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LADA and CARDS: A Prospective Study of Clinical Outcome in Established Adult-Onset Autoimmune Diabetes

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OBJECTIVE

Diabetes-associated autoantibodies can be detected in adult-onset diabetes, even when initially non–insulin requiring, i.e., with latent autoimmune diabetes. We aimed to identify adult-onset autoimmune diabetes in patients with established "type 2 diabetes" participating in the Collaborative Atorvastatin Diabetes Study (CARDS) to characterize their phenotype and clinical outcome.

RESEARCH DESIGN AND METHODS

We prospectively studied 2,425 European patients with presumed type 2 diabetes (mean age 62 years, diabetes duration 7.9 years) for outcomes at 3.9 years after randomization to either atorvastatin or placebo. Subjects were screened for autoantibodies to GAD (GADA), insulinoma-associated antigen-2 (IA-2A), and zinc-transporter 8 (ZnT8A).

RESULTS

A total of 173 patients (7.1%) had GADA, of whom 11 (0.5%) and 5 (0.2%) were also positive for IA-2A and ZnT8A, respectively. At baseline, 44% of GADA-positive patients were not on insulin. Fewer autoantibody-positive than autoantibody-negative patients had metabolic syndrome (64 vs. 80%), and more were on insulin (56 vs. 17%) ($P < 0.0001$ for each) without lower HbA_{1c} (69 mmol/mol [8.5%] vs. 62 mmol/mol [7.8%]). The frequency of microvascular and macrovascular events was similar in both cohorts, independent of atorvastatin.

CONCLUSIONS

Adult-onset autoimmune diabetes was prevalent, even in patients with established diabetes presumed to have type 2 diabetes. After 11.8 years' diabetes duration, nearly half the patients with autoimmune diabetes were not on insulin treatment and almost two-thirds had metabolic syndrome. The type of diabetes, whether autoimmune diabetes or type 2 diabetes, did not impact the risk of microvascular disease.

Adult-onset autoimmune diabetes has many of the immunogenetic features of childhood-onset autoimmune diabetes, and the definition of autoimmune type 1 diabetes encompasses both forms of the disease. But the clinical phenotype of adult-onset autoimmune diabetes is broad and, at diagnosis, includes patients with frank insulin-dependent diabetes as well as patients with non–insulin-requiring diabetes. These latter patients are designated as having latent autoimmune

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diabetes in adults (LADA) when not started on insulin treatment within 6 months of diagnosis. Recent large studies indicate that the proportion (7–10%) of adult-onset diabetic patients who have autoimmune diabetes, including LADA, is such that this is the most prevalent form of autoimmune type 1 diabetes (1,2). Nonetheless, we know little of the natural history of this form of autoimmune diabetes.

To explore the natural history of adult-onset autoimmune diabetes (LADA) in a large cohort of patients with established diabetes, we determined diabetes-associated autoantibodies from patients in the Collaborative Atorvastatin Diabetes Study (CARDS). CARDS was a multicenter trial of atorvastatin for the primary prevention of cardiovascular disease (CVD), which also estimated microvascular complications in adult patients with presumed type 2 diabetes. These patients had established diabetes of some years duration and were followed for an average of 3.9 years until the study was terminated (3,4).

Previous studies of LADA have indicated that this form of adult-onset autoimmune diabetes at the time of diagnosis is characterized by the predominant presence of autoantibodies to GAD (GADA), reduced frequency of metabolic syndrome, and an increased likelihood of progression to insulin treatment (5). Outcome studies, to date, have been underpowered because of short duration of review and limited numbers of cases under review (6–9). We now present an initial analysis of the CARDS cohort to address these shortcomings.

RESEARCH DESIGN AND METHODS

Study Population

CARDS was a double-blind, randomized, placebo-controlled, multicenter trial of atorvastatin (10 mg/day) for the primary prevention of CVD in type 2 diabetes (3,4). Type 2 diabetes was diagnosed as defined using the 1985 World Health Organization (WHO) criteria. The study received ethics approval both centrally and at each participating institution, and each patient gave written informed consent. The study included 2,838 randomized patients (68% men) between 40 and 75 years of age (mean age 62 years and mean duration of disease 7.9 years; median 6 years [25th–75th percentile 3.0–11.0) who took at least one dose of the study drug. The primary end point of the trial was the first acute coronary heart disease event (myocardial infarction, hospitalized unstable angina, acute coronary heart disease [CVD]), coronary revascularization procedure, or stroke. In addition, information about all causes of death was collected. LADA was defined as reported by presence of diabetes-associated autoantibodies in patients (age 30–75) without insulin therapy for at least 6 months postdiagnosis.

Inclusion Criteria

Patients included in the study were free of macrovascular disease, with serum LDL cholesterol concentrations ≤4.14 mmol/L (≤160 mg/dL) and fasting serum triglyceride concentrations ≤6.78 mmol/L (≤600 mg/dL). In addition, study participants were required to have at least one of the following cardiovascular risk factors: hypertension on treatment, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg on two successive occasions; any retinopathy as assessed by early screening according to the National Institute for Health and Care Excellence guidelines (www.nice.org.uk); proteinuria including microalbuminuria (elevated 30–300 mg/day), used as an indicator of progressive renal failure; or current smoking. Retinopathy was defined as any of the following: nonproliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease, or history of photocoagulation.

The trial was terminated 2 years earlier than planned at the request of the Safety Committee because of the clear benefit of active treatment ($P < 0.001$, two-tailed test) (3,4). The median patient participation in the trial was 3.9 years.

Laboratory Methods

Blood samples from patients were collected at the time of inclusion into the study, and serum samples were stored at −20°C prior to analysis. All patients were tested in a central laboratory (London) for serum GADA and serum autoantibodies to IA-2 (IA-2A) and ZnT8 (ZnT8A) on all GADA-positive samples and randomly selected GADA negative samples, using established radioimmunoprecipitation assays (10,11). Each assay included serially diluted sera from a prediabetic individual. These in-house standards were diluted to an end point; a separate positive serum sample (equivalent to the WHO standard of 250 WHO units) was used as an in-house control to standardize each assay for unit calculation. All GADA-positive samples and a randomly selected group of GADA-negative samples (n = 200) were tested for IA-2 (IA-2A) and ZnT8 (ZnT8A). Positive results were duplicated, reducing false positives to <0.02%. GADA positivity was further divided into high (>200 units) or low (40–200 units) titer. To further differentiate autoantibody positivity, according to autoantibody titers on the whole cohort we used the QQ plot analysis. The QQ plot confirmed the selection of the laboratory-based cutoff for positivity at 40 WHO IU in this cohort based on the end point dilution of the standard curve used independently, as well as identified two distinct cohorts among GADA-positive subjects, with an inflection at 40 (GADA low) and another at 200 WHO IU (GADA high). In the 2008 Diabetes Antibody Standardization Program (DASP) (12,13), London, assay characteristics to identify known positive samples were as follows: GADA sensitivity 72%, specificity 95%, andIA-2A sensitivity 68%, specificity 98%. In the latest DASP 2010 program, GADA sensitivity was 90% and specificity 93%, IA-2A sensitivity 68% and specificity 95%, and ZnT8A sensitivity 60% and specificity 88% (data unpublished). The pJH4·1 probe for ZnT8A was provided by Dr. J. Hutton (University of Colorado, Denver, CO).

Statistical Analysis

For continuous variables, the comparisons between GADA groups were based on the t test as univariate analysis and ANCOVA as multivariate analysis that adjusted for age, duration of diabetes, and sex. Similarly, for categorical variables, the χ^2 test and logistic regression were used, respectively, in univariate and multivariate analyses. Owing to a highly skewed distribution, triglycerides and C-reactive protein (CRP) were log transformed before the comparison. All analyses were performed using SAS. Nominal P values were reported without adjustment for multiplicity. A P value <0.05 was considered statistically significant. The study protocol is in accordance with the Declaration of Helsinki and was approved by local ethics committees in each study area. Informed written consent was obtained from all

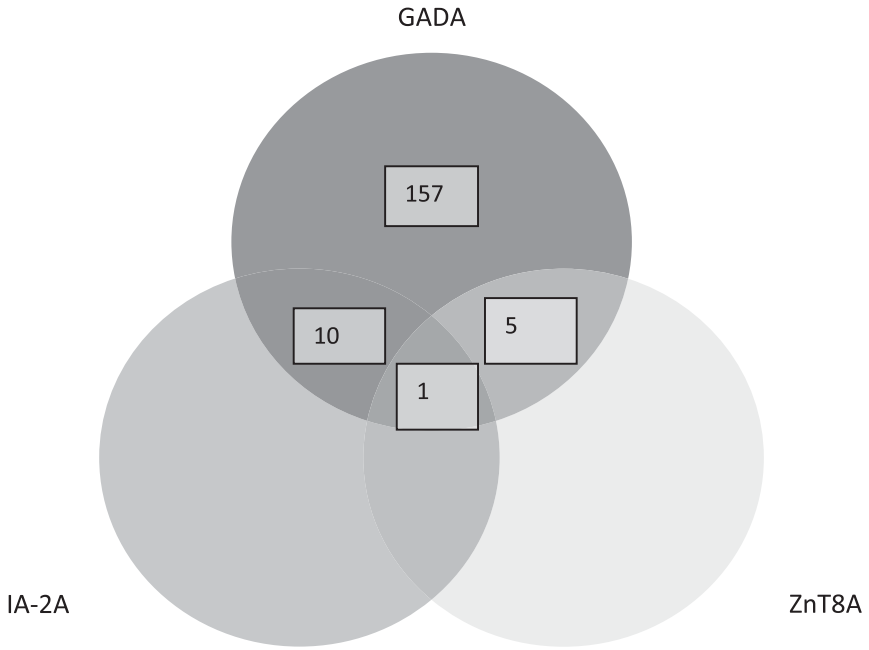

Figure 1—A total of 173 individuals were positive for GADA, and 16 of these were positive for a second antibody (11 were IA-2A positive, and 6 were ZnT8A positive). One individual was positive for all three antibodies. None of the GADA-negative samples tested as a control group were positive for IA2A or ZnT8A.

subjects before blood sampling. The study was approved by the U.K. National Research Ethics Committee (reference MREC 199/2/76).

RESULTS

Of 2,838 samples from the CARDS study cohort, 2,425 (representing those samples in which there was sufficient serum for analysis) were tested for GADA, and of these 173 (7.1%) were GADA positive. Other diabetes-associated autoantibodies were only found in GADA-positive cases of which 16 (0.7%) were positive for IA-2A and 6 (0.2%) positive for ZnT8A; one patient was positive for all three autoantibodies (Fig. 1). GADA-positive patients, in comparison with the GADA-negative patients, tended to be younger at diagnosis (51.5 vs. 55.0 years; $P < 0.01$) and leaner (27.3 ± 3.7 vs. 28.9 ± 3.5 kg/m^2; $P < 0.001$) with a longer disease duration (10.2 ± 7.0 vs. 7.6 ± 6.2 years; $P < 0.0001$) (Tables 1 and 2). The prevalence of LADA was higher in patients diagnosed with diabetes at a younger age, and GADA$^+$ patients were 3.5 years younger ($P = 0.01$) (Table 1). Furthermore, GADA was more often detected in patients diagnosed with diabetes at a younger age: 30–40 years old age-group 12% compared with those ≥61 years or older 4.7% ($P = 0.0024$, data not shown). These characteristics of GADA-positive patients were true irrespective of GADA titer.

In keeping with decreased metabolic syndrome (defined by International Diabetes Federation [IDF] criteria [14]) in participants who were GADA positive, the waist measurement, BMI, and fasting triglycerides were lower and HDL

Table 1—Clinical characteristics at baseline of GADA$^+$ and GADA$^-$ individuals

Baseline	GADA$^+$	GADA$^-$	*P*
n	173	2,252	
Age at diagnosis (years)	51.5 ± 9.3	55.0 ± 9.4	0.01
Diabetes duration (years)	10.2 ± 7.0	7.6 ± 6.2	<0.0001
BMI (kg/m^2)	27.3 ± 3.6	28.9 ± 3.5	<0.0001
HbA_{1c} (mmol/mol)	69 ± 16	62 ± 15	<0.0001
SBP (mmHg)	142.1 ± 17.4	144.0 ± 15.7	0.15
DBP (mmHg)	81.6 ± 9.1	82.9 ± 8.3	0.18
LDL cholesterol (mmol/L)	3.1 ± 0.7	3.0 ± 0.7	0.1
HDL cholesterol (mmol/L)	1.6 ± 0.4	1.4 ± 0.3	<0.0001
CRP (mg/L)	2.8 ± 5.1	3.1 ± 6.4	0.13
Apolipoprotein A1 (mg/dL)	162.6 ± 30.1	152.0 ± 27.8	<0.0001
Apolipoprotein B (mg/dL)	112.7 ± 23.8	116.3 ± 24.0	0.05
Atorvastatin treatment	49.1	51.0	0.52
High waist measure (WHO)	67.6	83.0	<0.0001
Metabolic syndrome (IDF definition)	63.6	80.4	<0.0001
Diet treated alone	5.8	15.7	0.02
Oral diabetes therapy	38.1	67.3	<0.0001
Insulin treated alone	56.1	17.1	<0.0001
Albuminuria$^+$ (macro/micro)	10.4	11.6	0.6
Any retinopathy	35.3	29.4	0.7
Proliferative retinopathy	10.4	6.3	0.2
Current smoker	27.8	21.8	0.03
Use of BP tablets	59	67.4	0.04

Data are percent unless otherwise indicated. The clinical characteristics of the individuals in accordance with GADA positivity are presented as mean ± SD. The data were processed by multivariate analysis, adjusted for age, duration of diabetes, and sex. BP, blood pressure.

Table 2—Clinical characteristics at baseline of GADA$^+$ (hi), GADA$^+$ (lo), and GADA$^-$ individuals

Baseline	GADA$^+$ hi	GADA$^+$ lo	GADA$^-$	*P* GADA$^+$ hi vs. GADA$^-$	*P* GADA$^+$ lo vs. GADA$^-$
n	108	65	2,252		
Age at diagnosis (years)	52.4 ± 9.3	50.1 ± 9.1	55.0 ± 9.4	0.311	0.003
Duration of diabetes (years)	10.2 ± 6.6	10.1 ± 7.8	7.6 ± 6.2	<0.0001	0.0003
BMI (kg/m^2)	27.0 ± 3.8	27.9 ± 3.4	28.9 ± 3.5	<0.0001	0.006
HbA_{1c} (mmol/mol [%])	70 ± 16 (8.6 ± 3.6%)	66 ± 17 (8.2 ± 3.2%)	62 ± 15 (7.8 ± 3.5%)	<0.0001	0.149
SBP (mmHg)	142.5 ± 18.0	141.4 ± 16.4	144.0 ± 15.7	0.216	0.430
DBP (mmHg)	82.0 ± 9.5	81.0 ± 8.3	82.9 ± 8.3	0.639	0.098
LDL cholesterol (mmol/L)	3.1 ± 0.7	3.1 ± 0.7	3.0 ± 0.7	0.126	0.490
HDL cholesterol (mmol/L)	1.6 ± 0.4	1.5 ± 0.4	1.4 ± 0.3	<0.0001	0.107
CRP (mg/L)	3.1 ± 6.2	2.2 ± 2.6	3.1 ± 6.4	0.345	0.189
Apolipoprotein A1 (mg/dL)	166.9 ± 30.5	155.5 ± 28.2	152.0 ± 27.8	<0.0001	0.494
Apolipoprotein B (mg/dL)	112.4 ± 24.6	113.4 ± 22.6	116.3 ± 24.0	0.093	0.270
Atorvastatin treatment	48.2	50.8	51.0	0.487	0.869
High waist measure (WHO)	66.7	69.2	83.0	<0.0001	0.006
Metabolic syndrome (IDF definition)	61.1	67.7	80.4	<0.0001	0.025
Diet treated alone	3.7	9.2	15.7	0.017	0.566
Oral diabetes therapy	29.6	52.3	67.3	<0.0001	0.041
Insulin treated alone	66.7	38.5	17.1	<0.0001	0.004
Albuminuria$^+$ (macro/micro)	13.0	6.2	11.6	0.689	0.173
Any retinopathy	34.3	36.9	29.4	0.697	0.891
Proliferative retinopathy	8.3	13.9	6.3	0.750	0.129
Current smoker	30.6	23.1	21.8	0.007	0.917
Use of BP tablets	57.4	61.5	67.5	0.026	0.521

Data are percent unless otherwise indicated. The clinical characteristics of the individuals in accordance with GADA positivity are presented as means ± SD. The data were analyzed pairwise for the GADA$^+$ hi (GAD value >200 units) and GAD$^+$ lo (GAD value 40–200 units) groups versus the GADA$^-$ group by multivariate analysis, adjusted for age, duration of diabetes, and sex.

cholesterol higher compared with those who were GADA negative (all $P < 0.001$). LDL cholesterol and blood pressure was similar in the two groups. Nonetheless, 63.6% of GADA-positive patients had metabolic syndrome compared with 80.4% of GADA-negative patients ($P < 0.0001$) (Table 1)—differences even apparent in patients with low-titer GADA (Table 2).

At baseline, GADA-positive patients were more often on insulin therapy than GADA-negative patients with diabetes (56.1% vs. 17.1%; $P < 0.0001$) (Table 1) irrespective of GADA titer (Table 2). At 3.9 years' follow-up analyses of insulin naïve patients, the cumulative use of insulin in the GADA-positive patients was higher than that in the GADA-negative patients (16.2% [95% CI 0.6–21.7] vs. 5.1% [4.2–6.0]; multivariate analysis, odds ratio [OR] 3.1 [95% CI 2.0–4.9], $P < 0.0001$) (Tables 3 and 4). Similarly, the GADA-positive patients were leaner at baseline and follow-up (BMI 27.2 ± 3.7 and 26.4 ± 3.8 kg/m^2, respectively) than GADA-negative patients (BMI 28.8 ± 3.7 and 29.0 ± 3.8 kg/m^2) ($P < 0.002$). Furthermore, despite the higher likelihood of insulin treatment in the GADA-positive patients, glycemic control (HbA_{1c}) remained similar if not worse in patients treated with insulin (univariate $P = 0.0016$; multivariate $P = 0.07$). The history of smoking was not reduced in GADA-positive cases as previously reported (15) (Table 1).

There was no difference in the frequency of microvascular disease between the groups. Of 173 GADA-positive patients, 28 (16%) developed either albuminuria or proliferative retinopathy compared with 315 (14.0%) GADA-negative type 2 diabetic patients (OR 0.9 [0.6–1.4]). The total incidence of microvascular disease at the final visit did not differ between the GADA-positive and GADA-negative participants (Table 5). Given the 17% rate in microvascular diabetes complications in

Table 3—Follow-up by GADA status

Follow-up (4 years)	GADA$^+$	GADA$^-$	Multivariate analysis
n	173	2,252	
Cumulative use of insulin at year 4 follow-up	*n* = 28 (16.2%)	*n* = 114 (5.1%)	3.1 (2.0–4.9); 0.0001
Developed microvascular disease (albuminuria or proliferative retinopathy)	*n* = 35 (20.2%)	*n* = 380 (16.9%)	0.9 (0.6–1.4); 0.7

Data are OR (95% CI); *P* value unless otherwise indicated. Follow-up data for GADA$^+$ and GADA$^-$ cases showing the cumulative use of insulin at 4 years' follow-up as well as the development of microvascular disease, analyzed by multivariate analysis.

Table 4—Follow-up by GADA status

Follow-up (4 years)	GADA$^+$ hi	GADA$^+$ lo	GADA$^-$	Multivariate analysis GADA$^+$ hi vs. GADA$^-$	Multivariate analysis GADA$^+$ lo vs. GADA$^-$
n	108	65	2,252		
Cumulative use of insulin at year 4 follow-up	*n* = 19 (17.6%)	*n* = 9 (13.9%)	*n* = 114 (5.1%)	3.5 (2.1–6.1); <0.0001	2.5 (1.2–5.2); 0.018
Developed microvascular disease (albuminuria or proliferative retinopathy)	*n* = 20 (18.5%)	*n* = 15 (23.1%)	*n* = 380 (16.9%)	0.8 (0.5–1.4); 0.415	1.2 (0.6–2.1); 0.644

Data are OR (95% CI); *P* value unless otherwise indicated. Follow-up data for GADA$^+$ and GADA$^-$ cases according to GADA titer showing the cumulative use of insulin at 4 years' follow-up as well as the development of microvascular disease, analyzed by multivariate analysis. GADA$^+$ hi, GAD value >200 units; GADA$^+$ lo, GAD value 40–200 units.

GADA-negative patients, this study has ~80% power to detect a 9% or larger difference in the rate of complications among GADA-positive patients. Only 13 GADA-positive patients had a CVD end point. No statistical difference was found for the CVD end point by GAD status (hazard ratio 1.36 [0.77–2.40]; Cox model corrected for age and sex).

CONCLUSIONS

WHO classifies diabetes into the following categories: type 1 diabetes, type 2 diabetes, other causes, and gestational diabetes mellitus. Currently, LADA is a subclassification of type 1 diabetes, since it is an autoimmune disease and shares many features in common with type 1 diabetes. Unlike those with type 1 diabetes, people diagnosed with LADA do not require immediate insulin treatment, but the presence of autoantibodies carries implications for future insulin usage, as shown here. Some suggest that LADA patients should always be treated with insulin; indeed, sulfonylureas may be detrimental (16). However, there remains uncertainty as to the clinical value of screening for diabetes-associated autoantibodies in adult-onset diabetes.

This is the first report of a large cohort of patients with established diabetes (mean initial disease duration 7.9 years) analyzed for the major diabetes-associated autoantibodies and followed prospectively for complications. From this analysis, we learned that 7% of these patients had GADA, that these GADA-positive case subjects had a phenotype similar to that previously reported for LADA (i.e., being younger and leaner and more often requiring insulin treatment than GADA-negative cases), that GADA was the dominant autoantibody; that on prospective study (11.8 years postdiagnosis) a large proportion of autoimmune diabetic patients still remain off insulin, and that almost two-thirds of GADA-positive patients had the metabolic syndrome. Furthermore, there was no marked difference in the risk of microvascular complications between the two groups and no history of smoking—the latter contrary to a recent report (15).

CARDS assessed the impact of atorvastatin on diabetes complications in a cohort of patients (mean age 62 years) with established type 2 diabetes and a degree of cardiovascular risk. It was surprising to discover that 7% of these cases, despite their age and diabetes duration (7.9 years postdiagnosis), had diabetes-associated autoantibodies. These autoantibody-positive cases, therefore, fulfilled the clinical diagnosis of adult-onset autoimmune diabetes and LADA (17). As with other large studies of adult-onset diabetes, the predominant autoantibody in the CARDS cohort was GADA, which here identified all autoantibody-positive patients. A much smaller proportion of cases (0.7%) had IA-2A or ZnT8A, but all of these patients also had GADA. The very low prevalence of both IA-2A or ZnT8A in this CARDS cohort with established diabetes contrasts with that in cohorts with recent-onset non–insulin-requiring diabetes, in line with the results from the second survey of the Norwegian HelseUndersøkelsen i Nord-Trøndelag Study (HUNT2), as well as the known tendency for both IA-2A and ZnT8A to disappear postdiagnosis (15,18–20). In HUNT2, 59% of LADA patients lost GADA on follow-up, but of those who remained autoantibody positive all but one had GADA; IA-2A and ZnT8A showed a decrease in the titer over 10 years, but GADA titer did not decline (21). We would, therefore, not recommend testing of either IA-2A or ZnT8A in patients with established, compared with newly diagnosed, type 2 diabetes.

Previous studies in China and Europe have established that GADA-positive adult-onset diabetic patients have an HLA genetic susceptibility similar to that of patients with childhood-onset autoimmune type 1 diabetes (22,23). Given immunogenetic similarities between childhood-onset and adult-onset autoimmune diabetes, it is possible that autoimmune diabetes is a continuous spectrum with a broad clinical phenotype, which encompasses insulin-dependent diabetes at one end of the spectrum and non–insulin-dependent diabetes at the other end. Two arguments challenge this position. First, GADA assays estimate signals with a 1% false positive rate. But in this study, we limited that error by duplicating the

Table 5—Incidence of microvascular disease at final visit by GADA status

Final visit (including year 5)	GADA$^+$	GADA$^-$	Multivariate analysis
n	173	2,252	
Microvascular disease (albuminuria or proliferative retinopathy)	*n* = 28 (16.2%)	*n* = 315 (14.0%)	0.9 (0.6–1.4); 0.70
Microalbuminuria$^+$	11.3	12.5	0.7 (0.4–1.2); 0.19
Any retinopathy	31.2	26.3	0.9 (0.7–1.3); 0.68
Proliferative retinopathy	5.2	3.0	1.2 (0.6–2.5); 0.62

Data are % or OR (95% CI); *P* unless otherwise indicated. Microvascular disease at final visit between GADA$^+$ and GADA$^-$ cases; data analyzed by multivariate analysis.

positive assays so that the error rate here was <0.02%, restricting the number of false GADA positive cases. Second, since GADA is not specific for autoimmune diabetes, a positive result could reflect an autoimmune tendency, independent of diabetes. Yet, in all the major studies of autoimmune diabetes, now amounting to many thousands of patients, those GADA-positive cases have a clinical phenotype different from that of the type 2 diabetic patients without GADA (15,22,24). Specifically, GADA-positive patients with adult-onset diabetes tend to have less metabolic syndrome and higher HbA_{1c} and are more likely to be on insulin therapy than GADA-negative patients with type 2 diabetes—differences even apparent in patients with low-titer GADA. Given that our present study was cross-sectional, we cannot exclude the possibility that GADA appeared postdiagnosis, though had that been the case it did not alter the broad clinical features of these GADA-positive patients. In other words, from China to Europe, GADA positivity does identify a consistent clinical phenotype, different from type 2 diabetes cases, indicating that GADA positivity is unlikely to be a diabetes-independent epiphenomenon.

The CARDS cohort is the first cohort of reasonable size to be followed prospectively for the development of diabetes complications but is still underpowered to detect anything other than very large differences between the GADA-positive and -negative patients. Since metabolic syndrome is less prevalent in adult-onset autoimmune diabetes than in type 2 diabetes, one might anticipate that those with the former are less prone to both macrovascular and microvascular complications. We found that the number of macrovascular events was insufficient to give a meaningful result, but the rate of progression to microvascular events (i.e., the development of albuminuria or proliferative retinopathy) was similar in both types of diabetes.

Importantly, the higher HbA_{1c} in the autoimmune diabetic patients could be sufficient to offset the benefits of having less metabolic syndrome, lower blood pressure, and less dyslipidemia. In CARDS, even 10 years postdiagnosis, many autoimmune diabetic patients are still not on insulin treatment; but for those autoimmune patients on insulin, the HbA_{1c} levels were not lower than in type 2 diabetic patients. A recent study also found that such adult-onset autoimmune patients tend to have higher HbA_{1c} levels, even when on insulin (8). So, putting recently diagnosed adult-onset autoimmune diabetes patients on insulin, as widely practiced in centers in which the GADA assay is available, does not predicate good glucose control (25). Clearly, we need to establish the optimum way to treat adult-onset autoimmune diabetes cases—a point broadly missed when engaging in semantic arguments about the definitions of LADA and adult-onset autoimmune diabetes. The present study highlights limitations in our current identification and treatment of such patients.

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Author Contributions. M.I.H. acquired data, analyzed and interpreted data, and drafted the manuscript. A.P.B. drafted the manuscript. T.O. acquired data. C.C.W. performed statistical analysis. D.D. critically revised the manuscript for important intellectual content. W.B. performed statistical analysis. D.J.B., J.H.F., and H.A.W.N. acquired data and critically revised the manuscript for important intellectual content. P.N.D. acquired data and analyzed and interpreted data. H.C. developed the study concept and design, acquired data, analyzed and interpreted data, and critically revised the manuscript for important intellectual content. R.D.L. and G.A.H. developed the study concept and design, analyzed and interpreted data, drafted the manuscript, and supervised the study. G.A.H. and D.D. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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