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Onset Features and Subsequent Clinical Evolution of Childhood Diabetes over Several Years

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Abstract

Aim—To explore whether it is possible to predict a child's eventual diabetes phenotype using characteristics at initial presentation, we reassessed 111 young patients on average 7.8± 4.2 (2.2–19.7) [mean±SD (range)] years after diagnosis.

Methods—Medical records at diagnosis for 111 patients, aged 0–17, were compared with their followup characteristics including stimulated C-peptide (CP), and islet autoantibodies (AB).

Results—Initially, 18 patients were obese; 9 displayed other type 2 diabetes (T2DM) features (polycystic ovary syndrome, acanthosis, diagnosed T2DM); the remaining 84 had a classic type 1 diabetes (T1DM) presentation. At follow-up, 83 patients (75%) with no measured CP were classified as T1DM; 17 (15%) were CP+ and AB- and thus considered T2DM. Eleven with both T1DM and T2DM features were classified as having mixed diabetes phenotype (MDM). One-fifth (22 subjects) changed presumed phenotype at follow-up. In multivariable models, T1DM patients were younger at diagnosis, had higher initial glucose values, were more likely to have experienced ketoacidosis, and less likely to be obese or of African-American ethnicity.

Conclusions/interpretation—10% of subjects had MDM and 15% had T2DM at ~8 years' duration. Although no onset feature was completely reliable, ketoacidosis and hyperglycemia were more likely to predict T1DM; obesity and African American ethnicity made T2DM more likely. At diagnosis, features of T2DM in addition to obesity were strongly predictive of eventual T2DM phenotype. Given the significant percentage who changed or had mixed phenotype, careful tracking of all young people with diabetes is essential to correctly determine eventual disease type.

Keywords

Diabetes Type 1; Diabetes Type 2; Mixed Diabetes Phenotype; Children and Adolescents; Epidemiology; Diagnosis; Natural History; Autoimmunity; Beta-cell Function Longitudinal Study; onset signs and symptoms

Background - Introduction

In developed countries, diabetes is the most common chronic disease of childhood after asthma, irrespective of ethnicity (1), and recent epidemiologic trends show that the risk for childhood diabetes is increasing in tandem with the rise in childhood obesity (2,3). Across the world, type 1 diabetes (T1DM) incidence rates are climbing by about 3% per annum (4). Reports of children who display a mixed phenotype combining features of both type 1 and

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type 2 diabetes are increasing (5), further complicating the problem of correctly identifying diabetes type at the onset of disease.

Clearly, if the phenotype of diabetes in childhood is not well understood, then inappropriate treatment may add to the risk of poor long-term outcomes for these young patients. In addition, it is critical to accurately distinguish T1DM, T2DM and mixed forms of childhood diabetes in order to conduct valid genetic, epidemiologic and intervention studies. In the vast majority of cases, the phenotype assigned at the time of diagnosis is the one adhered to over time, thus determining clinical management as well as enrollment eligibility for research subjects. The purpose of this analysis was to address the still-unresolved question of whether it is possible to predict a child's eventual phenotype using characteristics at the onset of diabetes. We therefore compared data from the onset medical records with physical, immunologic and metabolic findings determined two or more years later.

Methods

Patients (n=111) were recruited in the Chicago metropolitan area if they were aged 0–17 years at the initial diagnosis of diabetes, if they had been diagnosed at least two years prior to their follow-up examination, and if their diabetes was not secondary to another medical condition. Clinical studies were conducted in participants' homes or in the General Clinical Research Centers at the University of Illinois at Chicago and the University of Chicago. Human subjects research committees at the University of Illinois at Chicago, the University of Chicago, and other collaborating institutions in the Chicago area approved the study protocol. Written informed consent was obtained from participants prior to the interview and clinical studies; written assent was obtained from children old enough to provide it.

Onset medical records

Medical records abstraction yielded information about onset characteristics, including demographic and clinical variables, signs and symptoms, comorbidities, family history of diabetes (if it was noted by a physician), and initial diagnosis type. We initially classified type 2 diabetes at onset based on documentation in the medical record of one or more of the following: an unequivocal diagnosis of T2DM; a physician note of "possible type 2", "unusual" or "atypical" diabetes, or markers of insulin resistance (acanthosis nigricans or polycystic ovary syndrome); or treatment with oral antidiabetic agents at discharge. Patients were initially classified as having 'type 1 diabetes with obesity' if they had a note on the medical record indicating obesity at onset, or a body mass index (BMI) that was ≥95th percentile for their gender and age in months (9), but no other feature of type 2 diabetes. Those who did not meet one or more of these criteria were considered to have classical type 1 diabetes. The variable “classic T1DM onset symptom” was defined as one or more of the following noted in the onset medical record: polyuria, polydipsia, polyphagia, weight loss, and diabetic ketoacidosis; these data were available for 97 subjects.

Follow-up examination

Patients were seen on average 7.8±4.2 (mean ±SD; range 2.2–19.7) years after their initial diagnosis. Information on family history and clinical course since diagnosis was gathered in detailed interviews. Race/ethnicity was defined as that reported for >=3 grandparents; if fewer than 3 grandparents were concordant, race was considered to be mixed. When grandparental race/ethnicity was unavailable, race/ethnicity was based on parental data, or, if information on a parent was missing, self-reported race/ethnicity was used. Patients who reported using ≥3 insulin injections per day or an insulin pump were considered to be on an intensive treatment regimen.

Clinical measurements

Participants were asked to fast overnight and to withhold their morning insulin dose (or the morning bolus if using an insulin pump). A venous blood sample was taken for biomarker determination, and participants were asked to drink 6 ml/kg of a standard nutrient solution consisting of approximately 68% carbohydrate, 17% protein and 15% fat (Boost, Novartis Pharmaceuticals, Fremont, MI). A second blood sample was taken 90 minutes after ingestion of the nutrient solution for C-peptide. Individuals with a fasting glucose level >8.25 mmol/L were not given the mixed meal challenge, as their fasting C-peptide was considered stimulated. Blood pressure (10) and anthropometric measurements (11) were taken by trained research assistants using standardized procedures; weight and percent body fat were measured barefoot with a bio-electrical impedance analyzer scale (Tanita TBF-300A, Arlington Heights, IL). One-half kilogram was subtracted from weight to account for indoor clothing. Lipids, HbA1c and urinary albumin:creatinine ratios were measured using desktop instruments (DCA-2000, Siemens Diagnostics, Deerfield, IL; Cholestech, Inverness Medical Innovations, Waltham, MA) which have demonstrated good agreement with standard laboratory methods (12,13). Adult subjects ≥20 years old were considered to have hypertension if their systolic blood pressure (BP) was ≥140 mmHg; or diastolic BP ≥90 mmHg; or if they reported taking antihypertensive medication. Adults were considered to have dyslipidemia if they met any of the following criteria: total cholesterol ≥6.26 mmol/L; HDL <1.55 mmol/L; triglycerides ≥1.70 mmol/L; LDL ≥2.59 mmol/L. Participants below age 20 were considered hypertensive or dyslipidemic if one of more of these levels exceeded their age-, sex-, and height (BP)-specific 95th percentile (14). The Michigan Neuropathy Screening Instrument (MNSI) exam was administered by a trained physician during the visit and participants completed the MNSI questionnaire (15). Neuropathy was defined by: 1) a self-reported physician diagnosis, and/or 2) a MNSI questionnaire score ≥5 and/or exam score >2 (16). The presence and severity of acanthosis nigricans was visually assessed by a physician and scored using a validated algorithm (17).

Autoantibodies

Antibodies to radiolabelled recombinant human GAD65 (whole) and human IA2/ ICA512 (349 AA cytoplasmic portion) were quantified by fluid-phase immunoprecipitation assay (18). These antigens were cloned from human islets and human glioblastoma, respectively, and are expressed in recombinant form by coupled in-vitro transcription and translation in the presence of ^{35}S-methionine. After incubation with subject serum in separate triplicate wells, immune complexes are precipitated using Protein A, washed, and counted for bound radioactivity. Using the mean of triplicates on each index serum and each unknown serum, an antibody “index” is calculated as: Index = (Unknown Serum-Index Negative)/(Index Pos-Index Neg). The WHO/JDF standard serum for GADA and IA2 were used in each assay. The assays were 94% and 80% sensitive, and 94% and 95% specific, for GAD and IA2, respectively, in the 2005 Diabetes Autoantibody Standardization Program sponsored by the CDC and the Immunology of Diabetes Society.

C-Peptide

All assays were conducted in the Diabetes Research and Training Center Ligand Core Laboratory at the University of Chicago. For participants examined before 2004 (n=39), plasma C-peptide was measured using a previously described immunoassay (19). The lower limit of sensitivity of this assay was 0.02 nmol/L and the intra-assay CV averaged 6%. For participants seen in 2004 or more recently (n=46), C-peptide was measured with a solid-phase, competitive chemiluminescent enzyme immunoassay (Immulite 2000; Siemens Corporation, Germany) in the same laboratory. A modified version of this assay was substituted by the manufacturer in October 2007 (Immulite 1000). The lower limit of detection for both Immulite assays was 0.17 nmol/L and the intra-assay coefficient of

variation was 6% on average. For purposes of this study, we defined residual beta cell function as a C-peptide value ≥0.035 nmol/L using the pre-2004 assay, and a value ≥0.17 nmol/L in the newer assays (20,21). We defined below-normal beta cell function as 0.035 to 0.10 nmol/L (above nil to 2 SD below mean) in the pre-2004 assay, and similarly, as 0.17 – 0.30 nmol/L for the newer Immulite assays.

Follow-up phenotyping

We were able to reassess the phenotypes of patients using information from their physical examinations and questionnaires after at least two years of diabetes. If they had no fasting or post-challenge C-peptide, i.e. no endogenous insulin production, they were classified as having 'true' type 1 diabetes (T1DM), irrespective of autoantibody status (n=83). Patients with residual beta cell function, no islet autoantibodies, and either not using insulin at all, or using ≤2 insulin shots/day (with or without concomitant oral antidiabetic medications), were classified as having type 2 diabetes (T2DM; n=17). We observed a substantial fraction of patients who had to be categorized as having mixed phenotype (MDM); these patients had either a) residual beta cell function and autoantibodies (n=8); or b) residual beta cell function, but treated with intensive insulin therapy alone since diagnosis (n=1); or c) residual beta cell function, on standard insulin monotherapy since diagnosis (2 injections daily), and reported developing DKA when they discontinued using insulin at some time after their first six months of diabetes (n=2).

Statistical analyses

Univariate associations between phenotype and patient characteristics were tested using Fisher's exact test, χ^2-tests, t-tests, and analysis of variance, without adjustment for multiple testing. Multivariable associations between non-type 1 (type 2 or mixed) phenotype at follow-up and onset characteristics were estimated using logistic regression, incorporating variables that were significant at $p<0.15$ in univariate analyses. Due to the small number of non-type 1 cases (17 type 2; 11 mixed), at most three covariates were included in any single model.

Results

There were 111 patients included in the study. Based on their onset records, 84 were classified as having T1DM at diagnosis, 18 had obesity without other indications of type 2, and 9 had evidence of T2DM in their onset records (Table 1). At follow-up, 83 patients were classified as having T1DM by virtue of having no residual beta cell function after >2 years' duration, 17 fit criteria for T2DM, and 11 patients had disease with mixed features. On average, the participants were 16.1 years of age at the time they were studied (range 4.1 to 32.3 years), with average diabetes duration of 7.8 (SD 4.2, range 2.2–19.7) years. The study group was diverse, including 62 non-Hispanic blacks (55.9%), 22 non-Hispanic whites (19.8%), 18 Latinos (16.2%), and nine patients of mixed or other ethnicity (8.1%), primarily Asian. There were 67 females (60.4%) who took part.

Overall, phenotypes of 22 children were re-categorized (Table 1). There were 84 subjects initially considered to have classic T1DM based on the absence of obesity or any other T2DM feature noted on the medical record. Of these, 71 (85%) were classified at follow-up as T1DM based on absent beta cell function, while five (6%) fit criteria for type 2, and eight (10%) had a mixed phenotype at the time they were examined. Thus the odds of eventually demonstrating a T1DM phenotype were 3.5 times greater for this group compared to those who were considered to have T1DM with obesity but no other T2DM feature at diagnosis.

Among the 18 subjects who were obese at diagnosis but otherwise had no T2DM feature, 11 (61%) were classified as type 1 at follow-up; five (28%) fit criteria for type 2, and two subjects (11%) demonstrated a mixed phenotype at the time they were examined (Table 1). The obesity-alone group was 6 times more likely to eventually exhibit T2DM phenotype than those with classic T1DM phenotype at onset.

The majority of those with T2DM features identified in their onset medical records (7 of 9) continued to fit criteria for type 2 at follow-up (OR for T2DM=9.1 comparing those with T2DM features at onset to those with obesity alone at diagnosis), while one subject had no residual beta-cell function (i.e. T1DM phenotype) after 5.2 years' duration and another had mixed features (residual c-peptide secretion and islet antibodies) after 9.5 years' duration.

Clinical picture at onset

Most of the youth-onset patients in this series exhibited the classical onset features of T1DM (Table 2), irrespective of their original or eventual phenotypic classification. Aside from markedly different ages at diagnosis, there were few differences among the three groups based on onset features. Interestingly, those with obesity but no other T2DM feature at diagnosis had more severe acidosis than either those with type 1 characteristics alone or those with type 2 features. Fewer of the obese-only patients had a first-degree relative with diabetes listed on the medical record at onset (Table 2).

Clinical picture at follow-up

All of those classified as T1DM and MDM at follow-up were using insulin only; 52 (63%) of those with T1DM and one of the MDM patients were on intensive insulin regimens (Table 3). The majority of T2DM patients were also using insulin, either with oral anti-diabetic agents (n=8) or alone (n=4); three were using pills only and the remaining two T2DM patients were simply following a diet plan. At the time of follow-up, 59 of 108 patients with autoantibody results were positive for either GAD (n=50) or IA2 antibodies (n=38), or both. To be classified with T2DM at follow-up subjects had to be negative for autoantibodies; positive antibody results were observed in similar fractions of type 1 and mixed phenotype patients, 64% and 73%, respectively.

By definition, only T2DM and MDM patients had residual beta cell function as evidenced by measurable C-peptide at follow-up. Low C-peptide (>2 SD below mean value) was noted in 5/11 mixed phenotype patients (all examined >5 years post-diagnosis), whereas all but one of the 17 patients with T2DM had higher levels of C-peptide. The only T2DM subject with a low C-peptide value was antibody negative at examination, and had a Hba1c of 8.7%, 41% body fat and a waist circumference of 96 cm at age 15.6 years [85th percentile = 91.6 cm for US females aged 16 years(14)]. Therefore, we believe that this individual was correctly characterized as having T2DM.

At follow-up, clinical measures for the MDM group generally were intermediate between the "true" type 1 and "true" type 2 groups (Table 3). The MDM and T1DM groups had similar gender distributions, while most of the T2DM subjects (77%) were female. MDM and T2DM patients were twice as likely to have a first-degree relative with diabetes, compared with the T1DM patients (Table 3). MDM patients fell between T1DM and T2DM on all measures of adiposity. Both systolic and diastolic blood pressure were significantly higher for T2DM compared to T1DM patients, with intermediate values for MDM patients, in post-hoc testing. Irrespective of their phenotype, the majority of patients had HbA1c values indicating poor metabolic control (>8%) and most subjects had at least one chronic diabetes complication, with 59% of T1DM, 88% of T2DM, and 73% of MDM patients demonstrating at least one complication (p=0.05).

In multivariable analysis, due to the limited number of individuals who had a T2DM or mixed phenotype, we were able to model just three covariates at once, so we present five alternative models in Table 4. Nonetheless, there were several onset features that could distinguish the eventual phenotype of these young patients. As age at diagnosis increased, the likelihood of ultimately demonstrating type 2 or mixed phenotype increased by about 40% per year. Being of African American ethnicity increased the OR for T2DM or mixed phenotype at follow-up by six to twelve-fold, depending upon the other variables in the model (Table 4). Obesity at onset or having a first-degree diabetic relative increased the estimated risk of eventually demonstrating a type 2 or mixed phenotype by three to six-fold. Conversely, having DKA at diagnosis reduced the odds for type 2 or mixed phenotype at follow-up by 80% (Table 4), though it is worth noting that five subjects with T2DM at follow-up (of 14 subjects with information) presented in DKA. The final models demonstrated pseudo R^2 values of 0.20 – 0.37. Similar multivariable models emerged when only patients who evolved into T1DM or T2DM were included, i.e. excluding mixed phenotype. Importantly, neither gender nor the presence of any of the 'classic' type 1 diabetes symptoms (excluding DKA) even met significance criteria for entry into any of the final models. Extending these multivariate coefficients into the clinical setting, the positive predictive value (PV+) of being below the median age at onset (8.7 years) predicted type 1 diabetes at follow-up with 95% accuracy, being of non-African American ethnicity carried a PV+ of 90%, and having DKA carried a PV+ of 83%.

Discussion

This study focused on a diverse group of childhood-onset patients whose phenotype was determined based on indicators of beta cell function, autoimmunity, and clinical course, after having diabetes for, on average, eight years. None of the onset characteristics reliably predicted diabetes type; indeed, obesity or non-Caucasian ethnicity was often present in T1DM and diabetic ketoacidosis was found in some of those with T2DM. This observation echoes numerous clinical reports that it is often difficult to correctly identify the diabetic phenotype in children at the time of diagnosis (5,6,21).

Many of those with obesity at onset in addition to other characteristics suggestive of T2DM did eventually have a phenotype consistent with T2DM. Perhaps as a result of our characterization of T1DM as those with no residual beta-cell function at follow-up, there remained a relatively large proportion of subjects, 10%, with a mixed phenotype. It is likely that some of these subjects represent an atypical form of T1DM. In particular, five of the eight subjects who were reclassified from T1DM to MDM had positive autoantibodies despite their residual beta cell function. Such patients may fit somewhere within the spectrum of slowly progressive T1DM, in which a role for obesity remains unclear. The three MDM subjects who were antibody negative but displayed residual C-peptide secretion may either represent a severe T2DM phenotype or T1DM in whom the autoantibodies previously disappeared.

The importance of studying the evolution of childhood diabetes over time is underscored by these findings. Specifically, with sufficient numbers of non-Hispanic white, non-Hispanic black, and Latino patients, we noted that the majority of all young patients exhibited no or extremely reduced beta cell function, irrespective of their ethnic background, when followed for a number of years. It is also increasingly clear that not all patients with T1DM are thin at diagnosis, and that obesity can contribute to T1DM risk (6,8). Indeed, 13% of the current subjects who were eventually characterized as T1DM were obese at diagnosis, suggesting that it is incorrect to assume that obese youth with new-onset diabetes will maintain their residual beta cell function over several years.

The limitations of this study involve several broad areas: limited and inconsistent medical records data regarding onset characteristics; potential errors in the phenotyping scheme; the use of a volunteer sample; and the relatively small number of non-T1DM patients. Data were obtained using medical records from >20 different institutions, with varying standards for recording clinical information, history and laboratory reports. Often we requested medical records which were more than 10 years old. Thus, inconsistencies and missing data were unavoidable.

We used a straightforward approach to determining the phenotype of patients at follow-up, yet the possibility of misclassification cannot be altogether ruled out. Certainly, some "true" T1DM patients may continue to demonstrate residual beta-cell function for many years. It is also possible that glucose toxicity associated with extremely poor glycemic control could mask the ability to produce insulin in those who would otherwise have been classified as T2DM patients. Among the 83 patients in our study who had no detectable C-peptide, there were 27 (32.5%) in very poor metabolic control (HbA1c ≥10%), a proportion not different among those with mixed or type 2 phenotype. Of the 27 T1DM subjects in very poor glycemic control, none were obese at follow-up, and the proportion of those with high-risk HLA-DQ haplotypes and antibody positivity was similar to that in the T1DM patients whose HbA1c values were below 10%. BMI, blood pressure and age were also not different comparing the T1DM patients with worse versus better control, though waist circumference was significantly lower in those in very poor metabolic control. Thus, we remain confident that the T1DM group in this analysis is largely homogeneous in lacking functional beta cells.

This cohort, though grossly representative of the ethnic and socioeconomic distribution of young people in the Chicago metropolitan area, was not randomly selected, but instead consisted of patients whose families were able to be contacted under stringent legal constraints (HIPAA), and who agreed to be examined. Finally, because non-T1DM in youth is a relatively infrequent outcome, the actual numbers of cases is still small, so the possibility of type II error remains, particularly for the multivariable analysis. Nonetheless, this study does represent a large group of young diabetes patients followed past the 'honeymoon' period, and includes a substantial number of minority patients.

The current analysis suggests poor outcomes for childhood-onset patients, irrespective of diabetes type at follow-up. There are likely to be several factors responsible for the disappointing clinical status of our participants, including economic deprivation and lack of resources for diabetes self-management. Appropriate disease management early in the course of disease is likely to improve outcomes (22,23). Because the number of reclassified subjects was fairly large, and, more ominously, because the majority of all subjects demonstrated signs of early diabetes complications, we cannot rule out that misclassification of phenotype at the time of diagnosis may have contributed to poor outcomes for some of these young patients. The subjects of this analysis were, on average, 17 years of age at the time of examination, implying that inadequate access to health care, associated with the transition from the pediatric to the adult care system, may become progressively more important in the future.

In summary, clinicians should recognize that young patients with T2DM features such as obesity or non-European ancestry may actually have T1DM. Further, a substantial fraction of young patients may have features of both T1DM and T2DM, and the optimal treatment for these individuals may change over time. We anticipate that the current report will stimulate additional descriptive epidemiologic and clinical research. Collecting further information, including genetic studies in those with mixed phenotype to determine the role of MODY genes or other mutations, will be particularly important as time goes on. Diabetes

in youth creates a formidable social burden both for the family and the community, which is often associated with sub-optimal metabolic control. Poor diabetes control could be further exacerbated in patients with unusual phenotypes in whom the most appropriate therapy may be difficult to determine. Increasing our understanding of the natural history of diabetes in youth is essential to improving the quality of care for these patients, and hopefully, to an ultimate cure for the disease.

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Abbreviations

AB	antibodies
BMI	body mass index
CP	C-peptide
DKA	diabetic ketoacidosis
GAD	glutamic acid decarboxylase
HbA1c	hemoglobin A1c
IA-2	insulinoma-associated 2 antibody
MDM	mixed diabetic phenotype
PCOS	polycystic ovarian syndrome
T1DM	type 1 diabetes
T2DM	type 2 diabetes

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Table 1

Diabetic Phenotype at Diagnosis and Followup: 111 Youth-onset Patients with >2 Years' Duration

	***Follow-up Phenotype*[#]**				
	Type 1 **n=83**	***Type 2*** **n=17**	***Mixed*** **n=11**	***Reclassified*** **n=22**	
Apparent Phenotype at Onset:	**n (%)**	**n (%)**	**n (%)**	**n (followup phenotype)**	
Type 1, Not Obese, n = 84	71 (84.5)	5 (6.0)	8 (9.5)	5 (T2)	8 (MDM)
Type 1, Obese, [*] n = 18	11 (61.1)	5 (27.8)	2(11.1)	5 (T2)	2 (MDM)
Type 2, [**] n = 9	1 (11.1)	7 (77.8)	1 (11.1)	1 (T1)	1 (MDM)

[#]Follow-up phenotype: Type 1 (T1), absent stimulated C-peptide; Type 2 (T2), C-peptide present and no islet autoantibodies; Mixed (MDM), either a) residual beta-cell function and autoantibodies (n=8); or b) residual beta-cell function, but treated with intensive insulin therapy alone since diagnosis (n=1); or c) residual beta-cell function, on standard insulin monotherapy since diagnosis (2 injections daily), and reported developing DKA when they discontinued using insulin after their first six months of diabetes (n=2).

[*]Obesity diagnosis or body mass index >95th age-sex percentile at onset; no other feature of type 2 diabetes listed in onset medical record

[**]Type 2 or 'atypical diabetes' diagnosis at onset or other type 2 feature (acanthosis nigricans; polycystic ovary syndrome; oral antidiabetic medication) listed in onset medical record; 5 of these were also characterized as obese

Table 2

Participants' Onset Characteristics by Diabetic Phenotype at Diagnosis: 111 Youth-onset Patients with >2 Years' Duration

	Apparent Phenotype at Diagnosis			
Participant Characteristics	***T1, not Obese*** **n=84**	***T1, Obese**** **n=18**	***Type 2**** **n=9**	***P-val***
Females, n (%)	51 (60.7)	8 (44.4)	8 (88.9)	0.083
Ethnicity, n (%):				NS
NHWhite	20 (23.8)	2 (11.1)	0	
NHBlack	44 (52.4)	10 (55.6)	8 (88.9)	
Latino	15 (17.9)	3 (16.7)	0	
Mixed-other	5 (6.0)	3 (16.7)	1 (11.1)	
Onset Characteristics from Medical Record				
Age at onset, yrs, mean (SD)	7.6 (4.0)	10.4 (3.9)	12.1 (2.2)	<.001
Parent +/or sib w/DM,^ n (%)	18 (22.2)	2 (12.5)	5 (55.6)	0.048
Initial glucose^, mmol/L, mean (SD)	33.36 (13.60)	29.36 (11.16)	31.25 (26.70)	NS
Initial blood pH^, mean (SD)	7.23 (0.14)	7.15 (0.14)	7.33 (0.13)	0.057
Ketoacidosis present,^ n (%)	41 (67.2)	10 (76.9)	2 (25.0)	0.046
Polyuria,^ n(%)	71 (100)	13 (81.3)	8 (100)	0.008
Polyphagia,^ n(%)	24 (42.9)	5 (38.5)	3 (37.5)	NS
Polydipsia,^ n(%)	68 (98.6)	12 (85.7)	7 (87.5)	0.042
Weight loss,^ n(%)	47 (81.0)	12 (80.0)	6 (75.0)	NS
Classic T1DM onset sx#, n(%)	73 (100)	15 (93.8)	8 (100)	NS
Asthma comorbidity, n (%)	12 (14.3)	3 (16.7)	2 (22.2)	NS

^Onset data available for 94 subjects (glucose); 68 subjects (pH); 82 subjects (ketoacidosis); 91 subjects (polydipsia); 95 subjects (polyuria); 77 subjects (polyphagia); 81 subjects (weight loss); 106 subjects (family history of diabetes).

*Obesity diagnosis or body mass index >95th age-sex percentile at onset; no other feature of type 2 diabetes listed in onset medical record

**Type 2 or 'atypical diabetes' diagnosis at onset or other type 2 feature (acanthosis nigricans; polycystic ovary syndrome; oral antidiabetic agent medication) listed in onset medical record; five (55.5%) were also obese

#Classic T1DM onset symptom, one or more of the following noted at onset: polyuria, polydipsia, polyphagia, weight loss, diabetic ketoacidosis (data available for 97 subjects).

Table 3

Participants' Clinical Characteristics by Diabetic Phenotype at Follow-up: 111 Youth-onset Patients with >2 Years' Duration

	Follow-up Phenotype			
Participant Characteristics	***Type 1*[#] n=83**	***Type 2*[#] n=17**	***Mixed*[#] n=11**	***P-value***
Females, n (%)	48 (57.8)	13 (76.5)	6 (54.5)	NS
Ethnicity, n (%): NHWhite	20 (24.1)	1 (5.9)	1 (9.1)	0.016
NHBlack	39 (47.0)	14 (82.4)	9 (81.8)	
Latino	18 (21.7)	0	0	
Mixed-other	6 (7.2)	2 (11.8)	1 (9.1)	
Classic T1DM onset sx*, n(%)	75 (100)	12 (92.3)	9 (100)	NS
Duration of DM, yrs, mean (SD)	7.3 (4.0)	9.5 (4.7)	8.3 (4.7)	NS^^
Parent+/or sib w/DM, n (%)	23 (27.7)	10 (58.8)	6 (54.5)	0.018
Percent body fat^, mean (SD)	25.5 (10.8)	36.9 (10.3)	28.5 (5.3)	0.021
Waist Circumf.^, cm, mean (SD)	72.3 (15.5)	93.0 (12.4)	80.9 (12.7)	0.003
BMI Z-score, mean (SD)	+0.03 (1.01)	+1.35 (0.71)	+0.76 (1.05)	<.001
Obese at examination*, n (%)	6 (7.2)	10 (58.8)	3 (27.3)	<.001
HbA1c %, mean (SD)	9.5 (2.3)	9.6 (2.6)	9.8 (2.6)	NS
HbA1c >8%, n (%)	58 (69.9)	13 (76.5)	8 (72.7)	NS
Systolic BP, mmHg, mean (SD)	109 (13)	117 (14)	116 (8)	0.035
Diastolic BP, mmHg, mean (SD)	72 (11)	85 (14)	77 (14)	<.001
Hypertension*, n (%)	14 (16.9)	8 (47.1)	3 (27.3)	0.022
Lipid abnormality*^, n (%)	30 (37.0)	11 (64.7)	5 (45.5)	0.123
Neuropathy Screen Pos*, n (%)	15 (18.1)	5 (29.4)	4 (36.4)	NS
Kidney function^, n with data	74	9	5	
Urine alb:creat 30+, n (%)	11 (14.9)	2 (22.2)	1 (20.0)	NS
Any complication* present, n (%)	49 (59.0)	15 (88.2)	8 (72.7)	0.050

[#]Followup phenotype: Type 1, absent stimulated C-peptide; Type 2, C-peptide present and no islet autoantibodies; Mixed, either a) residual beta-cell function and autoantibodies (n=8); or b) residual beta-cell function, but treated with intensive insulin therapy alone since diagnosis (n=1); or c) residual beta-cell function, on standard insulin monotherapy since diagnosis (2 injections daily), and reported developing DKA when discontinuing insulin after the first six months of diabetes (n=2).

*Classic T1DM onset symptom, one or more of the following noted at onset: polyuria, polydipsia, polyphagia, weight loss, diabetic ketoacidosis (data available for 97 subjects); Obese at examination current age-sex-specfic BMI Z-score ≥2.0; Lipid abnormality Total cholesterol ≥85th age-sex-specific percentiles (children) or ≥6.26 mmol/L (adults) or HDL ≤15th age-sex-specific percentiles (children) or HDL <1.55 mmol/L (adults), or triglycerides ≥1.70 mmol/L (adults), or LDL ≥2.59 mmol/L (adults); Neuropathy screen positive MNSI exam score ≥2 or positive MNSI questionnaire or self-reported diagnosis of neuropathy; Hypertension on antihypertensive medications, or BP >140/90 (adults), or BP≥95th percentile for age, sex, and height in those <20 years old; Any complication Lipid abnormality and/or positive neuropathy screen and/or hypertension and/or microalbuminuria.

^Followup data for 69 subjects (percent body fat); 76 subjects (waist circumference); 109 subjects (lipids); 88 subjects (albumin:creatinine ratio)

^^Kruskal-Wallis ANOVA p=0.182

Table 4

Multivariable Logistic Regression:* Onset Variables Predicting Follow-up Phenotype

Type 2/Mixed vs Type 1 (n=111)	OR	95% CI	Pseudo-R^2
Model I:			0.36
Older Age at Onset, per year	1.41	1.14 – 1.75	
Non-hispanic black ethnicity vs. NHW/Latino/mixed-other	12.14	2.10 – 70.21	
DKA present	0.21	0.05 – 0.82	
Model II:			0.37
Older Age at Onset, per year	1.42	1.15 – 1.74	
Non-hispanic black ethnicity vs. NHW/Latino/mixed-other	5.94	1.43 – 24.72	
Lower initial glucose, per 0.55 mmol/L	0.96	0.93 – 0.998	
Model III:			0.24
DKA present	0.22	0.07 – 0.77	
Non-hispanic black ethnicity vs. NHW/Latino/mixed-other	10.80	2.11 – 55.19	
Obesity at onset	3.95	1.04 – 14.97	
Model IV:			0.20
DKA present	0.28	0.08 – 0.96	
Diabetic 1st-degree relative	6.04	1.63 – 22.37	
Obesity at onset	6.36	1.64 – 24.72	
Model V:			0.24
Obesity at onset	3.51	1.01 – 12.27	
Non-hispanic black ethnicity vs. NHW/Latino/mixed-other	8.84	2.15 – 36.31	
Lower initial glucose, per 0.55 mmol/L	0.97	0.94 – 0.997	

*Note: 28 non-Type 1 cases limited multivariable models to 3 covariates at most. Multivariable associations shown remained significant when comparing followup type 1 to type 2, excluding mixed phenotype. Variables initially entered into models were age at onset; ethnicity; obesity at onset; polyuria; DKA present; 1st-degree diabetic relative noted on medical record; initial glucose value; asthma comorbidity