Etiological Approach to Characterization of Diabetes Type

The SEARCH for Diabetes in Youth Study

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OBJECTIVE—To describe an etiologic approach to classification of diabetes types in youth based on the 1997 American Diabetes Association (ADA) framework, using data from the SEARCH for Diabetes in Youth Study.

RESEARCH DESIGN AND METHODS—SEARCH conducted a comprehensive assessment of 2,291 subjects aged <20 years with recently diagnosed diabetes. Using autoimmunity (at least one of two diabetes autoantibodies) and insulin sensitivity (equation validated against hyperinsulinemic-euglycemic clamps) as the main etiologic markers, we described four categories along a bidimensional spectrum: autoimmune plus insulin-sensitive (IS), autoimmune plus insulin-resistant (IR), nonautoimmune plus IS, and nonautoimmune plus IR. We then explored how characteristics, including genetic susceptibility to autoimmunity (HLA genotypes), insulin deficiency, and clinical factors varied across these four categories.

RESULTS—Most subjects fell into either the autoimmune plus IS (54.5%) or nonautoimmune plus IR categories (15.9%) and had characteristics that align with traditional descriptions of type 1 or type 2 diabetes. The group classified as autoimmune plus IR (19.5%) had similar prevalence and titers of diabetes autoantibodies and similar distribution of HLA risk genotypes to those in the autoimmune plus IS group, suggesting that it includes individuals with type 1 diabetes who are obese. The group classified as nonautoimmune plus IS (10.1%) likely includes individuals with undetected autoimmunity but may also include those with monogenic diabetes and thus requires further testing.

CONCLUSIONS—The SEARCH study offers researchers and clinicians a practical application for the etiologic classification of diabetes type and at the same time identifies a group of youths who would benefit from further testing.

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Prior to 1979, no uniform classification of diabetes type existed. To address this, the National Institutes of Health assembled an expert committee that recommended the use of clinical characteristics, such as age of onset and "method of treatment" to define diabetes type (1). Due largely to the widespread obesity epidemic, however, clinical factors have become less effective as hallmarks of specific diabetes phenotypes (2). Moreover, a classification system based on therapy has become unsatisfactory because of the increasing clinical trend toward early insulin use regardless of the presumed diabetes type (2).

In 1997, the American Diabetes Association (ADA) convened a second expert committee (2) that proposed a physiologic framework to classification of diabetes type. The committee concluded that most diabetes cases fell into two broad categories: type 1, an absolute deficiency of insulin usually attributed to autoimmune destruction of the β-cells, and type 2, a combination of insulin resistance and relative insulin deficiency.

This framework poses important practical challenges for researchers and clinicians because it does not provide operational definitions for the markers used to define diabetes types (i.e., autoimmunity, insulin resistance, and insulin deficiency). In addition, it assumes that there are two distinct diabetes types with little or no overlap. The issue is likely to be even more complex for pediatric diabetes because, until recently, diabetes diagnosed in children and adolescents was almost entirely considered to be type 1 diabetes (2).

SEARCH for Diabetes in Youth is a multicenter study of pediatric diabetes in the U.S. This study describes the approach used in SEARCH to classify diabetes type using the 1997 ADA framework and to identify youths who require additional tests to identify specific etiologies. SEARCH used two main etiologic markers, autoimmunity (measured by two diabetes-related autoantibodies) and insulin sensitivity (measured by a clinical algorithm validated against

hyperinsulinemic-euglycemic clamps), to identify etiologic subgroups of youths with diabetes. SEARCH then explored how other characteristics, including genetic susceptibility to autoimmunity, degree of insulin deficiency, and clinical factors, vary across these categories. This study describes the development, application, strengths, and limitations of this approach. SEARCH recognizes that defining diabetes type remains difficult and controversial (3) and that only through the careful study of large numbers of youths with diabetes, not selected because of their presumed type, can we learn which characteristics actually differentiate subgroups of youths with diabetes.

RESEARCH DESIGN AND METHODS

Overview of SEARCH for Diabetes in Youth

SEARCH is a multicenter study that conducts population-based ascertainment of newly diagnosed cases of nongestational diabetes in youths aged <20 years (4). Youths with diabetes were identified in defined geographic regions or among health care management organization members (4). For all cases, core information, including date of birth, sex, date of diagnosis, and diabetes type, were obtained from medical records. Clinical diabetes type assigned by the health care professional was categorized as follows: type 1 (combining type 1, type 1a, and type 1b), type 2, and other types (including hybrid type, type unknown, and type designated as other). Self-reported race and ethnicity data were collected through a survey using the 2000 U.S. Census questions (5). Youth with nonsecondary diabetes were invited to a baseline study visit. Written informed consent was obtained observing guidelines established by the local institutional review boards.

Data collection

Study visits occurred after an 8-h overnight fast. Participants did not take diabetes medications the morning of the visit, and long-acting insulin was administered the evening before the visit and then discontinued. Blood was drawn when subjects were fasting, and a urine sample was collected. Specimens were processed locally and shipped within 24 h to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories), where they were analyzed. DNA was obtained from all consenting participants and stored by the central laboratory. Physical examinations were conducted according to standardized protocols by trained and certified staff members.

Height and weight were measured, and BMI was calculated and converted to BMI–*z*-score using standard Centers for Disease Control and Prevention approach (6). Waist circumference was measured using the U.S. National Health and Nutrition Examination Survey (NHANES) protocol (7). Acanthosis nigricans was documented using Burke's method (8). History of insulin use and family history of diabetes in first-degree relatives were assessed by self-report. Presence of diabetic ketoacidosis (DKA) at diabetes onset was based on medical record abstraction. For DKA to be present, one of the following criteria had to be met in the context of hyperglycemia: *1*) blood bicarbonate <15 mmol/L or pH <7.25 (venous) or <7.30 (arterial or capillary), *2*) ICD-9 code 250.1 at discharge, and *3*) diagnosis of DKA mentioned in the medical charts (9).

Laboratory analyses

Samples were analyzed for GAD-65 antibodies (GADA) and insulinoma-associated-2 antibodies (IA-2A)—using a standardized protocol (10). The cutoff values for positivity were 33 National Institute of Diabetes and Digestive and Kidney Diseases Units/mL for GADA and 5 National Institute of Diabetes and Digestive and Kidney Diseases Units/mL for IA-2A. The specificity and sensitivity were 97 and 76%, respectively, for GADA and 99 and 64%, respectively, for IA-2A (10). Fasting C-peptide (FCP) was measured by a two-site immunoenzymetric assay (TOSOH Bioscience, San Francisco, CA). Measurements of serum cholesterol, triglyceride, and HDL cholesterol were performed on a Hitachi 917 autoanalyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). HbA_{1c} was measured by a dedicated ion exchange high–performance liquid chromatography instrument (TOSOH Bioscience). HLA class II genotyping (HLA *DR-DQ*) was performed with a PCR-based sequence–specific oligonucleotide probe system in the laboratories of Drs. L. Gaur (University of Washington, Seattle, WA) and H. Erlich (Roche Molecular Systems, Indianapolis, IN) on all consenting participants (11).

Operational definitions

Autoimmunity was defined by positive titers for either GADA or IA-2A. Because many participants were treated with insulin, insulin autoantibodies were not used.

Insulin sensitivity was estimated using the following equation:

$$\begin{aligned} \textit{Insulin sensitivity} = \exp[&4.64725 - 0.02032 \\ &\times (\textit{waist [cm]}) - 0.09779 \\ &\times (\textit{HbA}_{1c}\textit{[\%]}) - 0.00235 \\ &\times (\textit{triglyceride [mg/dL]}) \end{aligned}$$

This equation was developed and validated in a previous study (12) using direct measurements of glucose disposal rate (GDR) from euglycemic-hyperinsulinemic clamps conducted among 88 of the 2,291 SEARCH participants included in this report, in addition to 22 matched nondiabetic control subjects. The major component of the formula explaining 60% of the variance in measured GDR was waist circumference, regardless of the provider-determined diabetes type, race/ethnicity, or case/control status (12). We used this formula to estimate insulin sensitivity among all 2,291 SEARCH participants. We then established the range of insulin sensitivity for nondiabetic youth by applying the aforementioned equation to 2,860 multiracial nondiabetic youth age 12–20 years participating in the U.S. National Health and Nutrition Examination Survey (NHANES) in 1999–2004. We defined insulin resistance among SEARCH participants in this study as insulin sensitivity values below the 25th percentile (insulin sensitivity <8.15) for the NHANES youth population.

Insulin deficiency was defined as an FCP value of <0.4 ng/mL, consistent with prior SEARCH publications (12) and other large diabetes studies, including the Diabetes Control and Complications Trial (13).

Genetic susceptibility to autoimmunity was defined based on HLA *DR-DQ* genotypes. HLA genotypes were categorized as follows: *1*) susceptible, *DR3/4* (four genotypes), *DR4/4* (four genotypes), *DR4/8* (four genotypes), *DR4/1* (one genotype), *DR4/13* (one genotype), *DR3/3* (one genotype), *DR3/9* (one genotype), *DR4/9* (two genotypes), and *DR9/9* (one genotype); *2*) neutral, *DR4**/*X**, *DR3/X* (where X = other non-–high-risk genotype), *DR3/4-non–DQB1*0302*, and *DR4/DR4-DQB1*0301*; and *3*) protective, *DR-0403*, *DR2-DQB1*0602*, *DR7-DQB1*0303*, and *DR14-DQB1*0503*, as recommended by the Type 1 Diabetes Genetic Consortium, with modifications for the multiethnic population (11).

Statistical analyses

SEARCH participants were cross-classified according to measured etiologic markers

of diabetes: autoimmunity (present/absent) and insulin sensitivity (insulin-resistant [IR]/insulin-sensitive [IS]). For the resulting four groups, descriptive statistics were computed for each variable of interest, including provider-determined diabetes type, HLA risk categories, presence of absolute insulin deficiency, and demographic, clinical, and biochemical characteristics. Comparisons between groups with normal and reduced insulin sensitivity within each autoimmunity category were conducted using *t* tests or nonparametric methods (as appropriate) for continuous variable and χ^2 tests for categorical variables.

RESULTS—The study population consisted of 2,291 youths who were diagnosed with diabetes in 2002–2006 at <20 years of age, who attended a fasting study visit, and who had complete data on autoantibodies and insulin sensitivity. This sample included 67.9% non-Hispanic whites (NHWs), 13.3% Hispanics, 13.4% African Americans (AAs), 4.1% Asian/Pacific Islanders (APIs), and 1.3% American Indians (AIs). This group represented approximately 35% of all SEARCH cases incident in 2002–2006 and was representative in terms of onset age, sex, and racial/ethnic distribution of the larger SEARCH population of registered cases. The AI population did not provide consent for storage of genetic samples and therefore was not included in any genetic analyses.

The prevalence of autoantibody positivity among study participants was as follows: 51.8% were positive for GADA, 60.4% were positive for IA-2A, 73.9% were positive for either GADA or IA-2A, and 38.2% were positive for both. According to our definition of autoimmunity, 1,694 youths (73.9%) were classified as having autoimmune diabetes, whereas 597 (26.1%) had no evidence of autoimmunity. According to our definition of IR (i.e., insulin sensitivity lower than the 25th percentile for healthy youths), 811 youths (35.4%) were classified as IR. This proportion was significantly lower in youths with autoimmune versus nonautoimmune diabetes (26.3 vs. 61.1%; $P < 0.0001$).

Table 1 presents characteristics of SEARCH participants classified by both autoimmunity and insulin sensitivity status. This classification resulted in four categories. Two categories were mutually exclusive in terms of the main etiologic markers (autoimmune plus IS; nonautoimmune plus IR). The other two categories were not mutually exclusive regarding the main etiologic markers: one was defined by presence of both markers (autoimmune plus IR), whereas the other one was defined by absence of both etiologic markers (nonautoimmune plus IS).

Characteristics of individuals in the four categories

The autoimmune plus IS group was overall the largest category, accounting for 54.5% of SEARCH participants. Almost all of the individuals in this group were classified as having type 1 diabetes by their providers (99.2%). Although only 39.0% had insulin deficiency, the clinical phenotype of these youths supported the providers' diagnosis of type 1 diabetes: 78.4% were of NHW origin; the average age of onset was 9.3 years; there was a slight excess of male representation (51.8%), a relatively low BMI *z* score (0.4) and prevalence of obesity (i.e., BMI ≥95th percentile: 6.8%), and nearly ubiquitous use of insulin (98.6%); and 29.1% presented in DKA at diabetes onset. Furthermore, this group had the lowest average FCP levels of the four categories (median 0.5 ng/ml). A total of 547 participants (43.8%) had susceptible HLA *DR-DQ* genotypes, whereas only 23 (1.8%) had protective genotypes.

The nonautoimmune plus IR group accounted overall for 15.9% of SEARCH participants. Most youths were classified as having type 2 diabetes by their providers (76.4%). In support of the providers' diagnosis, these youths had a clinical phenotype consistent with type 2 diabetes described as follows: 73.4% were of minority racial/ethnic origin, their average onset age was around puberty (age 13.9 years), there was an excess of female representation (62.5%), a high BMI *z* score (2.0), a large waist circumference (age and sex adjusted 103.1 cm), high prevalence of obesity (77.6%), high prevalence of acanthosis (62.6%), less widespread but frequent use of insulin (56.9%), and lower frequency of DKA at onset (13.1%). The median FCP was high (3.4 ng/mL), and only 4.1% had insulin deficiency. Only 33 participants (9.0%) had susceptible HLA *DR-DQ* genotypes, whereas 53 (14.5%) had protective genotypes.

The autoimmune plus IR group accounted for 19.5% of all SEARCH participants. Most youths were classified as having type 1 diabetes by their providers (92.4%). This group had a number of characteristics that were statistically different from the autoimmune plus IS group, including older onset age (12.9 vs. 9.3 years; $P < 0.0001$), a smaller proportion of NHW race/ethnicity (69.1 vs. 78.4%; $P < 0.0001$), higher BMI *z* score (1.2 vs. 0.4, $P < 0.0001$), higher waist circumference (age and sex adjusted 83.0 vs. 67.7 cm; $P < 0.0001$), and higher prevalence of obesity (33.6 vs. 6.8%; $P < 0.001$). However, there was no difference in the proportion presenting in DKA between this and the autoimmune plus IS group and only a clinically modest difference in proportion with insulin deficiency (31.6 vs. 39.0%; $P = 0.005$). Moreover, there were no significant differences in the prevalence and titers of DA or in the distribution of HLA risk categories between the two groups.

The nonautoimmune plus IS group accounted for 10.1% of all SEARCH participants. The largest proportion was categorized as having type 1 diabetes by their diabetes providers (89.2%). Several characteristics were consistent with type 1 diabetes, including prepubertal onset age (9.4 years), preponderance of NHW race/ethnicity (74.1%), male overrepresentation (56.0%), low BMI *z* score (0.2), waist circumference (71.7 cm after adjustment for age and sex), low prevalence of obesity (6.6%), high proportion of insulin use (91.3%), and high proportion presenting in DKA (23.1%). With the exception of the lack of autoimmunity, all other characteristics were significantly different from those exhibited by the nonautoimmune plus IR group. Regarding HLA genotypes, 24.6% had susceptible and 6.5% had protective genotypes.

Figure 1 presents the proportional distribution of the four categories described above among NHW, Hispanic, AA, API, and AI participants. There were important differences across the racial/ethnic groups. The autoimmune plus IS group was the major category among NHW and Hispanic participants, while the nonautoimmune plus IR group accounted for most diabetes cases among AA, API, and AI individuals. The main variation across racial/ethnic groups resulted from distributional differences of the two etiologically distinct categories (i.e., autoimmune plus IS and nonautoimmune plus IR) rather than differences in the proportional distribution of the two less distinct groups (autoimmune plus IR and nonautoimmune plus IS).

CONCLUSIONS

Main findings

There are five major findings of this study. *1*) Most youths <20 years of age with

Table 1—*Characteristics of SEARCH participants according to autoimmunity and insulin sensitivity status*

	Autoimmune			Nonautoimmune		
	IS	IR	*P*	IS	IR	*P*
N (%)	1,248 (54.5)	446 (19.5)		232 (10.1)	365 (15.9)	
Clinical diabetes type, *N* (%)			< 0.001			<0.001
Type 1 diabetes	1,238 (99.2)	412 (92.4)		207 (89.2)	86 (23.6)	
Type 2 diabetes/other	10 (0.8)	34 (7.6)		25 (10.8)	279 (76.4)	
HLA risk category, *N* (%)*			0.12			<0.001
Susceptible	547 (43.8)	173 (38.8)		57 (24.6)	33 (9.0)	
Neutral	567 (45.4)	232 (52.0)		130 (56.0)	236 (64.7)	
Protective	23 (1.8)	8 (1.8)		15 (6.5)	53 (14.5)	
Insulin deficiency (FCP <0.4 ng/mL), *N* (%)	487 (39.0)	141 (31.6)	0.005	75 (32.3)	15 (4.1)	<0.001
Demographic characteristics						
NHW, *N* (%)	979 (78.4)	308 (69.1)	<0.001	172 (74.1)	97 (26.6)	<0.001
Onset age (years)	9.3 ± 3.7	12.9 ± 2.8	<0.001	9.4 ± 4.1	13.9 ± 2.6	<0.001
Onset age <10 years, *N* (%)	660 (52.9)	49 (11.0)	<0.001	117 (50.4)	17 (4.7)	<0.001
Current age (years)	10.4 ± 3.7	14.2 ± 2.9	<0.001	10.5 ± 4.1	15.1 ± 2.7	<0.001
Diabetes duration (months)	9.6 ± 5.9	11.5 ± 6.6	<0.001	10.0 ± 6.2	11.3 ± 6.9	0.03
Male, *N* (%)	646 (51.8)	218 (48.9)	0.30	130 (56.0)	137 (37.5)	<0.001
Family history of diabetes, *N* (%)*	155 (15.9)	74 (21.8)	0.014	41 (22.9)	155 (52.5)	<0.001
Clinical characteristics						
BMI *z* score*	0.4 ± 0.9	1.2 ± 0.9	<0.001	0.2 ± 1.0	2 ± 0.8	<0.001
BMI percentiles, *N* (%)*			<0.001			<0.001
<85	961 (77.3)	161 (36.3)		179 (78.5)	35 (9.7)	
85–95	197 (15.8)	134 (30.2)		34 (14.9)	46 (12.7)	
≥95	85 (6.8)	149 (33.6)		15 (6.6)	281(77.6)	
Waist (cm)†	67.7 ± 0.3	83.0 ± 0.5	<0.001	71.7 ± 1.1	103.1 ± 0.9	<0.001
Acanthosis, *N* (%)*	27 (2.2)	51 (11.8)	<0.001	9 (3.9)	221(62.6)	<0.001
Insulin use, *N* (%)*	1,228 (98.6)	422 (94.6)	<0.001	210 (91.3)	207 (56.9)	<0.001
DKA at onset, *N* (%)*	270 (29.1)	98 (29.9)	0.79	39 (23.1)	36 (13.1)	0.007
Biochemical characteristics						
FCP (ng/mL), median (25th–75th)	0.5 (0.2–0.9)	0.7 (0.3–1.4)	<0.001	0.6 (0.3–1.2)	3.4 (1.9–4.8)	<0.001
IS score	11.9 ± 2.4	6.3 ± 1.5	<0.001	12.2 ± 3.0	4.5 ± 1.8	<0.001
GADA-positive, *N* (%)	859 (68.8)	327 (73.3)	0.08	—	—	N/A
GADA titers, median (25th–75th)	103.4 (16.3–418.5)	106.6 (26.2–397.4)	0.45	0 (0–8.2)	0 (0–0)	N/A
IA-2A positive, *N* (%)	1,032 (82.7)	351 (78.7)	0.06	—	—	N/A
IA-2A titers, median (25th–75th)	233.3 (29.7–438.3)	290.7 (13.5–452.5)	0.50	0 (0–0)	0 (0–0)	N/A
GADA and IA-2A positive, median (25th–75th)	643 (51.5)	232 (52.0)	0.86	—	—	N/A

Data are means ± SD unless otherwise noted. *P* for associations between IR and IS within each autoimmunity category. N/A, not applicable. *Missing values. †Adjusted for age and sex.

diabetes fell into categories that align with traditional descriptions of type 1 (autoimmune plus IS) and type 2 diabetes (nonautoimmune plus IR). 2) As expected, the proportional distribution of these groups varied substantially across racial/ethnic groups. 3) The group classified as autoimmune plus IR is likely to represent individuals with type 1 autoimmune diabetes and obesity, a group that is expanding as a result of the recent increase in the frequency of obesity but that is not a new etiologic entity. 4) The group classified as nonautoimmune plus IS represents an etiologically mixed category and requires further testing. 5) For the purpose of public health surveillance, the provider assignment of diabetes type agrees well with the etiological assessment, at least for cases that fit the typical picture of type 1 and type 2 diabetes.

The autoimmune plus IS group had clinical characteristics that were consistent with the traditional description of type 1 diabetes, including prepubertal age of onset, absence of obesity, and widespread insulin use (14). A total of 43.8% had susceptible HLA *DR-DQ* genotypes—a proportion similar to that reported among white youths and young adults with type 1 diabetes from Europe (15) and Australia (16). These data suggest that the presence of susceptible HLA *DR-DQ* genotypes is not a necessary condition for the development of autoimmune diabetes in youth. Consistent with prior clinical trials (17), 61% of youths in this group have preserved β-cell secretion (FCP ≥ 0.4 ng/mL) within the first year of diagnosis. This challenges the paradigm that type 1 diabetes is a state of absolute insulin deficiency in youths with diabetes at short duration and recommends the use of FCP as a physiological descriptor of disease status and evolution rather than a marker of disease etiology.

At the other extreme of our bidimensional etiologic spectrum, the non-autoimmune plus IR group had characteristics that were consistent with the current description of early-onset type 2

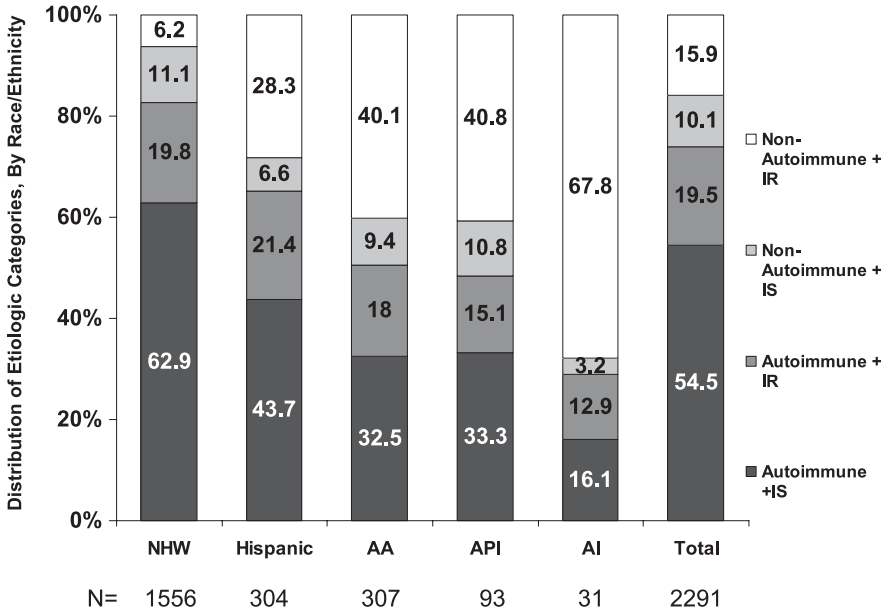

Figure 1—*Proportional distribution of etiologic categories among SEARCH participants by race/ethnicity*

diabetes, including pubertal age of onset, obesity and other markers of IR, female excess, strong family history, and preponderance of minority racial/ethnic representation (18). Consistent with other reports (19), insulin use was quite frequent (56.9%) and, therefore, not a good surrogate for etiologic classification. The proportion with susceptible HLA *DR-DQ* genotypes (9.0%) was similar to that seen among 200 nondiabetic young adults in the UK Prospective Diabetes tudy (9%) (20), providing indirect evidence that this diabetes phenotype is unlikely to be associated with autoimmunity. A total of 95.9% of youth in this group had clinically significant residual β-cell secretion, suggesting a less aggressive β-cell loss than the other groups.

In addition to the two categories above, which support the ADA notion that most diabetes cases fall into two distinct categories, our approach allowed the characterization of less distinct etiologic categories. The autoimmune plus IR group was specifically designed to identify individuals with evidence of both autoimmunity and insulin resistance. Investigators and clinicians have previously described this group as having "hybrid" diabetes (21), suggesting a mixed etiology. However, this group had many features that were observed in the autoimmune plus IS group and aligned with traditional characteristics of type 1 diabetes. Specifically, there was a similar prevalence and titers of autoantibodies and similar distribution of HLA *DR-DQ* risk genotypes, suggesting similar contributions of immune-mediated disease processes. In addition, and importantly, this group represented 26.3% of all autoimmune case subjects. This proportion is not higher than expected, given that our definition of insulin resistance is based on the lowest 25th percentile in the general population. Therefore, our data suggest that this group is not a distinct etiologic category but, rather, the upper tail of the distribution of insulin resistance and obesity among youths with autoimmune diabetes. Nevertheless, because this is a nontraditional presentation of type 1 diabetes in youth, the study of this group's clinical course, including the development of diabetes-related complications, is of considerable interest.

The last category, characterized by absence of both etiological markers of diabetes (nonautoimmune plus IS group), had several characteristics associated with type 1 autoimmune diabetes, including an overrepresentation of susceptible HLA *DR-DQ* genotypes (24.6%) compared with the general population (9%) (20). It is possible that some patients in this group have seroconverted to antibody negativity (22) or present other immune markers than those currently measured, such as insulin autoantibodies (23) or the recently discovered autoantibody against Zinc transporter 8 (ZnT8) (24). This group may also include individuals with single-gene mutations affecting β-cell function, historically referred to as maturity-onset diabetes of the young (MODY). Preliminary SEARCH data suggest that most cases with single gene mutations in *HNF1-α*, *HNF4-α*, or *glucokinase-MODY* present with a phenotype consisting of insulin sensitivity and neutral/protective HLA genotypes (25).

Limitations and strengths

This study has a number of limitations. First, only two autoantibodies were measured. Thus, individuals having autoimmune markers other than GADA or IA-2A were misclassified as having nonautoimmune diabetes. Unpublished data in a sample of SEARCH participants suggest that almost 20% of youths who are negative for GADA and IA-2A are positive for ZnT8, which is why we are planning to measure ZnT8 antibodies in stored samples once assays are standardized. However, the timing of autoantibody measurements is unlikely to have affected our findings because, in a sample of SEARCH participants, the prevalence of DA positivity (positive GADA and/or IA-2A) was similar at diabetes onset (73.3%) and at the SEARCH visit (75.4%). Second, we chose the bottom 25th percentile of estimated insulin sensitivity among NHANES youth age 12–20 years to define insulin resistance. Because of the known effect of puberty decreasing insulin sensitivity, the 25th percentile for the insulin sensitivity index in the NHANES group may have overestimated the number of SEARCH participants age <12 years who were classified as IR. However, only 155 SEARCH participants age <12 years (6.8%) were classified as IR. In addition, we recognize that this is an arbitrary cut point based on percentile distribution of a surrogate marker of insulin sensitivity in the general population. However, analyses using different cut points for insulin sensitivity (e.g., bottom 15th percentile) or waist circumference only (the major component of the insulin sensitivity equation) resulted in similar group characteristics. Finally, etiologic markers of diabetes type are influenced by a variety of factors, including diabetes duration and glycemic control, so characteristics described here represent cross-sectional assessments of diabetes phenotypes in youths with short disease duration.

Despite these limitations, this study has a number of strengths. Unlike most other childhood diabetes registries, this large multiethnic cohort has been ascertained without regard to presumed diabetes type or related factors, such as treatment, age, or race/ethnicity. Using diabetes

autoantibodies and an algorithm to assess insulin sensitivity based on routine clinical measures, this approach classifies >90% of youths with new-onset diabetes into one of the traditional categories, consistent with the current nomenclature of type 1 (evidence of autoimmunity regardless of insulin sensitivity status) and type 2 diabetes (no autoimmunity and insulin resistance). The SEARCH study thus offers researchers and clinicians a practical application for the etiologic classification of diabetes type, at the same time identifying a group of youths (those with insulin sensitivity without evidence of autoimmunity) who would benefit from further testing (novel autoantibodies, metabolic profiling, and genetic testing for monogenic diabetes) to further elucidate the etiology.

In summary, to our knowledge, this study is the first attempt to provide operational definitions of types of diabetes using an etiological approach, as recommended by the ADA expert committee. SEARCH is planning to use this approach to better describe the changing epidemiology of pediatric diabetes, to evaluate public health surveillance systems for diabetes in children, and to explore novel hypotheses about the effect of diabetes type on the development of diabetes-related health outcomes.

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