Etiological Investigation of Diabetes in Young Adults Presenting With Apparent Type 2 Diabetes

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OBJECTIVE — Young adults with newly diagnosed apparent type 2 diabetes present the clinician with a wide differential diagnosis of possible etiology, including autoimmune and genetic causes as well as young-onset type 2 diabetes (YT2D). The characteristics of these groups have been described, but it is not known in which subjects investigation for etiology may be beneficial.

RESEARCH DESIGN AND METHODS — A total of 268 unselected U.K. Caucasian subjects diagnosed at ages 18–45 years and not treated with permanent insulin for ≤6 months were studied. All subjects underwent clinical assessment and screening for GAD antibodies (GADA) and tyrosine phosphatase IA-2 antibodies (IA-2A). Screening for a common mutation in the hepatocyte nuclear factor-1α (HNF-1α) gene and the common mitochondrial mutation was performed in the antibody-negative subjects. Subjects without insulin resistance were selected for sequencing of the HNF-1α gene.

RESULTS — A specific etiology was defined in 11.6% of the 268 subjects and in 24.7% of the lean subjects. Twenty-six subjects (9.7%) were positive for a β-cell antibody, one subject had familial partial lipodystrophy and the lamin A/C mutation R482W, and two subjects had the mitochondrial mutation A3243G. Two of 15 selected subjects had HNF-1α mutations, the novel missense mutation A501T, and the previously reported R583Q.

CONCLUSIONS — This unselected series shows that there is considerable heterogeneity in apparent YT2D. β-Cell autoantibodies should be performed in all those presenting at ages 18–45 years. Genetic investigations can be targeted to phenotypically defined subjects. The finding of a specific etiology will allow individualization of management and give patients valuable information about their condition.

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Recent classification of diabetes by the World Health Organization (1) and American Diabetes Association (2) has emphasized the importance of etiology in diagnosis. Knowledge of etiology has expanded as monogenic causes of diabetes such as maturity-onset diabetes of the young (MODY) and severe insulin resistance have been defined. At the same time as these molecular advances, we are seeing a substantial expansion in the population of those with common type 2 diabetes (3–5). Most of the monogenic forms of diabetes present in the 2nd to 4th decades, the same age group that type 2 diabetes is now forming a large proportion of new cases. This means that the clinician is faced with a wide differential diagnosis of diabetes, including autoimmune and genetic etiologies as well as type 2 diabetes. The relative proportion of type 2 diabetes cases will depend on the population studied, but as most are likely to be type 2, we need to develop strategies to identify those in whom investigation will be beneficial in order to direct resources appropriately.

Previous studies of apparent type 2 diabetes in young adults have identified the features distinguishing specific etiologies from type 2. Typical type 1 diabetes may present at any age; however, in adults the onset may be more insidious and clinically indistinguishable from type 2 diabetes, termed latent autoimmune diabetes of adulthood (LADA). There are no consensus criteria for diagnosing LADA (1,2), but these subjects can be identified by the presence of pancreatic β-cell antibodies, of which the most useful is GAD. These patients have a different disease profile from type 2 diabetes, being lean and insulin sensitive with a more rapid progression to insulin treatment (6,7).

MODY represents a group of monogenic causes of β-cell dysfunction presenting most often in the 2nd to 4th decades and probably accounting for 1–2% of U.K. type 2 diabetic subjects. The most common form of MODY is caused by mutations in the hepatocyte nuclear factor-1α (HNF-1α) gene (8), accounting for 65% of U.K. cases. As with LADA, young-adult subjects with HNF-1α MODY frequently cannot be distinguished from those with type 2 diabetes on the basis of diabetes presentation. The traditional criteria used to diagnose HNF-1α [age of onset <25 years and parental history of diabetes (9)] are also insufficient to differentiate from type 2 diabetes when one-third of HNF-1α subjects are diagnosed over age 25 years (8), many type 2 diabetic subjects are diagnosed younger, and approximately equal numbers of HNF-1α and type 2 subjects report a parent with diabetes (10). Features that were helpful in differentiating HNF-1α MODY from young-onset type 2

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Abbreviations: GADA, GAD antibodies; HNF-1α, hepatocyte nuclear factor-1α; IA-2A, IA-2 antibodies; LADA, latent autoimmune diabetes of adulthood; LOD, logarithm of odds; MIDD, maternally inherited diabetes and deafness; MODY, maturity-onset diabetes of the young; OGTT, oral glucose tolerance test; Y2TD, young-onset type 2 diabetes; WHR, waist-to-hip ratio.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

diabetes (YT2D) diagnosed at the same age were markers of insulin resistance, such as obesity, fasting triglycerides, and hypertension (10). Mutations in the mitochondrial genome (11) and genetic causes of severe insulin resistance, such as lipodystrophy (12–14), may also cause diabetes in young adults.

Finding a specific etiological diagnosis will be beneficial to the individual in terms of treatment, prognosis, and providing information to relatives. Knowledge of genetic subgroups already allows us to individualize treatment—those with HNF-1α MODY are sensitive to sulfonylureas (15), and those with lipodystrophy syndromes respond to thiazolidinedione and leptin treatment (16,17).

The aim of the current study was to examine an unselected cohort of subjects presenting with apparent YT2D for specific etiologies.

RESEARCH DESIGN AND METHODS

— Figure 1 shows a flow chart explaining the methods. The YT2D collection is a cohort of subjects with apparent type 2 diabetes diagnosed at ages 18–45 years. Subjects are U.K. Caucasian, recruited from both hospital clinic and primary care. All patients diagnosed in this age group were recruited into the study. Patients were either identified through primary care, where all patients were invited to take part, or from the diabetes clinic in secondary care. No patients were selected or excluded on the basis of clinical criteria except those commencing permanent insulin treatment within 6 months of diagnosis to exclude typical type 1 diabetes. Clinical assessment was used to identify rare causes of diabetes in all patients.

Baseline data collected on the subjects included diabetes treatment, current medication, family history of diabetes, and anthropometry. Data on diabetic complications were available on 189 of the subjects, ascertained from hospital notes and self-reporting. Macrovascular complications were classified as coronary artery disease, cerebrovascular disease, or peripheral vascular disease, requiring review by a vascular surgeon. Microvascular complications were divided into retinopathy treated with laser therapy and presence of microalbuminuria according to current U.K. guidelines (18). HbA_{1c} and lipids were measured. GAD antibodies

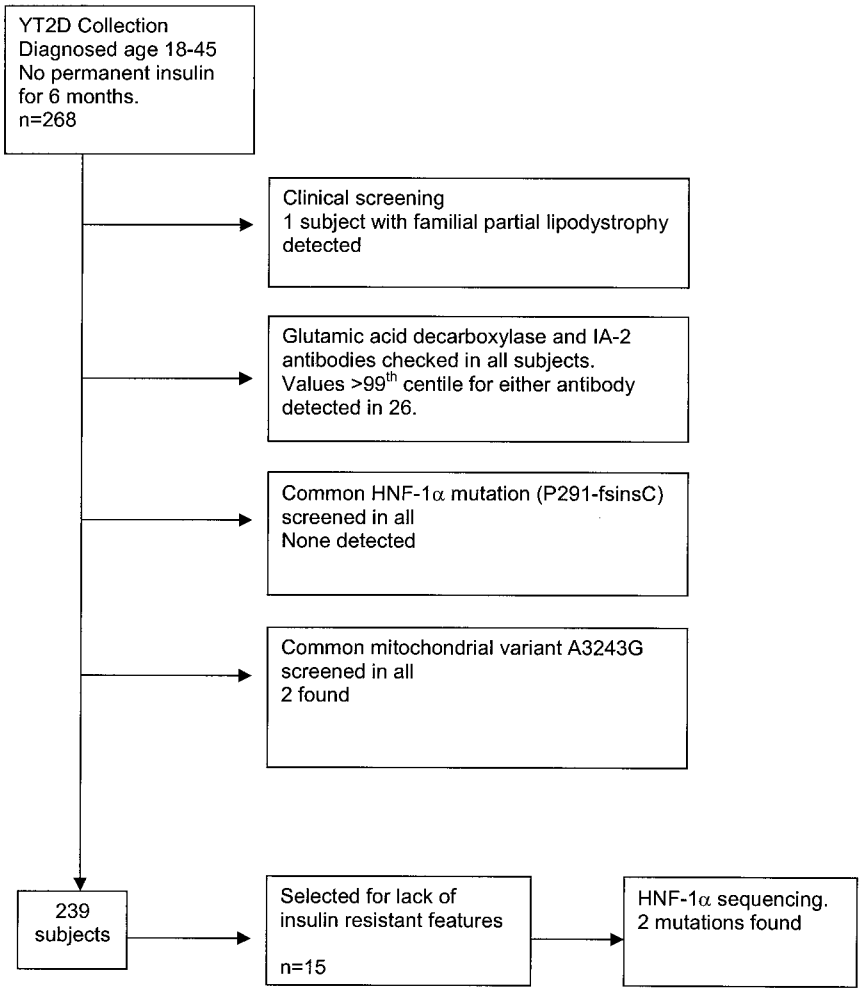

Figure 1—*Flow diagram of methods and results*

(GADA) and protein tyrosine phosphatase IA-2 antibodies (IA-2A) were measured as previously described (19). Subjects were defined as antibody positive if their antibody titer was greater than the 99th percentile for a control cohort of healthy school children for either of the antibodies measured.

Genomic DNA was obtained from peripheral white cells using the Promega Wizard kit according to manufacturer's instructions (Promega, Southampton, U.K.). The antibody-negative subjects were then screened for *1*) The common mitochondrial mutation, A3243G, using PCR amplification with previously described primers and conditions (20) and restriction fragment–length polymorphism using the *Apa*I restriction enzyme; and *2*) a common HNF-1α mutation, P291fsinsC (accounting for ≤20% of U.K. cases) as previously described (21).

Subjects were then selected for mutation analysis by direct sequencing of the HNF-1α gene. Those without features of insulin resistance were selected, which was defined as: not requiring treatment for hypertension or a recorded blood pressure of <150 mmHg systolic or <90 mmHg diastolic; not requiring treatment for dyslipidemia or a recorded fasting triglyceride <2 mmol/l; or BMI <28 kg/m^2.

The 10 coding exons and promoter region of the HNF-1α gene were amplified by PCR using previously described primers and conditions (22). PCR products were purified on Quiagen columns, and direct sequencing was performed using dye terminator reaction using Big Dye v2 (Applied Biosystems, Warrington, U.K.). Reactions were run on an ABI 377 sequencer and analyzed with Sequence Navigator version 1.0.1 software.

When mutations were identified in the HNF-1α gene, family members of the index subject were collected where avail-

Table 1—*Characteristics of the subjects*

	Whole group	Genetic etiology HNF-1α/A3243G/LMNA	Antibody$^+$ subjects	Type 2 diabetes (No defined etiology)	*P* (antibody$^+$ vs. type 2)
n	268	5	26	237	
Men	53.7 (144)	0	50.0 (13)	55.3 (131)	0.6
Diagnosis age (years)	40.5 (36–44)	39/29/24	41 (37–44)	40.5 (36–44)	0.8
Duration of diabetes (years)	14 (7–22)	25/4/1	15 (8–20)	14 (7–22)	0.8
Initial treatment (%) (diet/oha/ins)	48/50/2	HNF-1α 100/0/0 A3243G 50/50/0 LMNA 100/0/0	35/61/4	49.5/49.5/1	0.3
Current insulin therapy	53 (142)	50/100/0	85 (22)	50 (119)	<0.001
Mean BMI (kg/m^2)	31.6 ± 6.8	24.9/22.1/23.9	27.8 ± 6.6	32.2 ± 6.7	0.002
WHR					
Male	0.96 (0.93–1.0)	—	0.94 (0.89–0.98)	0.97 (0.94–1.01)	0.09
Female	0.88 (0.84–0.92)	0.89/0.82/0.90	0.85 (0.82–0.88)	0.88 (0.84–0.93)	0.04
Anti-hypertensive therapy	57 (152)	0/0/100	27 (7)	61 (144)	0.003
Cholesterol (mmol/l)	5.1 (4.5–5.8)	6.1/4.2/6.1	5.3 (5.1–5.8)	5.0 (4.5–5.8)	0.07
Triglycerides (mmol/l)	2.17 (1.5–3.3)	1.5/4.1/4.0*	1.62 (1.0–2.2)	2.19 (1.5–3.4)	0.01
HbA_{1c} (%)	8.7 (7.7–9.5)	8.1/7.8/7.0	9.3 (8.7–10.1)	8.7 (7.6–9.5)	0.08
Family history diabetes (%) (mother/father/sib)	35/16/19	HNF-1α 50/0/0 A3243G 100/0/50 LMNA 100/0/0	27/12/8	35/17/20	0.13 (at least 1 with DM)
Complications (*n*)			18	171	
Macrovascular					
Coronary artery			5.6 (1)	25 (43)	Pooled 0.09
Cerebrovascular			11 (2)	9.4 (16)	
Peripheral vasc			0	11 (18)	
Microvascular					
Retinopathy			39 (7)	22 (37)	0.14
Microalbuminuria			28 (5)	25 (42)	0.8

Data are % (*n*), median (interquartile range), and means ± SD unless otherwise indicated *Fasting TG n/a. DM, diabetes mellitus. Antibody$^+$, antibody positive.

able and diabetic and mutation status ascertained to confirm cosegregation of the mutation with diabetes.

Statistical analysis

The characteristics of the antibody-positive subjects were compared with those of the subjects with no defined etiology using Student's *t* test, Mann-Whitney *U* test, or χ^2 test (with Fisher's correction) where appropriate. $P < 0.05$ was taken as significant. SPSS version 9 was used for statistical testing.

RESULTS

Characteristics of the subjects

The study consisted of 268 subjects. Table 1 shows the baseline characteristics of the whole group, the subjects with genetic etiology, the β-cell antibody-positive group, and the group without defined etiology (true type 2 group). Complication profile in a subgroup of the antibody-positive and type 2 group is also shown in Table 1.

Clinical assessment

One subject who presented at the age of 24 years was found to have abnormal fat distribution with decreased subcutaneous fat on the limbs and trunk and increased fat around the face and neck. She had acanthosis nigricans, hypertension, and dyslipidemia. The suggestion of severe insulin resistance was confirmed by the finding of raised fasting insulin and C-peptide levels. Her mother and maternal grandfather had diabetes and similar fat distribution. On this basis, a diagnosis of familial partial lipodystrophy (Dunnigan-Kobberling syndrome) was made, later confirmed by the finding of the previously reported R482W mutation (12) in the LMNA gene.

Screening for autoimmune diabetes

GADA and IA-2A greater than the 99th percentile for control subjects were found in 24 and 5 of the subjects, respectively. Three of those with raised IA-2A also had raised GADA. Therefore, at least one antibody was found to be raised in 26 (9.7%) of the subjects. The characteristics of the antibody-positive probands are listed in Table 1. Compared with the type 2 group, there was no difference in age of onset or duration of diabetes. The antibody-positive subjects were leaner with lower triglycerides for the same glycemia, more required insulin treatment, and they had a lower prevalence of hypertension. There was no difference in the percentage of subjects reporting a first-degree relative with diabetes. Complication profile showed a Mantel-Haenszel pooled odds ratio of 3.0 (CI 0.9–9.8) for macrovascular disease in the type 2 diabetic group, but this did not reach statistical significance ($P = 0.09$). No difference was observed in the prevalence of laser-treated retinopathy or microalbuminuria.

Screening for variants in HNF-1α gene and mitochondrial genome

The common HNF-1α mutation P291-fsinsC was not detected in any of the

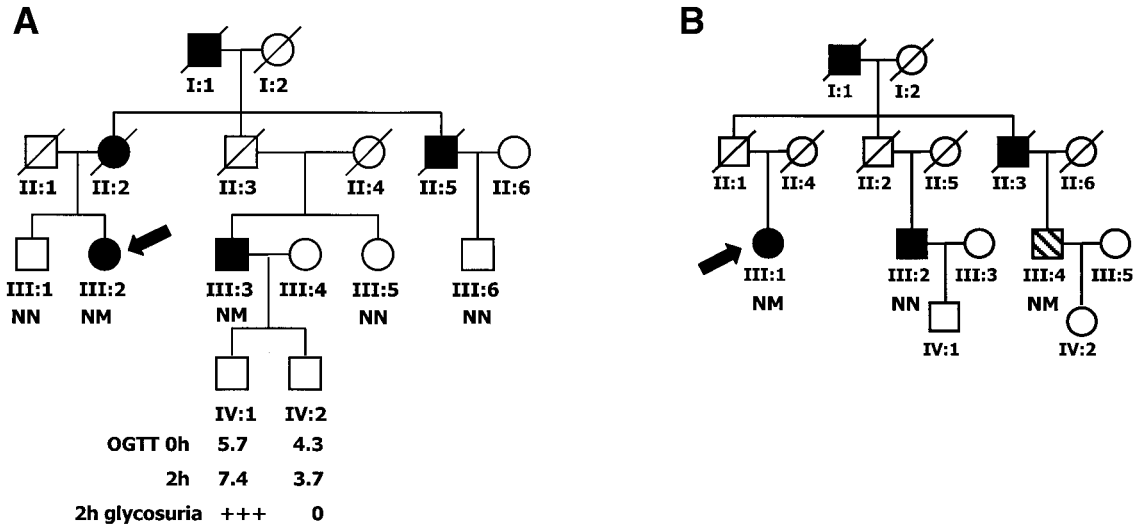

Figure 2—*Pedigrees of families with HNF-1α mutations.* A: *A501T mutation.* B: *R583Q mutation. Proband indicated by an arrow in both panels. Squares, male subjects; circles, female subjects; filled symbols, subjects with diabetes; hatched symbol, subject with impaired fasting glycemia.*

study probands. Two subjects were found to have the mitochondrial variant A3243G. In the first case, features included diagnosis at the age of 28 years, nonobese, requiring insulin treatment 1 year after diagnosis, and a family history of type 2 diabetes in her mother and gestational diabetes in her sister. Both the proband and her mother also gave a history of sensorineural deafness. The second subject was diagnosed at the age of 30 years, was non-obese, and progressed to insulin treatment 3 years after diagnosis. There was a family history of diabetes in her mother, maternal grandmother, and maternal uncles and of deafness in her mother and maternal uncles.

Sequencing of the HNF-1α gene

Fifteen subjects were selected for HNF-1α sequencing as described above. Two missense mutations were detected, as well as previously reported polymorphisms.

Family 1 (Fig. 2*A*): A novel missense mutation A501T was found in exon 7 (base change GCC→ACC) in a highly conserved amino acid. The proband was diagnosed at the age of 36 years. She was treated with diet at diagnosis, progressing to gliclazide and metformin treatment. She had a three-generation history of type 2 diabetes with a first cousin diagnosed at the age of 50 years. Her brother and three cousins were screened for diabetes and mutation status, and the mutation was shown to cosegregate with diabetes with a logarithm of odds (LOD) score of 1.8. The nondiabetic offspring of her diabetic cousin (III:3) aged 30 and 34 years were screened with a 75-g OGTT. Both were normoglycemic, but IV:1 had glycosuria following the oral glucose load, a finding associated with mutation carrier status in other HNF-1α families (23).

Family 2 (Fig. 2*B*): A missense mutation R583Q in exon 9 was found (base change CGG→CAG) in a highly conserved residue. The proband was diagnosed at the age of 41 years. She was treated with diet at diagnosis progressing to insulin treatment after 20 years. There was no parental diabetes, but both parents had died before the age of 40 years. A paternal grandfather, paternal uncle, and paternal first cousin all had diabetes diagnosed after the age of 50, and a paternal cousin had impaired fasting glycemia. Her two paternal first cousins were screened for mutation status and HbA_{1c}. One cousin with impaired fasting glycemia and a Diabetes Control and Complications Trial–aligned HbA_{1c} of 6.5% (reference range <6.05%) was found to carry the same mutation.

CONCLUSIONS — Accurate diagnosis of diabetes in children and young adults is becoming increasingly problematic, partly because of wider awareness of rare subgroups and partly because of the increase in type 2 diabetes. It can no longer be assumed that the vast majority of those diagnosed ≤30 years of age will have type 1 diabetes.

Investigation in this cohort of young adults presenting with apparent type 2 diabetes showed them to be a heterogeneous group. Diagnoses of autoimmune diabetes, maternally inherited diabetes and deafness (MIDD), HNF-1α MODY, and familial partial lipodystrophy were made using a combination of clinical assessment and laboratory testing. In total a specific etiology was found in 11.6% of the subjects. In the nonobese group (BMI <28 kg/m^2), an etiology was found in 24.7%, reflecting that the specific etiologies that have been characterized so far largely affect either the β-cell or are associated with insulin resistance in the absence of obesity.

Of the tests available, some can be easily performed relatively cheaply on a large number of samples. This category includes β-cell antibodies and the tests for common variants in the mitochondrial genome and HNF-1α gene. From our results, it seems that testing all for β-cell antibodies is worthwhile, but that in an unselected population, testing for A3243G or P291fsinsC is unlikely to be beneficial. Although two subjects were found with A3243G, they both gave a classic history of MIDD and thus could have been selected for testing on clinical grounds. These results support previous similar screening of a cohort of 157 apparent type 2 diabetic subjects (24) to exclude non–type 2 diabetic subjects. GADA was found in 8%, P291fsinsC in none, and A3243G in five probands, only

two of which had a diabetic mother and only one was lean.

The presence of β-cell antibodies is specific for type 1 diabetes, and although positive titers may not change immediate management, it does identify an insulin-sensitive subgroup with relatively rapid progression to insulin treatment (7,25), where persevering with lifestyle interventions is unlikely to be effective. Of the commonly available antibodies, GAD persists long-term in the circulation (25) and is therefore useful in situations where the subjects have variable durations of diabetes. Testing for β-cell antibodies at diagnosis is likely to be even more beneficial, as this enables testing for multiple antibodies and thus greater sensitivity of testing. Of our cohort, 9.7% were positive for at least one antibody. This is lower than that reported for the newly diagnosed type 2 diabetic subjects in this age group recruited for the U.K. Prospective Diabetes Study (7), but we excluded subjects requiring insulin in the first 6 months after diagnosis, and the testing we performed was not at diagnosis in the majority of cases. A higher prevalence (19.3%) was also observed in this age group in a cohort from Finland (6), but this population is known to have a higher prevalence of type 1 diabetes.

Classically, MODY due to HNF-1α mutations has been reported in families with characteristic onset of non–insulin-dependent diabetes in the 2nd or 3rd decade. It follows that principally families with this phenotype have been investigated and diagnosed with HNF-1α MODY. Ultimately this will lead to difficulties in diagnosis as type 2 diabetes is increasingly seen in children and young adults who tend to have a strong family history of diabetes. Thus in this study we elected to use selection criteria based on pathophysiology as suggested by our previous study, which looked at HNF-1α patients diagnosed after age 25 years. Our criteria of absence of obesity and clinical features suggestive of the insulin resistance syndrome resulted in two mutations in HNF-1α being found from 15 sequenced subjects (13%). The novel missense mutation, A501T, cosegregates with diabetes in the family with an LOD score of 1.8 and is highly conserved among other species. This suggests that it is pathogenic. The other mutation, R583Q, has been previously reported in 2 of 245 Danish subjects (26) screened for HNF-1α mutations. These subjects were older at onset than generally reported in MODY but were nonobese. It is possible that this variant may represent a rare polymorphism; however, we have not reported it in the sequencing of the HNF-1α gene in >150 unrelated subjects, mainly of U.K. origin. A further reported variation at the same codon (R583G) was reported in a Japanese patient originally diagnosed with type 1 diabetes (27). This amino acid is conserved across species, suggesting that it may have functional importance.

In our family, the mutation was not clearly associated with a typical HNF-1α phenotype (there is also a phenocopy in this pedigree; individual III:2 who is a nonmutation carrier with type 2 diabetes). It is likely that the spectrum of diabetes caused by mutations in the HNF-1α gene is wider than that originally described and will include some examples of variants with lower penetrance of the diabetic phenotype than those previously reported. Other variants may be predisposing rather than causative. The private mutation, G319S, in the Canadian Oji Cree population (28) and the G574S variant seen in African-American populations (29) are examples of this. R583Q may fall into one of these categories and warrants further investigation.

The finding of one subject in the cohort with the rare Dunnigan-Kobberling syndrome emphasizes the importance of clinical assessment of all patients with YT2D. The abnormal fat distribution may be difficult to detect in male subjects and is frequently concealed in female patients (30). The assessment of a new patient with apparent type 2 diabetes should include presence of acanthosis nigricans; the finding of this in the absence of obesity would suggest a diagnosis of severe insulin resistance.

This study has some limitations. As subjects had varying duration of diabetes, it is possible that there was a bias toward long-term survivors without cardiovascular morbidity being recruited who may be more likely to have a specific etiology. In addition, because not all subjects were sequenced for HNF-1α mutations, we do not know how commonly these will be observed in those with features of insulin resistance, therefore we cannot comment on the sensitivity or specificity of these criteria. We did not measure insulin sensitivity directly and used the clinical surrogates of fasting triglycerides, presence of hypertension, and obesity. It is likely that direct methods of assessing insulin sensitivity will be more accurate in selecting subjects for investigation, although they are less readily available in clinical practice. A prospective study would address this.

A minority of subjects may have more than one etiological factor; GADA-positive patients with MODY mutations have been reported (31,32). Usually in the clinical setting, the finding of an individual with β-cell antibodies at diagnosis would lead to a diagnosis of type 1 diabetes without further investigation unless other features (e.g., family history) are suggestive of MODY.

In summary, newly diagnosed apparent type 2 diabetes in young adults and children represents a difficult diagnostic problem, and strategies need to be in place to identify those in whom investigation will be beneficial. Rare subgroups of diabetes, such as MIDD and the lipodystrophies, are likely to be associated with specific clinical features that will guide investigation.

Our results suggest that it is worthwhile investigating for well-characterized specific etiologies of β-cell dysfunction such as LADA and HNF-1α MODY in those diagnosed under 45 years, particularly in patients lacking clinical features of the insulin resistance syndrome, since a specific cause was found in 25% of lean subjects. Finding of a specific etiology will be advantageous to patients, allowing individualization of management and access to information about prognosis and risk of diabetes in family members.

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