

Phenotypic Characteristics of GAD Antibody–Positive Recently Diagnosed Patients With Type 2 Diabetes in North America and Europe

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A number of patients with type 2 diabetes are GAD antibody positive. A Diabetes Outcome Progression Trial (ADOPT) is a randomized, double-blind clinical trial in recently diagnosed drug-naïve patients with type 2 diabetes that allows for the evaluation of GAD positivity in the context of anthropometric and biochemical characteristics. Of the 4,134 subjects enrolled in ADOPT for whom GAD status was obtained, 174 (4.2%) were GAD positive, with the prevalence of GAD antibodies being similar in North America (4.7%) and Europe (3.7%). Although BMI and age were similar, GAD-positive patients had a lower fasting insulin level, compatible with them being more insulin sensitive. The lower fasting insulin concentration was accompanied by a decreased early insulin response to oral glucose. However, when this insulin response was corrected for the degree of insulin sensitivity, GAD-positive and -negative patients had similar β -cell function. Consistent with the difference in insulin sensitivity, GAD-positive patients had higher HDL cholesterol and lower triglyceride levels. In the GAD-positive individuals, the prevalence of the metabolic syndrome as defined by NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) was also lower (74.1 vs. 83.7%, $P = 0.0009$). These phenotypic differences may underlie a potential difference in the natural history of hyperglycemia and its clinical outcomes. *Diabetes* 53:3193–3200, 2004

A number of patients with phenotypic type 2 diabetes are GAD antibody positive. These individuals have been referred to as having LADA (latent autoimmune diabetes in adults) or type 1.5 diabetes (1–4). However, there is limited information

regarding the phenotypic and metabolic characteristics of these patients in comparison to the majority of patients with type 2 diabetes who are GAD antibody negative (5). In particular, there are little data on phenotypic characteristics of GAD-positive recently diagnosed drug-naïve patients with type 2 diabetes (6). Although the prevalence of GAD antibodies has been well studied in Europe, no data are available on large cohorts in North America, and there have been no evaluations of GAD antibody status between North American and European subjects with type 2 diabetes in a single study using a single assay.

There is heterogeneity in the relative importance of insulin resistance and β -cell dysfunction in the pathogenesis of type 2 diabetes (7). GAD positivity may contribute to this heterogeneity in the subset of patients who have this antibody marker because it is typically more commonly associated with type 1 diabetes (8), which is largely a disease of reduced β -cell function (9).

The phenotypic characteristics and natural history of GAD-positive patients have been incompletely characterized in adults with suspected type 2 diabetes and are of interest for two reasons. First, it is important to phenotypically characterize subjects who are GAD positive to determine whether they have a different presentation and can be identified clinically. Second, there may be differences in the natural history of diabetes and/or response to treatment in subjects who are GAD positive compared with those who are GAD negative. In this article, using A Diabetes Outcome Progression Trial's (ADOPT's) cohort of >4,000 recently diagnosed drug-naïve patients with type 2 diabetes from North America and Europe (10), we examine the first question and determine whether type 2 diabetic subjects who are GAD antibody positive or negative differ phenotypically.

RESEARCH DESIGN AND METHODS

The ADOPT cohort comprised 4,357 individuals with recently diagnosed (within 3 years) drug-naïve type 2 diabetes recruited in 488 centers in North America (U.S. and Canada) and 15 countries in Europe (Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Ireland, the Netherlands, Norway, Spain, Sweden, and the U.K.). From this cohort, GAD antibody status was available on 4,134 individuals (95%), and these subjects are the basis for this report. Institutional review boards at each center approved the protocol, and subjects gave written informed consent before participation in the study.

The design of the study has been described in detail previously (10). Briefly, it is a randomized double-blind parallel-group trial consisting of a screening period and a 4- to 6-year treatment period. Eligible individuals were aged 30–75 years and had to have an insufficiently controlled fasting plasma glucose concentration (between 7 and 10 mmol/l) with routine diet and

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ADOPT, A Diabetes Outcome Progression Trial; HOMA-IR, homeostasis model assessment for insulin resistance; OGTT, oral glucose tolerance test; UKPDS, U.K. Prospective Diabetes Study.

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TABLE 1
Baseline characteristics by GAD antibody status

	GAD positive	GAD negative	<i>P</i>
<i>n</i>	174	3,960	—
Age (years)	57.0 ± 0.799	56.5 ± 0.159	0.524
Male (%)	55.8	57.7	0.605
BMI (kg/m ²)	31.4 ± 0.466	32.0 ± 0.091	0.231
Waist circumference (cm)	103.9 ± 1.17	105.5 ± 0.233	0.178
Waist-to-hip ratio	0.942 ± 0.007	0.948 ± 0.001	0.391
Fasting plasma glucose (mmol/l)	8.49 ± 0.105	8.39 ± 0.022	0.357
HbA _{1c} (%)	7.49 ± 0.070	7.35 ± 0.015	0.066
Fasting plasma insulin (pmol/l)	133 ± 9.89	150 ± 1.73	0.045
HOMA-IR ([μU/ml]/[mmol/l])	5.36 (4.83–5.95)	6.38 (6.25–6.51)	0.0005
Systolic blood pressure (mmHg)	131.2 ± 1.19	132.9 ± 0.25	0.144
Diastolic blood pressure (mmHg)	78.6 ± 0.71	79.7 ± 0.14	0.132
HDL cholesterol (mmol/l)	1.26 (1.22–1.31)	1.21 (1.20–1.22)	0.035
Non-HDL cholesterol (mmol/l)	3.83 (3.68–4.00)	3.97 (3.94–4.00)	0.091
Triglycerides (mmol/l)	1.67 (1.52–1.83)	1.86 (1.83–1.90)	0.011

Data are means ± SE or geometric mean (95% CI).

exercise intervention during the screening period. Patients were randomized to receive double-blinded rosiglitazone, glyburide, or metformin, with the goal being to attain ADA (American Diabetes Association) glycemic control guidelines (11) by titrating as necessary up to maximal dosage of each agent.

At baseline, subjects had standard anthropometric measurements and blood pressure performed. Fasting samples for routine lipid measurements and HbA_{1c} were taken before the performance of a 75-g oral glucose tolerance test (OGTT). The latter was performed to obtain estimates of insulin sensitivity and β-cell function and involved a fasting sample and a sample 30 min after commencing ingestion of the glucose load. The OGTT samples were used to measure plasma glucose and insulin levels.

Assays and calculations. All assays were performed at a central laboratory as described previously (10). Fasting plasma glucose was measured using a hexokinase assay (Olympus America, Melville, NY) method, and HbA_{1c} was determined using the Biorad Variant Hemoglobin A_{1c} assay (Hercules, CA). Serum immunoreactive insulin was quantified using a double-antibody radioimmunoassay (Linco, St. Louis, MO). This assay is specific for insulin only and has negligible cross-reactivity with proinsulin and its major circulating conversion intermediate des 31,32 human proinsulin (intact human proinsulin <0.2%; des 31,32 human proinsulin <0.2%; des 64,65 human proinsulin 76%). Total cholesterol and triglycerides were measured by enzymatic methods (Olympus America). HDL cholesterol was determined using a precipitation method (Olympus America). Non-HDL cholesterol was calculated as the difference between total cholesterol and HDL cholesterol.

GAD antibodies were measured using a commercially available radioimmunoassay manufactured by RSR (Cardiff, Wales, U.K.) and distributed by Kronus (Boise, ID). The assay recognizes autoantibodies to GAD65 in serum and has a clinical cutoff of 1.0 units/ml with an intra-assay coefficient of variation (CV) of 3.1% and an interassay CV of 5.1%. This clinical cutoff was determined from samples from 100 individual healthy blood donors that gave a mean of 0.055 ± 0.22 units/ml with a range of 0–1.45 units/ml. A total of 91 sera gave values indistinguishable from 0 units/ml, and 95 samples contained <0.35 units/ml. Three sera gave values of ≥1.0 units/ml, and all three were reduced by incubation with unlabelled GAD, suggesting that they contained specific GAD antibodies. The assay was assessed in the recent Diabetes Antibody Standardization Program (12), with 1 unit in this assay being equivalent to 25 WHO (World Health Organization) units. In this program, the assay had a sensitivity of 84% and a specificity of 90%.

The insulin response to glucose was determined as the insulinogenic index, $\Delta I_{(0-30)}/\Delta G_{(0-30)}$, which is the ratio of the incremental insulin (*I*) and glucose (*G*) responses from 0 to 30 min after commencement of glucose ingestion in the OGTT. To account for the effect of insulin sensitivity to modulate this response, this response was adjusted for the fasting insulin concentration (*I*), which is a well-established estimate of insulin sensitivity (13,14). Insulin sensitivity was also determined using the homeostasis model assessment for insulin resistance (HOMA-IR) index, calculated as [insulin (μU/ml)] × [glucose (mmol/l)]/22.5, with lower values being more insulin sensitive and higher values more insulin resistant (15).

NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) criteria for the metabolic syndrome were used to determine whether individuals did or did not have the syndrome (16). These criteria were blood pressure ≥130/85 mmHg, HDL cholesterol <1.0 mmol/l (men) or <1.3 mmol/l

(women), triglycerides ≥1.7 mmol/l, waist circumference >102 cm (men) or >88 cm (women), and fasting plasma glucose ≥6.1 mmol/l. The diagnosis of the metabolic syndrome required individuals to have at least three of these five criteria. Because all of the subjects in this report had diabetes, they only had to have two of the remaining four criteria to meet the definition. Subjects with blood pressure <130/85 mmHg who were taking antihypertensive medications and reported a diagnosis of hypertension were considered to have met the blood pressure criterion. Furthermore, those individuals who had triglyceride levels <1.7 mmol/l but were taking a fibrate at baseline were deemed to have met the triglyceride criterion.

Statistical methods. Comparisons between GAD antibody-positive and -negative subjects were performed by χ^2 analysis for frequency of dichotomous variables, whereas continuous variables were compared using a two-sample *t* test. Variables were log-transformed when necessary to improve normality of distribution. Ratios were analyzed using the Wilcoxon's rank-sum test. Data are presented as means ± SE unless otherwise specified. A two-sided *P* ≤ 0.05 was considered significant.

RESULTS

GAD antibody status and subject characteristics. Of the 4,134 subjects, 174 were GAD antibody positive, which represents 4.2% of the cohort. In North America, 103 of 2,212 (4.7%) were GAD antibody positive, whereas in Europe 71 of 1,922 (3.7%) were GAD positive (*P* = 0.12).

The characteristics of the subjects based on GAD antibody status at baseline are shown in Table 1. The two groups did not differ with respect to age, sex, BMI, waist circumference, fasting glucose, non-HDL cholesterol, or HbA_{1c} levels. In contrast, HDL cholesterol levels were higher and triglyceride levels were lower in GAD-positive individuals. We examined whether atypical type 2 diabetic subjects, i.e., younger and less obese subjects, had higher prevalence of GAD positivity. We found no relationship of GAD positivity with age (*P* = 0.37) (Fig. 1A). However, we did find that less obese subjects had a higher prevalence of GAD positivity (*P* = 0.01) (Fig. 1B).

Insulin sensitivity and β-cell function. As illustrated in Fig. 2A, the GAD-positive patients had significantly lower fasting insulin levels (133 ± 9.9 vs. 150 ± 1.7 pmol/l, *P* = 0.045), suggesting that they were more insulin sensitive. Because fasting insulin and the HOMA-IR index are highly correlated (*r* = 0.959 in this study), it is thus not surprising that GAD-positive subjects similarly had a lower HOMA-IR index (Table 1).

The insulinogenic index, $\Delta I_{(0-30)}/\Delta G_{(0-30)}$, represents

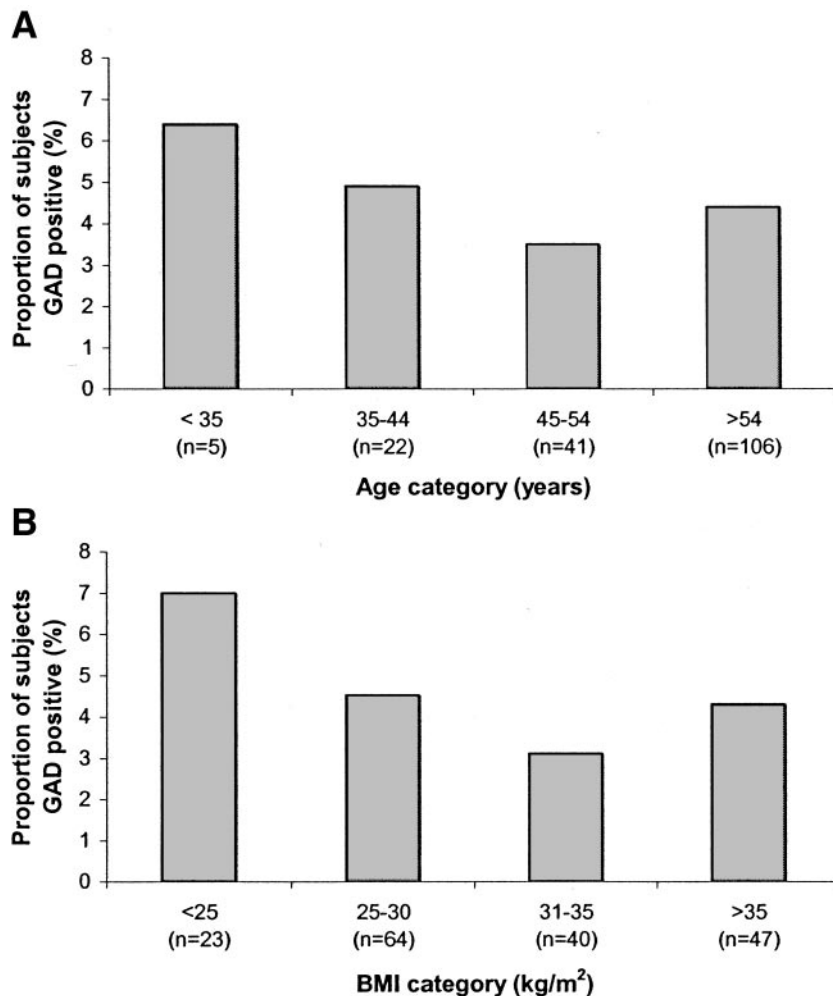


FIG. 1. Effect of age (A) and BMI (B) on the prevalence of GAD positivity in 174 GAD antibody-positive recently diagnosed drug-naïve patients with type 2 diabetes. There was no significant difference in the incidence of GAD positivity between age categories, whereas the incidence was significantly different based on BMI ($P < 0.05$).

the early insulin response during the OGTT, and this measure was decreased in the GAD-positive compared with the GAD-negative subjects: median (interquartile range): 25.9 (13.8–51.9) vs. 33.0 (18.8–58.2) pmol/mmol, $P < 0.001$ (Fig. 2B). To obtain a measure of β -cell function that accounts for the effect of insulin sensitivity, we adjusted the insulinogenic index by dividing it by the fasting insulin concentration. After this adjustment, β -cell function did not differ between the GAD-positive and -negative groups: 0.255 (0.150–0.397) vs. 0.276 (0.172–0.425) pmol²/mmol, $P = 0.12$ (Fig. 2C).

Metabolic syndrome. Although highly prevalent in both groups, the prevalence of the metabolic syndrome was significantly lower in the GAD-positive individuals (74.1% compared with 83.7% in the GAD-negative subjects, $P < 0.001$). The prevalence of subjects satisfying the individual components of the metabolic syndrome is shown in Table 2. Interestingly, whereas there were no significant differences in the proportion of patients meeting the different metabolic syndrome criteria, the GAD-negative subjects tended to have a higher proportion meeting the different criteria, and this would explain the overall greater prevalence of the syndrome in this group.

DISCUSSION

Most reports of GAD positivity in type 2 diabetes are from Europe, with two studies examining cohorts of >1,000

subjects. In the U.K. Prospective Diabetes Study (UKPDS), the overall prevalence of GAD antibodies was 10% (6), whereas in the Botnia Study in western Finland, the prevalence of GAD positivity was 9% (3,5). Although there is a paucity of information regarding the prevalence of GAD antibodies in subjects with type 2 diabetes in North America, two smaller studies, each with <200 subjects, have found somewhat conflicting data in that the prevalence rate in one was 16% (17) and in the other was 3.4% (18). Based on these limited data, it is difficult to truly evaluate whether there is a difference in the prevalence of GAD positivity in type 2 diabetes between North America and Europe. ADOPT is the only study to evaluate this issue on these two continents using a common assay with standardized recruitment criteria. With this approach, we have found that in a drug-naïve population of type 2 diabetic subjects diagnosed within 3 years, the prevalence of GAD antibody positivity was 4.2%, and there was no difference in the prevalence of these antibodies in North America and Europe (4.7 and 3.7%, respectively). Based on these findings, we would conclude that the prevalence of LADA/type 1.5 diabetes is similar in North America and Europe.

Our finding of a prevalence of 3.7% in Europe is clearly lower than that found in the UKPDS and Botnia Study. This difference could have at least three possible explanations. First, there could be heterogeneity across popula-

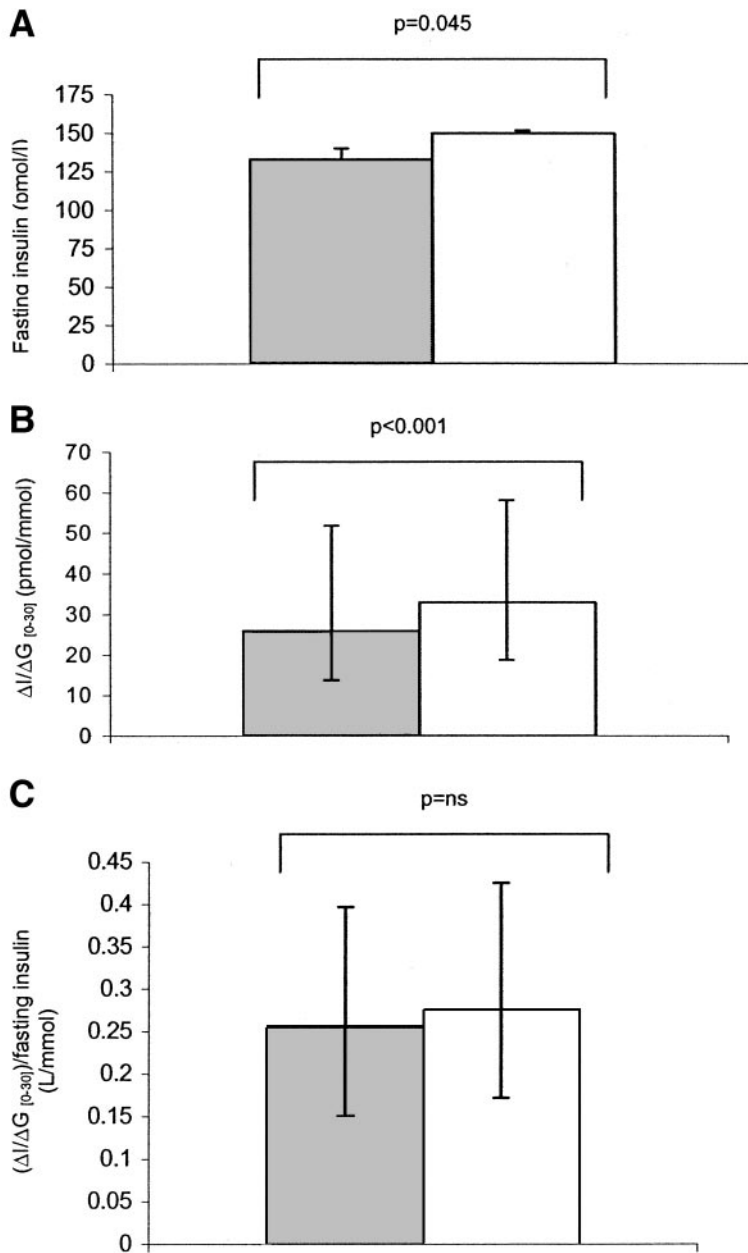


FIG. 2. A: Insulin sensitivity determined by fasting insulin. **B:** Insulin response to oral glucose as the insulinogenic index ($\Delta I/\Delta G_{[0-30]}$). **C:** β -Cell function as $\Delta I/\Delta G_{[0-30]}$ /fasting insulin from an OGTT in 174 GAD antibody-positive (■) and 3,960 GAD antibody-negative (□) recently diagnosed drug-naïve patients with type 2 diabetes. Data are expressed as the means \pm SE for fasting insulin and as median and interquartile range for the insulin response and β -cell function.

tions. The European cohort in ADOPT is comprised of individuals from 15 European countries, whereas these other two studies examined subjects exclusively from either the U.K. or Finland. That this may be the explanation is supported by findings in a Sardinian population of

1,436 individuals with type 2 diabetes that demonstrated a GAD antibody prevalence of 5.1% (A. Lernmark, personal communication). Second, it is possible that the difference may be caused by assay variability. Possible assay differences have recently been the focus of an international

TABLE 2

Prevalence of NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) metabolic syndrome criteria by GAD antibody status

	GAD positive	GAD negative	P
<i>n</i>	174	3,960	—
Metabolic syndrome positive	74.1	83.7	<0.001
Fasting glucose >6.1 mmol/l	100	100	—
Waist circumference >102 cm (male), >88 cm (female)	66.7	70.0	0.335
Blood pressure \geq 130 systolic or diastolic \geq 85 mmHg	77.0	78.6	0.627
Triglycerides \geq 1.7 mmol/l	57.5	65.2	0.054
HDL cholesterol <1.0 mmol/l (male), <1.3 mmol/l (female)	33.3	39.3	0.144

Data are percent unless otherwise indicated.

group aiming to standardize GAD assay methodology and reference reagents (12). Third, it is also possible that the different inclusion and exclusion criteria for the different studies (e.g., duration of diabetes and glucose control) resulted in the selection of cohorts with slightly different phenotypic characteristics and levels of GAD positivity between studies. In this context, because subjects in ADOPT had to be drug naïve and could have had diabetes for up to 3 years, it is possible that some GAD antibody subjects may have had more rapid β -cell destruction resulting in initiation of therapy and thus exclusion from the current study's cohort.

Type 2 diabetes is characterized by both insulin resistance and β -cell dysfunction, whereas type 1 diabetes is primarily a disease of the β -cell. Thus, one may anticipate that the GAD-positive individuals would have a phenotype more typical of type 1 diabetes. In the present cohort of subjects, we found that the GAD-positive individuals were more insulin sensitive based on both the fasting insulin concentration and HOMA-IR, two indirect but well validated measures of insulin sensitivity (13,15,19). In the GAD-positive subjects, the mean fasting insulin level was 11% lower than in the GAD-negative individuals, whereas the median insulin response to oral glucose, determined as the insulinogenic index, was 22% lower in these same subjects. Based on the known reciprocal relationship between insulin sensitivity and the insulin response as a determinant of glucose metabolism (13), when this insulin response was adjusted for insulin sensitivity to provide a measure of β -cell function, we found that β -cell function was not different between the two groups. Insulin sensitivity and the insulin response have also been evaluated in GAD-positive subjects and individuals with MODY (maturity-onset diabetes of the young) (20). This study similarly demonstrated the heterogeneity of the phenotype and the value of assessing both of these variables that are important in the pathogenesis of hyperglycemia in type 2 diabetes.

The metabolic syndrome has been defined by a number of groups, most recently in 2001 by the National Cholesterol Education Panel (16). It was previously demonstrated in the NHANES III (Third National Health and Nutrition Education Survey) that the prevalence of the metabolic syndrome in subjects with type 2 diabetes aged ≥ 50 years was 86% (21). We found a similar overall prevalence of the syndrome in our cohort. However, in GAD-positive individuals, we found the prevalence of this syndrome to be significantly lower, consistent with their lower prevalence of insulin resistance. When examined as continuous variables, subjects who were GAD positive had both significantly lower triglycerides and higher HDL cholesterol levels compared with their GAD-negative counterparts. Thus, the GAD-positive subjects, although anthropometrically similar to the GAD-negative subjects, have a biochemical profile suggesting a lower cardiovascular risk. These findings are consistent with those made in the Botnia Study (5,22). Additional phenotypic and clinical outcome differences may become apparent with further clinical follow-up.

In summary, our findings indicate that patients with type 2 diabetes who are GAD positive are distinguishable in that despite similar levels of overall adiposity, they have

lesser degrees of insulin resistance and as a consequence have a lower probability of the metabolic syndrome. These phenotypic differences could relate to differences in visceral adiposity that are not readily apparent by standard clinical assessments, such as waist circumference or waist-to-hip ratio. Furthermore, these differences may underlie a potential difference in the natural history of hyperglycemia and clinical outcome independent of glucose. Because ADOPT is a prospective clinical trial, it may afford the opportunity to determine the effect of different treatment modalities on GAD positivity and clinical outcome in recently diagnosed drug-naïve type 2 diabetic subjects.

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