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Obesity and Youth Diabetes: Distinguishing Characteristics between Islet Cell Antibody Positive vs. Negative Patients Over Time

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Abstract

Objective—Obese youth clinically diagnosed with type 2 diabetes (T2DM) frequently have evidence of islet cell autoimmunity. We investigated the clinical and biochemical differences, and therapeutic modalities amongst autoantibody positive (Ab+) vs. autoantibody negative (Ab-) youth at the time of diagnosis and over time in a multi-provider clinical setting.

Study Design—Chart review of 145 obese youth diagnosed with T2DM from January 2003 through July 2012. Of these, 70 patients were Ab+ and 75 Ab-. The two groups were compared with respect to clinical presentation, physical characteristics, laboratory data and therapeutic modalities at diagnosis and during follow up to assess the changes in these parameters associated with disease progression.

Results—At presentation, Ab+ youth with a clinical diagnosis of T2DM were younger, had higher rates of ketosis, higher HbA1c and glucose levels, and lower insulin and c-peptide concentrations compared with the Ab- group. The Ab- group had a higher BMI z-score and cardio-metabolic risk factors at diagnosis and such difference remained over time. Univariate analysis revealed that treatment modality had no effect on BMI in either group. Generalized estimating equations for longitudinal data analysis revealed that a) BMI z-score and DBP were significantly affected by duration of diabetes, b) SBP and ALT were affected by changes in BMI z-score, c) changes in HbA1c had an effect on lipid profile and cardio-metabolic risk factors regardless of antibody status.

Conclusions—Irrespective of antibody status and treatment modality, youth who present with obesity and diabetes, show no improvement in obesity status over time, with the deterioration in

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BMI z-score affecting BP and ALT, but the lipid profile being mostly impacted by HbA1c and glycemic control. Effective control of BMI and glycemia are needed to lessen the future macrovascular complications irrespective of antibody status.

Keywords

Pediatrics; Type 2 diabetes mellitus; Islet cell autoantibodies

Introduction

Youth type 2 diabetes (T2DM) is characterized by varying degrees of insulin resistance and relative insulin deficiency (1). This is in contrast to type 1 diabetes (T1DM), in which there is an absolute insulin deficiency due in most cases to an autoimmune destruction of the islet cells (2,3). Obesity is the hallmark of T2DM, with up to 85% of affected children with T2DM in North America being overweight or obese at diagnosis. However, between 10 and 75% of obese youth with physician-diagnosed T2DM have islet cell autoantibodies (4), the hallmark of T1DM. With the escalating rates of obesity in the general population, children with autoimmune T1DM are also becoming obese at the time of diagnosis (5). The overlap in the presentation between obese adolescents with T2DM or T1DM makes the clinical distinction difficult. The diagnosis of T2DM is made using clinical criteria where obesity is the major entity, along with physical findings of insulin resistance such as acanthosis nigricans, and family history of T2DM (2,3). Studies using clamp experiments, have demonstrated that obese youth clinically diagnosed with T2DM with evidence of islet cell autoimmunity have severe insulin deficiency and β -cell failure, as compared with youth with negative islet cell auto-antibodies, who have severe impairment in insulin action (6,7,8).

Few studies have assessed the clinical distinguishing features between obese Ab+ and Ab- youth with diabetes at the time of diagnosis (9,10, 11), but information on the future course of their disease is missing. In the TODAY study, at screening ~10 percent of youth with physician-diagnosed T2DM had positive autoantibodies (glutamic decarboxylase-65 and insulinoma antigen-2 autoantibodies) diagnostic of T1DM (12). Because Ab+ patients were excluded from randomization in TODAY, there was no follow up data on their clinical course. Therefore, the impetus of our study was to gain insight into the clinical course of obese youth with Ab+ clinician-diagnosed T2DM. The aim was to evaluate the clinical, therapeutic and biochemical characteristics of clinician-diagnosed Ab+ vs. Ab- youth with T2DM over time, from diagnosis through their follow up, in a large multi provider diabetes clinical setting.

Research Design and Methods

The medical records of 145 patients with a clinical diagnosis of T2DM seen at the Children's Hospital of Pittsburgh of UPMC from January 2003 through July 2012 were reviewed from admission to their last outpatient clinic follow up, following approval from the Institutional Review Board of the University of Pittsburgh. The diagnosis of T2DM was made by a pediatric endocrinologist and was based on ADA diagnostic criteria (2). Patients had islet-cell autoantibody testing, for glutamic acid decarboxylase-65 autoantibody (GAD-65 Ab) and insulinoma associated protein-2 autoantibody (IA2 Ab) using the National Institute of

Diabetes and Digestive and Kidney Disease (NIDDK) sponsored harmonization assay (3). Patients were considered to be Ab+ if one or both autoantibodies were positive. Ab+ vs. Ab- groups were compared with respect to their physical, clinical and biochemical characteristics, and treatment at presentation (Table 1) and over time based on windows centered on outpatient follow up time.

At baseline categorical variables were analyzed using chi-square/ Fisher's exact tests and continuous variables using Mann-Whitney U tests. Generalized estimating equations (GEE) analysis was used for the longitudinal analysis of continuous outcomes, to evaluate the independent association between variables and repetitive outcomes over time while adjusting for missing data and variability in numbers. By using this model we were able to create windows centered on follow up time. If a patient had more than one visit during a follow up window, we created average values of measurements within the window and in the GEE model we specified unstructured correlation between the windows for the same subject.

For the longitudinal analysis we created 2 models. The first model evaluated HbA1c by controlling for antibody status, BMI z-score, age, and duration of diabetes. The second model evaluated blood pressure, liver profile and cardiometabolic risk factors, by controlling for antibody status, BMI z-score, age, duration of diabetes and HbA1c. We evaluated for interactions between antibody status and duration of diabetes and included them if significant. Numeric data are presented as median and interquartile range (IQR) and significance was defined by $p \leq 0.05$.

Results

Of the 145 patients with clinically-diagnosed T2DM, 70 were Ab+ and 75 were Ab-. Of the Ab+ group, 25 were positive for a single antibody and 45 were positive for both antibodies.

Characteristics at Diagnosis (Table 1)

At diagnosis, the Ab- group was significantly older than the Ab+ group, had a higher percentage of females, and Non-Hispanic Blacks, more frequent family history of type 2 diabetes, and acanthosis nigricans, as well as significantly worse dysmetabolic syndrome components (lipids, systolic BP and liver enzymes) (Table 1). On the other hand, the Ab+ group had significantly higher rates of DKA, and worse glycemia, and lower insulin and c-peptide concentrations (Table 1). At diagnosis, the Ab+ group was more likely to be started on insulin therapy alone (71.4%) and the Ab- group on either metformin alone or in combination with insulin (73.3% combined) (Table 1).

Characteristics During Follow up

The average follow up duration for the Ab+ group was 20 ± 7 months and 16 ± 6 months for the Ab- group ($p=0.09$). Of those patients diagnosed between 2003-2007, [T1DM (n=25) and T2DM (n=11)], only 31% and 21% respectively were still being followed in our clinic after 5 years from diagnosis.

HbA1c over time (Figure 1A) declined within the first 6 months in both Ab+ and Ab- groups, but progressively increased in both groups as disease progressed. The Ab- group had a significantly higher BMI z-score at diagnosis and throughout the follow up period (Figure 1B) and so did the Non-HDL cholesterol and triglycerides. HbA1c and BMI z-scores were compared in the three therapeutic interventions, insulin alone, metformin alone and insulin plus metformin, by antibody group. There were no significant differences in HbA1c and BMI z-scores by antibody group in the subjects treated with insulin plus metformin (Figure 2A, 2B). At diagnosis patients in the Ab- group who were started on insulin plus metformin had higher HbA1c than the group on metformin alone (96 mmol/mol vs 49 mmol/mol respectively, $p=0.009$) (Figure 2C), which may have led to the clinician's decision of choosing metformin alone vs. combination of metformin plus insulin. The better HbA1c at diagnosis in the Ab- metformin only treated group persisted over the follow up. BMI z-scores did not differ at diagnosis or follow up in Ab- patients on the three treatments (Figure 2D). Moreover, insulin treatment alone or in combination did not appear to have an effect on BMI z-score in the Ab- group.

Applying the GEE model revealed that changes in HbA1c over time were not affected by antibody status, BMI z-score, age, and diabetes duration. For BMI z-score, controlled for HbA1c, duration of diabetes and antibody status, diabetes duration had a significant effect; for every month of diabetes duration the BMI z-score increased by 0.003 ($p=0.02$).

The GEE model was also applied to evaluate cardio metabolic risk factors over time (SBP, DBP, Cholesterol, Triglycerides, LDL, HDL, non-HDL cholesterol, TG/HDL ratio, AST, and ALT) controlled for HbA1c, BMI z-score, antibody status, age, and diabetes duration. SBP was mainly affected by changes in BMI z-score: for every 0.5 increase in BMI z-score SBP increased by 10.9 mmHg ($p=0.003$). On the other hand DBP was affected by diabetes duration; for every month of diabetes, DBP increased by 0.119mmHg ($p<0.001$). HbA1c, age, and antibody status had no effect on SBP or DBP. With regards to the lipid profile, for every 1% change in HbA1c, total cholesterol increased by 2.3 mg/dl ($p=0.017$), HDL decrease by 0.928 mg/dl ($p<0.001$), LDL increased by 2.1 mg/dl ($p=0.037$), non-HDL cholesterol increased by 3.4 mg/dl ($p=0.002$), and TG/HDL ratio increased by 0.402 ($p=0.003$). Diabetes duration and BMI z-score had no effect on lipid profile, however antibody status had an effect, with Ab- patients having higher triglycerides (54.9 mg/dl, $p=0.002$), higher total cholesterol (15.1 mg/dl, $p=0.01$), higher non-HDL cholesterol (28.6 mg/dl, $p<0.001$), higher TG/HDL ratio (2.08, $p=0.003$), and AST concentrations (8.3 IU/L, $p=0.001$) over time compared with the Ab+. Lastly, ALT was affected by change in BMI z-score; with ALT increasing by 4.15 IU/L ($p=0.0016$) for a 0.5 change in BMI z-score. Duration of diabetes and HbA1c had no effect on AST or ALT.

Discussion

The present study allowed for the evaluation of the clinical course of obesity-associated diabetes in youth, who were initially and clinically diagnosed to have T2DM, but following antibody testing were divided into Ab+ vs. Ab- groups. Our examination of the follow up of these youth in a large multi provider diabetes clinic practice revealed that: a) irrespective of antibody status, HbA1c improved remarkably in the first six months, and changes in HbA1c

over time were not affected by antibody status, BMI z-scores, age or diabetes duration, b) BMI z-scores were higher in Ab- vs. Ab+ youth at diagnosis and during follow up, and BMI z-scores increased overtime, c) at diagnosis and over time the lipid components of the dysmetabolic syndrome were worse in Ab- patients and changes were affected by HbA1c, d) over time changes in systolic and diastolic blood pressures were differentially affected, the former increasing with increasing BMI z-scores, and the latter increasing with increasing diabetes duration, and lastly, e) antibody status had an effect on AST over time, while ALT was affected with changes in BMI z-scores, even though both were higher in Ab- vs. Ab+ youth at diagnosis.

Our data agree with the existing literature with respect to the presentation characteristics of Ab+ vs. Ab- obese youth clinically diagnosed with T2DM, but in addition, and for the first time, advances our knowledge to their clinical follow up course and changes in metabolic and CVD risk factors over time. Not infrequently, the clinical distinction between obese youth with T1DM vs. T2DM may be difficult necessitating pancreatic autoantibody determination (9,10,13,14,15,16). The reported rates of positive autoantibodies in clinician-diagnosed type 2 diabetes vary from 10% to 75% (9,10). In the present study nearly 50% of patients were found to have positive pancreatic antibodies. These differences in the rates of positive autoantibodies could be explained by either differences in patient population or the method of antibody testing. An important factor also is the reliability and or the sensitivity of the antibody assay, with the commercial assays falling short in detecting low titer antibodies, hence our choice of the NIDDK harmonization assay. Our findings with regards to the clinical and biochemical characteristics at the time of presentation of diabetes are consistent with the TODAY data (15). While there was a higher incidence of DKA in the Ab+ group, interestingly 5% of the Ab- group presented with DKA at diagnosis. The different therapeutic approaches between the two groups were most likely driven by clinician judgment and severity of clinical presentation and HbA1c levels. At diagnosis, insulin alone was the predominant treatment choice for the Ab+ group (71%) and metformin plus insulin (44%) for the Ab- group. In the Ab- group, those patients with higher HbA1c (94 mmol/mol) appear to have been initiated on insulin plus metformin vs. those with lower HbA1c (49 mmol/mol).

An interesting observation during the follow up was that the numbers of patients remaining in follow up declined faster in the Ab- group. One can speculate that age was a factor, as this group was older at the time of diagnosis and they could have had earlier transition to adult care providers. However, this is consistent with clinical impressions and a prior study showing that 60% of youth with T2DM dropped out of care after a mean follow up of 7.1 months (17). Surprisingly, the follow up rate even in the obese Ab+ group dropped to less than 50% after 2 years of diagnosis similar to the reported high rates of recidivism in obesity clinics (18) and in contrast to T1DM clinics (19).

The lower HbA1c levels in the Ab- vs. Ab+ patients at initial diagnosis persisted over time. The Ab- group who was started on insulin plus metformin at diagnosis, was more likely to be on metformin alone after 18 months. The latter group had better glycemic control, but there were no differences in BMI z-scores between the metformin alone and insulin plus metformin groups. This contradicts previous studies showing that insulin therapy was

associated with weight gain in T2DM youth (20). The Ab+ group started on insulin alone, was more likely to be on insulin plus metformin by 2 years after diagnosis, with higher HbA1c and BMI z-scores compared with the group on insulin alone.

Cardio-metabolic risk factors were higher in the Ab- group despite having better glycemic control, supporting reports that youth with T2DM have higher rates of diabetic complications at a younger age than youth with T1DM (21). Lastly, the GEE model showed that changes in HbA1c were not affected by antibody status, BMI-z-scores, age or duration of diabetes. However, changes in HbA1c had an effect on lipid profile and cardio-metabolic risk factors, while changes in BMI z-scores influenced systolic blood pressure and ALT.

A limitation of this study is its retrospective nature, the declining patient numbers during follow up and the absence of a protocol followed by all providers. Despite this however, the information gained from this study enhances our limited knowledge in the clinical course of these obese youth with diabetes.

In summary, irrespective of antibody status and treatment modality, youth who present with obesity and diabetes, show no improvement in obesity status over time, with the deterioration in BMI z-score affecting BP and ALT, but the lipid profile being mostly impacted by HbA1c/glycemic control. Effective efforts at controlling BMI and hyperglycemia are needed to lessen the future macrovascular complications irrespective of antibody status. Finally, our findings should pave the road for protocol-driven prospective studies in obese youth with diabetes and evidence of pancreatic autoimmunity to carefully address their heightened risk, not only related to diabetes, but also dysmetabolic syndrome and CVD.

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Abbreviations

Ab+	Antibody positive
Ab –	Antibody negative
BMI	Body mass index
GAD-65	glutamic acid decarboxylase 65
HbA1c	hemoglobin A1c
IA2	Insulinoma antigen 2
T2DM	type 2 diabetes mellitus

T1DM	type 1 diabetes mellitus
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

Figure 1. Univariate analysis of a) HbA1c, b) BMI z-score, c) Non-HDL Cholesterol, d) Triglycerides per antibody status

Figure 2. Univariate analysis therapeutic approach according to changes in HbA1c and BMI z-score per antibody group. 2 A and 2B show HbA1c and BMI z-score respectively in the Ab+ group and figure 2C and 2D show HbA1c and BMI z-score respectively in the Ab- group.

Table 1
Physical, Clinical and Biochemical Characteristics of Antibody Positive vs. Antibody Negative Patients at Diagnosis of Diabetes

Characteristics At Diagnosis	Antibody Positive (N=70)	Antibody Negative (N=75)	P value
Age (yrs) *	12.5 (10.5-15.1)	14.3 (12.6-15.8)	0.003
Sex (Female %)	41	68	0.001
Race (%)			
Non-Hispanics Blacks	17	40	0.004
Non-Hispanics White	80	55	0.004
Hispanics	3	5	0.004
Family History T2DM (%)	53	87	<0.001
Acanthosis Nigricans (%)	47	77	<0.001
DKA at Diagnosis	23	5	0.003
BMI z-score *	1.96 (1.6-2.3)	2.4 (2.1-2.6)	<0.001
Glucose (mmol/L) *	21 (15-27)	13 (9-18)	<0.001
HbA1c (mmol/mol) *	95 (78-111)	87 (56-108)	0.021
Insulin (uU/ml) *	11 (7-15)	28 (20-64)	<0.001
c-peptide (ng/ml) *	1.2 (0.9-2)	3.4 (2-5.5)	<0.001
GAD-65 (un/ml) *	164.7 (112-216)	2.02 (1-3.1)	<0.001
IA-2 (un/ml) *	245 (212-278)	0.7 (0.5-1)	<0.001
Cholesterol (mg/dl) *	147 (126-170)	174 (148-202)	0.001
Triglycerides (mg/dl) *	95 (71-129)	142 (102-212)	<0.001
HDL (mg/dl) *	31 (27-39)	29 (25-37)	0.663
LDL (mg/dl) *	95 (72-115)	112 (79-139)	0.024
TG/HDL ratio *	3.1 (1.9-4.7)	5 (2.8-7.2)	<0.001
Non-HDL Cholesterol (mg/dl) *	114 (94-139)	137 (111-169)	<0.001
AST / SGOT (IU/L) *	21 (19-32)	27 (22-48)	0.002
ALT / SGPT (IU/L) *	24 (20-36)	33 (21-59)	0.056

Characteristics At Diagnosis	Antibody Positive (N=70)	Antibody Negative (N=75)	P value
BUN (mg/dl) *	12 (9-15)	11 (9-13)	0.369
Creatinine (mg/dl) *	0.6 (0.5-0.8)	0.6 (0.5-0.6)	0.394
Systolic Blood Pressure (mmHg) *	119 (110-129)	122 (115-132)	0.046
Diastolic Blood Pressure (mmHg) *	67 (60-73)	68 (60-75)	0.420
Treatment Modality (%)			
Insulin alone	71.4	25.3	<0.001
Metformin alone	2.9	29.3	<0.001
Insulin and Metformin	24.3	44	<0.001
No treatment	1.4	1.4	NS

*
(Median and IQR)

Table 2
Patient follow up per window

Follow up windows	Antibody Positive	Antibody Negative
Baseline	70 (100%)	75 (100%)
0-6 month follow up	61 (87%)	58 (77%)
6-12 month follow up	49 (70%)	42 (56%)
12-18 month follow up	41 (58%)	41 (55%)
18-24 month follow up	35 (50%)	31 (41%)
24-30 month follow up	31 (44%)	22 (29%)
30-36 month follow up	23 (33%)	18 (24%)
36-48 month follow up	24 (34%)	11 (15%)
48-60 month follow up	13 (19%)	6 (8%)
60+ month follow up	10 (14%)	4 (5%)