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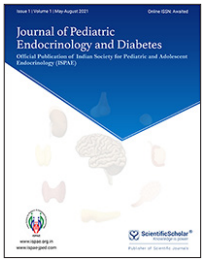

Original Article

Pancreatic autoantibodies in individuals with a clinical diagnosis of type 2 diabetes mellitus

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ABSTRACT

Objectives: It can be challenging to accurately diagnose type 2 diabetes (T2D) in children based on clinical features alone. We aimed to describe pediatric patients with a clinical diagnosis of T2D who are positive for pancreatic autoantibodies and compare their clinical features to patients with T2D without autoantibodies.

Material and Methods: This cross-sectional study and medical record review included patients aged 10–30 years with T2D seen at our pediatric diabetes clinic between January 01, 2013, and December 31, 2020. We compared the characteristics of autoantibody-positive patients with autoantibody-negative patients using Chi-square tests for binary variables and *t*-tests for continuous variables.

Results: Eleven out of 87 (12.6%) patients with a clinical diagnosis of T2D had positive autoantibody results. The groups with and without antibodies were not significantly different in terms of age, sex, and body mass index (BMI) Z-score. However, the hemoglobin A1c (HbA1c) closest to the time of the first autoantibody test was significantly lower in the autoantibody-positive group. Two of the 11 antibody-positive patients had two positive autoantibodies and one had four positive autoantibodies. The other eight patients were positive for one autoantibody only. One of the 11 antibody-positive patients had an episode of diabetic ketoacidosis (DKA).

Conclusion: While age, sex, and BMI were similar in both groups, patients with autoantibodies had significantly lower HbA1c at the time of antibody testing and one patient went into DKA. Autoantibodies should be measured in all patients diagnosed with diabetes to avoid the consequences of potential misclassification.

Keywords: Diabetes diagnostics, Type 2 diabetes, Pancreatic autoantibodies

INTRODUCTION

Accurate diagnosis of new-onset diabetes in children is important in reaching an optimal plan of care and minimizing potential comorbidities. Unfortunately, it is becoming more difficult to distinguish between type 1 diabetes (T1D) and type 2 diabetes (T2D) using clinical features alone. Studies exist that examine the clinical features that distinguish T1D from T2D at the time of diagnosis.[1-3] Historically, children with T1D were characterized as having a lower body weight and shorter duration of symptoms as compared to children with T2D who have fewer symptoms, rarely have ketoacidosis, and tend to be obese with the corresponding features of insulin resistance.[4,5] T2D in children and adolescents used to be considered rare but has been increasing in prevalence, especially in the United States.[6,7] Obesity, historically attributed to children with T2D, is no longer unique, as the rate of childhood obesity also continues to rise in the United States. From 1971–

1974 to 2017–2018, the percentage of obese children in the United States aged 2–19 years of age increased from 5.2% to 19.3%.[8] Concurrent with the rise of childhood obesity, so too are the rates of children with T1D who are obese at diagnosis. Quantifiably, the prevalence of obesity at the onset of insulin-treated diabetes tripled from the 1980s to the 1990s.[9]

As clinical features are becoming less reliable in distinguishing T1D and T2D at diagnosis, it is important to better understand the role of laboratory findings that may be useful in distinguishing the two disease processes. T2D most often occurs in children who are overweight or obese, often with a family history of T2D and features of insulin resistance such as acanthosis nigricans.[10-12] T1D, described by high blood sugar levels caused by a lack of insulin, most often occurs due to the autoimmune destruction of pancreatic beta-cells.[11,12] There are currently 5 known pancreatic autoantibodies that are measured clinically and have been described as contributing to the autoimmune destruction of the pancreatic beta-cells in T1D: Islet Cell Antigen 512 (ICA 512), Insulin (INHS), glutamic acid decarboxylase 65-kilodalton isoform (GAD65), Zinc Transporter 8 (ZnT8A), and Islet Antigen 2 (IA2).[13]

However, on laboratory testing, rates of positive autoantibodies have been reported to be 10–75% in pediatric patients diagnosed clinically with T2D, indicating that relying solely on clinical signs could lead to significant misclassification of patients with diabetes. Furthermore, this discrepancy indicates that there may be a potential pathophysiological overlap between the two conditions.[1,2,14] Optimizing treatment for children with newly diagnosed diabetes requires a deeper understanding of the biochemical processes underpinning their specific pathology. Our study aims to describe pediatric patients from a large pediatric diabetes center in the San Francisco Bay Area with T2D who are positive for pancreatic autoantibodies and compare their clinical features to those patients with T2D without autoantibodies. Our study builds on previous work by including all five of the currently measured autoantibodies and includes patients from our diverse local population.

MATERIAL AND METHODS

Patient and public involvement

None.

Patient characteristics

Data from all patients seen at UCSF Benioff Children's Hospital San Francisco pediatric diabetes clinics between January 01, 2013, and December 31, 2020, that had a diabetes mellitus diagnosis (with the International Classification of Diseases [ICD] nine codes of %250.% or ICD 10 codes of %E10.%, %E11.%, %E13.%, and %E08.%) were collected from all encounters after approval from the Institutional Review Board of the University of California, San Francisco. Patients in these clinics are seen by pediatric endocrinologists or pediatric nurse practitioners with specific expertise in pediatric diabetes. Patients were excluded if their age was <10 years old, >30 years old, if they had no record of autoantibody testing, were initially diagnosed with T1D, and had no diagnosis of diabetes mellitus, or if they had another diabetes diagnosis such as maturity-onset diabetes of the young or steroid-induced hyperglycemia. Some patients had encounters with linked diagnosis codes for both T1D and T2D and in those cases, a chart review was performed to confirm the initial clinical diagnosis. Diagnosis of T2D was made by a pediatric endocrinologist using ADA diagnostic criteria.[15]

Data were extracted from the electronic health record using automatic queries and manual record review.

Antibodies examined included ICA 512, INHS, GAD65, ZnT8A, and IA2. Blood was obtained through phlebotomy using a venipuncture either in the hospital or outpatient. Patients were considered antibody positive if any of the above-listed antibodies resulted above the reference range provided by the processing laboratory [footnotes of Table 1]. Physical, clinical, and biochemical characteristics collected included, but were not limited to, age, sex, height, weight, BMI, diabetes mellitus diagnosis code, and hemoglobin A1c (HbA1c). We used the age at the time of the autoantibody tests closest to diagnosis and the body mass index (BMI), HbA1c, and other measurements closest to the date of those autoantibody tests.

Statistical analysis

Data are presented as mean ± standard deviation for normally distributed continuous variables, and *n* (percentage) for categorical variables. We compared autoantibody-positive with autoantibody-negative patients using Chi-square for binary variables and *t*-tests for continuous variables. BMI Z-scores were calculated using the standard Centers for Disease Control and Prevention growth curves. Two-tailed $P \leq 0.05$ were considered statistically significant.

RESULTS

Eighty-seven patients with a clinical diagnosis of T2D were tested for pancreatic autoantibodies during the study period. Of those, 11 (12.6%) tested positive for at least one autoantibody. Table 2 outlines the demographic characteristics of the study patients. About 54.5% of patients identified as individuals of color. There were no differences between the antibody positive and negative groups in terms of age (mean 15.5 vs. 15.4 years, $P = 0.84$), sex (proportion male 36% in both groups, $P = 0.96$), racial and ethnic group ($P = 0.8$), and BMI Z-score (mean BMI Z-score 0.98 in both groups, $P = 0.84$). HbA1c closest to the time of the first

autoantibody test was significantly lower in the autoantibody-positive group (7.5% vs. 9.4%, $P = 0.03$). The characteristics of antibody positive patients are shown in [Table 1].

Two of the 11 antibody-positive patients were positive for two tests (ICA 512 and GAD 65; ICA 512 and IA2) and one was positive for four tests (ZNT8, ICA 512, GAD and IA2). The other eight patients were positive for one test: ZnT8A (4), ICA 512 (1), INHS (2), and IA2 (1). One out of the 11 antibody-positive patients had an episode of diabetic ketoacidosis (DKA).

DISCUSSION

With the increase in the prevalence of obesity in all children, a type-specific diabetes diagnosis is becoming more challenging. With this, the use of pancreatic autoantibodies is currently the most objective way to help distinguish between T1D and T2D.

Table 1: Description of Ab + T2D patients

Subject	Age*	Gender	BMI**	BMI Z-score**	HbA1c**	ZNT8	ICA 512	INHS	GAD 65	IA2	# of + Ab
A	17	F	39.7	2.27	5.9	81					1
B	15	F	39.1	2.44	7.5	33					1
C	16	M	37.3	2.57	10	10					1
D	20	M	30.2	1.60	7.4	23					1
E	16	F	28.2	1.56	5.7		1.5			1.1	2
F	14	M	30.4	2.07	10.5		1.3				1
G	20	F	43.3	2.24	10			2.2			1
H	14	F	28.0	1.70	5.8			4.7			1
I	14	F	23.5	1.03	6.9		41		2.2		2
J	12	M	28.8	2.07	5.9	>500	80		5	>50	4
K	13	F	39.3	2.47	6.3					5.7	1

ZNT8 results in Kronus Units/mL (ref range 0.0 – 15.0 U/mL, > 15.0 U/mL is considered positive) ICA 512 results in Units/mL (ref range 0.0 – 7.4 U/mL, >7.4 U/mL is considered positive), INHS results in Kronus Units/mL (ref range 0.0 – 0.4 U/mL, > 0.4 U/mL is considered positive), GAD 65 results in International Units/mL (ref range 0.0 – 5.0 IU/mL, >5.0 IU/mL is considered positive) IA2 results in Units/mL (ref range 0.0 – 7.4 U/mL, >7.4 U/mL is considered positive), *At the time of the first antibody test, **BMI values were calculated from the age, sex, weight and height data recorded at patient visits closest to the time of antibody testing. A1C values recorded closest to the time of first antibody test

Table 2: Demographic comparison of autoantibody positive and negative T2D patients

	Autoantibodies		CI	*P*-Value
	Positive	Negative		
N	11	76		
Age Mean, SD	15.5 (2.6)	15.4 (3.0)	-1.7 to 2.1	0.8425
Gender				
Male N, %	4 (36.4%)	27 (35%)	-29.6% to 31.2%	0.9568
BMI*				
BMI Mean, SD	33.4 (6.4)	34.2 (8.4)	-6.0 to 4.5	0.7807
BMI Z-score	2.00 (0.48)	2.04 (0.58)	-0.40 to 0.33	0.8383
BMI %ile	0.98	0.98		
HbA1c*	7.5 (1.8)	9.4 (2.7)	-3.5 to -0.2	0.0253
Race				
Asian	0.0%	12.0%		*P*=0.8
Black or African American	9.1%	14.5%		
White or Caucasian	45.5%	22.9%		
Native Hawaiian	0.0%	4.8%		
American Indian or Alaska Native	0.0%	3.6%		
Other or Mixed Race	45.5%	37.3%		
Unknown/Declined	0.0%	4.8%		
Ethnicity				
Not Hispanic or Latino	45.5%	48.2%		
Hispanic or Latino	45.5%	45.8%		
Unknown/Declined	9.1%	6.0%		

*Nearest to the date of the first antibody test

In our study, 12% of overweight and obese patients, sampled from a dedicated pediatric diabetes clinic who were initially clinically diagnosed with T2D, were found to have laboratory evidence suggesting a disease pathology that may currently or in the future be more consistent with T1D. The present study also provides insight into some physical, clinical, and biochemical differences in patients with an initial diagnosis of T2D stratified by the subsequent presence or absence of diabetes-associated autoantibodies. Our data suggest that patients with positive autoantibodies have significantly lower HbA1c closest to diagnosis compared to those with T2D and negative autoantibodies. One potential explanation for HbA1c results could be the natural time course of T1D versus T2D. Patients with T2D may be asymptomatic and have a longer and more aggressive disease course before diagnosis, thus presenting with a higher HbA1c. However, our sample size was too small to draw more definitive conclusions. We did not find significant differences in age, sex, race/ethnicity, or BMI Z-score that differentiate patients with positive autoantibodies from those without.

The treatment options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial showed that about 10% of youth with clinically diagnosed T2D were positive for GAD65 or IA2 antibodies.[16] SEARCH for Diabetes in Youth also reported on this and showed that 21.2% of youth aged 10 years or older with a clinical diagnosis of T2D had positive GAD 65 antibodies.[17] The proportion of youth with antibodies in SEARCH is significantly higher and could be related to the method of ascertainment of participants in their observational study and due to improvements in antibody assays with a reduction in the number of false positives since the SEARCH study was done. In our study, it appears that the number of participants with positive antibodies has not increased over time despite testing for additional autoantibodies.

Based on previous studies and our results, there is a case to be made in recommending routine autoantibody screening for pediatric patients 10 years of age and greater who are presenting with new-onset diabetes mellitus, and with clinical suspicion for T2D (not evidently T1D, no DKA, etc.) to avoid potential misclassification of the etiology of their diabetes diagnosis. Clinical misclassification of T1D as T2D could lead to delays in insulin initiation and an increased risk of developing DKA. In addition, these patients can be connected with resources that are routinely offered to patients with T1D such as insulin pumps and continuous glucose monitors. In our study, one child with T2D with autoantibodies and one child with T2D without autoantibodies had insulin pump CPT codes.

It is important to note that testing for pancreatic autoantibodies comes with a significant financial cost which can be a barrier in some care settings. We believe that patients initially clinically diagnosed as having T2D who are found to have positive autoantibodies should be reframed as having a disease phenotype in line with current or future T1D, even though they are overweight or obese, as they may require different monitoring and treatment to prevent the risk of DKA. It is also important to note that there were no differences by race and ethnicity in the presence of pancreatic autoantibodies; therefore, screening for pancreatic autoantibodies should be done regardless of racial or ethnic group.

A major strength of our study is that our sample was drawn from a dedicated pediatric diabetes clinic staffed by trained providers in a diverse part of Northern California. This cohort was diverse racially and ethnically, as seen in [Table 2], making this study more generalizable. In addition, we collected data on all five clinically available autoantibody tests.

Limitations include aspects that are inherent to a retrospective chart review. In addition, our results are from a single center and may not be generalizable to all pediatric populations. Given our limited number of patients with positive antibodies, we could not describe clinical characteristics based on antibody type or titer. We, further, recognize that antibody-negative T1D has been described yet is not addressed in this investigation. Due to the retrospective nature of this study and the limitations of the dataset, we were unable to comment on differences in other clinical characteristics in the Ab+ and Ab− groups, such as acanthosis nigricans, skin tags, and abdominal obesity. Furthermore, we do not routinely obtain C-peptide levels as part of our clinical practice and, therefore, are not able to report differences in C-peptide levels between the groups.

CONCLUSION

A significant proportion of youth with an initial clinical diagnosis of T2D have positive pancreatic autoantibodies. This highlights the potential for diabetes misclassification in children and that clinical features alone are not always sufficient to make an accurate diagnosis. Future large-scale studies should further evaluate potential differences in clinical characteristics of autoantibody-positive patients with clinical features of T2D based on antibody type and titer.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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