetes. *Difference between GADA+ DM− and GADA− DM−. †Time until diagnosis of diabetes or until last visit.
strongest association with type 2 diabetes, TCF7L2, which has been shown to decrease insulin secretion and which was as common in LADA as in type 2 diabetes (35,36). Although the low number of GADA\textsuperscript{+} population control subjects precludes any firm conclusions on the difference in risk, it could explain the difference between our study and the two previous studies looking at the predictive value of GADAs for diabetes in the general population, where no increased risk was found during a comparable 8-year follow-up (16,27). Another difference between the studies was the number of GADA\textsuperscript{+} subjects, which was only 18 in the Italian Cremona Health Study (16) and 23 in the Swedish Västerbotten County Health Project. However, in another part of the Västerbotten Study, 7 of 25 (28\%) initially GADA\textsuperscript{+} subjects were reported to have developed diabetes after a mean time of 9.2 ± 2.9 years compared with 86 of 2,209 (3.9\%) of GADA\textsuperscript{-} subjects (P < 0.0001). Only one of the seven was diagnosed with type 1 diabetes (15).

In conclusion, GADA positivity clustered in families with type 1 diabetes or LADA. GADA positivity predicted diabetes independently of family history of diabetes, and this risk increased with high GADA concentrations.

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