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Clinical Utility and Outcome Prediction of Early ZnT8-IgG Testing and Titer in Type 1 Diabetes

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What is already known on this topic?

Type 1 diabetes mellitus occurs due to the autoimmune destruction of pancreatic beta cells. Autoantibodies to components of these beta cells are markers for this disease. It is known that autoantibodies against Zinc transporter 8 (ZnT8) are more commonly seen in children with diabetes than in adults. Several studies have shown conflicting results regarding the clinical disease presentation in the presence or absence of ZnT8 autoantibodies, some showing that they are associated with older age, higher body mass index (BMI) and a more aggressive disease onset (more diabetic ketoacidosis), other studies have contradicted these results. One study has follow-up data on the clinical course of diabetes post-diagnosis (2 years) suggesting that those with ZnT8 autoantibodies have a more aggressive disease course (higher insulin requirements).

What this study adds?

Our study adds to the very limited literature on ZnT8 autoantibody positivity in pediatric diabetes. We looked at disease onset and the subsequent disease course and showed that at disease onset, there were no differences in age, BMI or severity of the disease between those children with and those without ZnT8 autoantibodies. We had a longer longitudinal follow-up than other studies and observed no statistically significant differences in the development of other autoimmune conditions, macrovascular or microvascular complications between ZnT8 positive and negative groups. We also studied ZnT8 antibody titers and found that the only difference seen in follow-up between the low and high titer groups was a slightly higher cumulative excess glucose in the low titer group compared to the high titer and ZnT8 antibody negative groups.

Abstract

Objective: Type 1 diabetes autoantibodies are directed against multiple antigens including: glutamic acid decarboxylase, protein tyrosine phosphatase-like islet antigen 2 (IA2), insulin (IAA), and Zinc transporter 8 protein (ZnT8). The aim of our study was to determine if the presence or titer of ZnT8 antibodies (Ab) was predictive for clinical presentation at diagnosis or for the subsequent disease course.
Methods: Between January, 2003 and May, 2019, 105 patients aged ≤21 years with a clinical diagnosis of type 1 diabetes mellitus had at least 1 autoantibody measured. A retrospective chart review was completed. At diagnosis, we evaluated the body mass index z-score, hemoglobin (HbA1c), and the presence of diabetic ketoacidosis (DKA). Complications analyzed post-diagnosis included episodes of DKA, the diagnosis of autoimmune disease, and the presence of vascular complications. We evaluated cumulative lifetime excess glucose as HbA1c area under the curve (AUC) >6%.

Conflict of interest: Sean Pittock reports grants, personal fees and non-financial support from Alexion Pharmaceuticals, Inc.; grants from Grifols, Autoimmune Encephalitis Alliance; grants, personal fees, non-financial support and other from MedImmune, Inc.; Dr. Pittock has a patent #9,891,219 (Application#12-573942) "Methods for Treating Neuromyelitis Optica (NMO) by Administration of Eculizumab to an individual that is Aquaporin-4 (AQP4)-IgG Autoantibody positive". Dr Pittock also has patents pending for the following IgGs as biomarkers of autoimmune neurological disorders (septin-5, Kelch-like protein 11, GFAP, PDE10A and MAP1B).

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Results: Seventy-one patients were ZnT8-Ab(+) (68%), with 19 having low titer ZnT8-Ab and 52 with high titer ZnT8-Ab. Follow-up ranged from 10 days to 15.7 years (median 2.08 years). There were no differences in the characteristics at disease onset or in the subsequent follow-up between those with and those without ZnT8-Ab or those with high or low titers of ZnT8 Ab, except for a small but statistically significant difference in cumulative excess glucose (HbA1c AUC >6%) between those with low and high titers ($p = 0.0095$).
Conclusion: Our study adds to the limited literature on the effect of the presence and titer of ZnT8-Ab in pediatric diabetes. The small effect of ZnT8-Ab titer on glucose excess as measured by HbA1c AUC warrants further study.
Keywords: Type 1 diabetes mellitus, autoantibodies, GAD65, IA2, IAA, ZnT8

Introduction

Type 1 diabetes mellitus (T1DM) is a common chronic disease which affects 187,000 children and adolescents younger than 20 years of age in the United States (1). T1DM is an autoimmune (AI) condition which results in beta cell destruction leading to insulin deprivation. Due to the current obesity epidemic, distinguishing between type 1 and type 2 diabetes in children can be difficult. Diabetes-associated autoantibodies can help delineate the diabetes classification. Autoantibodies to pancreatic beta cell components are currently the best indicator of ongoing beta cell destruction in humans leading to AI T1DM. The diabetes specific autoantibodies are directed against glutamic acid decarboxylase (GAD65), protein tyrosine phosphatase-like islet antigen 2 (IA2), insulin (IAA), and Zinc transporter 8 protein (ZnT8) (2,3,4,5,6,7). Of the four autoantibodies, ZnT8-Ab is the newest diabetes specific autoantibody in clinical use and is more commonly present in children than in adults (2,8). Additionally, the presence of multiple autoantibodies (2 or more) is more common in children (8).

T1DM can present with a severe, potentially life-threatening form known as diabetic ketoacidosis (DKA), defined as hyperglycemia, acidosis, and the presence of ketones (9,10). Between 15% and 67% of patients with newly diagnosed T1DM present with DKA (11). The severity of DKA is dependent on the degree of acidosis. DKA can occur not only at the time of initial diagnosis, but also any time post-diagnosis when there is inter-current illness, trauma, or stress in conjunction with inadequate insulin delivery.

Due to the chronic nature of T1DM, patients are at risk of diabetes related complications from long standing hyperglycemia. These include both microvascular (peripheral neuropathy, diabetic kidney disease, retinopathy, and gastroparesis) and macrovascular (cerebral infarction and myocardial infarction) complications (12,13). Patients with T1DM are also at a higher risk of other AI diseases, such as hypothyroidism, celiac disease, and Addison's disease, which can lead to additional burdens and can impact their quality of life (14,15,16,17).

The aim of our study was to determine if the presence and titer of ZnT8 antibodies (Ab) was predictive of clinical presentation at diagnosis or in the subsequent disease course. The novel aspect of our study was that we had up to 15 years of follow-up available in order to analyze the subsequent disease course.

Research Design and Methods

This clinical-serological cohort study was approved by the Institutional Review Board at Mayo Clinic with a waiver of consent for the clinical data obtained as part of serological test validation (study: 08-006647, date: 15.07.2020). All Mayo Clinic patients whose medical charts were analyzed provided written consent for medical research.

Patients

Mayo Clinic Laboratories have been analyzing diabetes specific autoantibodies since 1997. GAD65-Ab testing became available in 1997, IAA (the IAA includes insulin autoantibody) in September 2009, IA2-Ab in March 2011, and ZnT8-Ab in May 2017. Since October 2017, a diabetes mellitus evaluation antibody panel, which includes all 4 autoantibodies, has been available for clinical use.

Between January, 1998 and May, 2019, we had 324 patients ≤21 years of age with a clinical diagnosis of T1DM, who had at least 1 of these autoantibodies tested. Of these patients, residual serum samples were available for 230 patients. We included those with autoantibody testing which was completed within 1 year from the date of diagnosis of T1DM. This resulted in a final analysis of 105 patients.

Residual serum samples are stored in our Neuro-Immunology Laboratory. Since the diabetes specific autoantibodies became available for analysis at different times, the ability to retrieve the residual serum samples allowed for complete analysis of all 4 Ab. Residual serum samples also allowed for the potential of a longer follow-up time period. For those patients in whom all 4 T1DM autoantibodies were not tested initially, stored serum was retrieved, thawed, and the remaining autoantibodies were tested.

Retrospective chart review was completed. Data retrieved included: date and age at diagnosis, ethnicity, length of follow-up, symptoms at diagnosis, body mass index (BMI), glycosylated hemoglobin (HbA1c), additional laboratory results to identify if DKA was present and its severity [central glucose, bicarbonate (HCO_3), pH, beta-hydroxybutyrate]. The severity of DKA was classified according to the initial laboratory evaluation in accordance with American Diabetes Association guidelines: mild = pH 7.25-7.3, HCO_3 15-18, moderate = pH 7-7.24, HCO_3 10-14, severe = pH < 7, HCO_3 < 10 (18). Post diabetes diagnosis analysis included evaluation for the number of admissions for DKA, and diagnoses of AI disease (hypothyroidism, hyperthyroidism, celiac disease, AI adrenal insufficiency, and other), and vascular complications (microvascular – peripheral neuropathy, diabetic kidney disease, retinopathy gastroparesis; macrovascular – cerebral infarction, and myocardial infarction).

BMI z-scores were determined for all ages according to Center for Disease Control guidelines (19). The equation for determining BMI z-scores was (patient BMI – population mean BMI/population standard deviation BMI, using age-specific population means and standard deviations). It was assumed that the population mean and standard deviation for BMI was constant for age ≥20 years.

All available HbA1c results since the diagnosis of diabetes were collected, and a life-long measure of dysglycemia was calculated using an HbA1c index [HbA1c area under the curve (AUC) > 6% which computed total AUC > 6.0% using the trapezoidal rule, divided by the time between diagnoses and study assessment] (20,21). HbA1c results ≥2 months from diagnosis were used to calculate HbA1c AUC > 6%.

Laboratory Data

All assays were clinically validated laboratory developed tests or Food and Drug Administration approved assays performed in accordance with CLIA, CAP, and New York State regulatory guidelines. GAD65-Ab, IA2-Ab, and IAA were measured by radioimmunoassay (normal reference range ≤0.02 nmol/L). ZnT8-Ab was detected by enzyme-linked immunosorbent assay (normal reference range ≤15 U/mL).

Statistical Analysis

Patient characteristics were summarized with frequencies and percentages, or medians and ranges, as appropriate. Comparisons by ZnT8-Ab status [negative vs. positive; negative vs. low positive titer (< 100 U/mL) vs. high positive titer (≥100 U/mL)] were assessed with chi-squared or Fisher's exact tests (categorical data) or Wilcoxon rank-sum or Kruskal-Wallis tests (ordinal or continuous data). The incidence rates (along with 95% confidence intervals) for total diabetes complications, DKA admissions, and AI diseases were summarized per 100 person years, and were estimated and compared between ZnT8-Ab groups with Poisson regression models. P values less than 0.01 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Between January, 2003 and May, 2019, we had a total of 105 T1DM patients, ≤21 years old, with a clinical diagnosis of type 1 diabetes and autoantibody results within 1 year of diagnosis. Males made up 67% of the total cohort (Table 1).

When looking at ZnT8-Ab status, 34/105 were ZnT8-Ab negative, 71 were ZnT8-Ab positive (68%). Of the ZnT8-Ab positive patients, 27% had a low ZnT8-Ab titer (< 100 U/mL) and 73% had a high ZnT8-Ab titer of ≥100 U/mL (Table 1). There was no significant difference found between genders with respect to ZnT8-Ab positivity (p = 0.04) or titer concentration (p = 0.12). Additionally, there was no significant difference in ZnT8-Ab positivity or titer by ethnicity (p = 0.71 and p = 0.49 respectively).

At Diabetes Diagnosis Analysis

At diabetes diagnosis, we did not find a difference in age (p = 0.94), BMI z-score (p = 0.83), rate of DKA (p = 0.26), or HbA1c (p = 0.38) relative to ZnT8-Ab positivity. There remained no significant difference when evaluating ZnT8-Ab titer concentrations between age at diagnosis (p = 0.87), BMI z-score (p = 0.96), or rate of DKA (p = 0.03).

Although the age at diagnosis was similar between the ZnT8-Ab negative and positive groups (median 12.8 for each group, p = 0.94), we found that the low titer positive patients had a slightly (non-significantly) higher age than the high titer patients (median 14.8 vs. 12.5, p = 0.58).

When evaluating rates of DKA at diagnosis, within the low titer ZnT8-Ab group, there were no episodes of DKA. Although this might be clinically significant, it did not reach statistical significance. Of the 21 patients who presented with DKA, 9 of them were ZnT8-Ab negative (43%), none had low titer ZnT8-Ab, and 12 had high titer ZnT8-Ab (57%).

The median BMI z-score was similar between the ZnT8-Ab negative, low titer ZnT8-Ab positive, and high titer ZnT8-Ab groups at 0.31, 0.36 and 0.23 respectively (p = 0.96).

Post Diabetes Analysis

We evaluated cumulative post diagnosis excess glucose as HbA1c AUC >6% divided by years of available follow-up following diabetes diagnosis. We found a statistically significant difference when comparing low positive titer ZnT8-Ab to high titer ZnT8-Ab HbA1c AUC >6%, with the low positive titer group having a higher AUC (p=0.0095). The HbA1c AUC >6% was not stepwise as the AUC for HbA1c >6% was similar between the ZnT8 Ab negative and high titer groups (p=0.23) (Table 1).

When we evaluated for the rate of post diabetes complications and ZnT8-Ab status along with ZnT8-Ab titer concentration, we did not find a statistical significance in diabetes complications (retinopathy, peripheral nephropathy, diabetes kidney disease, and gastroparesis), subsequent DKA admissions, or concomitant AI disease (Table 2).

There were 10 patients in total who experienced at least one diabetes complication following diagnosis. Although the incidence rate of complications was highest for the ZnT8-Ab negative patients (incidence rate per 100 person years: 4.46) as compared to the low positive titer (1.76) and high titer (3.15) patients, this was not statistically significant.

Only 18 subjects had one or more DKA admission following their initial diagnosis. The incidence rates of DKA were 14.64, 15.80, and 10.73 per 100 person years, for the negative, low positive titer, and high titer groups, respectively (not significant).

Table 1. Characteristics at diagnosis stratified by ZnT8-Ab status and titer

	ZnT8-Ab(-) (n=34)	ZnT8-Ab(+) <100 (n=19)	ZnT8-Ab(+) ≥100 (n=52)	Overall p value
Sex				
F	16 (47.1%)	5 (26.3%)	14 (26.9%)	0.12
M	18 (52.9%)	14 (73.7%)	38 (73.1%)	
Age at diagnosis				
Median	12.8	14.8	12.5	0.87
Range	(2.2-21.2)	(4.4-21.7)	(2.1-21.9)	
Age at diagnosis (categorized)				
<6 yrs	4 (11.8%)	3 (15.8%)	8 (15.4%)	0.72
6-<12 yrs	11 (32.4%)	3 (15.8%)	16 (30.8%)	
12-21 yrs	19 (55.9%)	13 (68.4%)	28 (53.8%)	
BMI z-score				
n	26	15	43	0.96
Median	0.3	0.4	0.2	
Range	(-5.8-2.5)	(-2.3-1.9)	(-2.6-2.8)	
Ethnicity				
n	30	18	46	0.49
Hispanic or Latino	3 (10.0%)	0	5 (10.9%)	
Not Hispanic or Latino	27 (90.0%)	18 (100%)	41 (89.1%)	
DKA				
n	32	18	48	**0.03**
No	23 (71.9%)	18 (100%)	36 (75.0%)	
Yes	9 (28.1%)	0	12 (25.0%)	
DKA severity at diagnosis (excludes unknowns)				
n	8	0	10	
Mild	4 (50.0%)		6 (60.0%)	1
Moderate	2 (25.0%)		2 (20.0%)	
Severity	2 (25.0%)		2 (20.0%)	
HbA1c at diagnosis (%)				
n	29	18	48	0.66
Median	12.0	10.9	11.2	
Range	(5.6-19.0)	(5.7-16.1)	(5.8-17.1)	
Any thyroid disease at or prior to baseline diabetes diagnosis	1 (2.9%)	0	3 (5.8%)	0.82
Any other* type of AI disease at or prior to baseline diabetes diagnosis	2 (5.9%)	1 (5.3%)	0	0.17
Days between diagnosis and specimen collection				
Median	19.5	15.0	25.0	0.58
Range	(4-358)	(0-290)	(0-309)	

*Other type of AI disease classified as Vitiligo (2) and juvenile idiopathic arthritis.
AI: autoimmune, yrs: years, DKA: diabetic ketoacidosis, F: female, M: male, ZnT8-Ab: Zinc transporter 8 protein-antibodies

There were 13 patients who had one or more AI disease following their diagnosis. Although the incidence rate of AI disease was slightly higher for the high titer ZnT8-Ab (5.67 per 100 person years) compared to the low positive titer (1.76) and negative (1.91) patients, this did not reach statistical significance (Table 2).

Discussion

ZnT8-Ab is the newest diabetes specific autoantibody used in clinical settings. Zinc is essential for the structural stabilization of insulin and the pancreas is one of the tissues with the highest Zinc concentration (2,5). Studies have shown that ZnT8-Ab is a valuable biological marker in the diagnosis of T1DM for both children and adults when obtained in addition to the classic diabetes autoantibodies (GAD, IA2, and insulin). ZnT8-Ab testing has led to significant improvements in the positive predictive value of autoantibody measurements at the time of diagnosis of T1DM (4). However, there is a paucity of data evaluating the predictive value of ZnT8-Ab titer concentrations.

Our study analyzed if ZnT8-Ab status positivity and ZnT8-Ab titer concentration resulted in a difference at diabetes diagnosis and in the post diabetes diagnosis course. Our rates of ZnT8-Ab positivity were similar to previous studies. Elmaoğulları et al. (2) evaluated 84 patients < 18 years of age, and they noted 58% prevalence at diabetes onset.

Our study differs from others in that we did not find a difference in age at diagnosis, BMI z-score, rates of DKA, or HbA1c based on ZnT8-Ab status. Juusola et al. (18) evaluated 723 patients < 15 years of age at diagnosis and followed up for 2 years thereafter. They concluded that positivity for ZnT8-Ab at diagnosis seemed to reflect a more aggressive disease process both before (more frequent episodes of DKA, older age at diagnosis), and after (higher insulin doses required) diagnosis (22). Our overall median time of follow-up was similar at 2.08 years (range: 10 days to 15.7 years) from the date of T1DM diagnosis. We have the added benefit of 55 subjects with follow-up times of ≥2 years up to 15.7 years (22 subjects with 2 to < 5 years of follow-up, 18 subjects with 5 to < 10 years of follow-up, and 15 subjects with ≥10 years of follow-up). This follow-up time allowed us to evaluate for the development of complications and rates of concomitant AI disease in conjunction with the autoantibody status, and there was no significant difference in the available follow-up times between the negative and ZnT8-Ab positive patients.

The association of ZnT8-Ab and DKA at presentation has been analyzed before but with conflicting results. Niechciał et al. (8) evaluated 218 pediatric patients, median age 9 years, and they found that ZnT8-Ab positive children had higher rates of DKA at diagnosis (p = 0.002) and that these children were found to have high ZnT8-Ab titers (range: 35.5-524.5 U/mL), p < 0.0001. They also noted that ZnT8-Ab positive subjects were more likely to be older than 5

Table 2. Characteristics post-diagnosis stratified by ZnT8-Ab status

	Incidence rate per 100 person years (95% CI)			p values		
Outcome[1]	**ZnT8-Ab (-) (n = 34)**	**ZnT8-Ab (+) < 100 (n = 19)**	**ZnT8-Ab (+) ≥100 (n = 52)**	**Low pos. vs. neg.**	**High pos. vs. neg.**	**High pos. vs. low pos.**
Vascular complication[2]	4.46 (2.64, 7.51)	1.76 (0.66, 4.66)	3.15 (1.70, 5.84)	0.10	0.40	0.32
DKA admission[3]	14.64 (8.58, 24.98)	15.80 (8.64, 28.91)	10.73 (5.76, 19.98)	0.85	0.46	0.38
AI disease[4]	1.91 (0.75, 4.88)	1.76 (0.56, 5.54)	5.67 (3.30, 9.75)	0.91	0.049	0.07
	Other follow-up characteristics, median (range)					
Total years from diagnosis to last follow up						
Median	2.4	2.7	1.8	0.29	0.20	0.05
Range	(0.03-12.9)	(0.1-14.8)	(0.05-15.7)			
AUC for HbA1c > 6%, divided by total years of available data						
n	23	17	39	0.27	0.23	**0.0095**
Median	1.3	1.9	1.2			
Range	(0-4.8)	(0.5-6.9)	(0-4.9)			

[1]Considering the total of each type of event per patient over total available follow-up time per patient.
[2]10 patients had at least one type of diabetes complication (6 negative, 2 low positive, and 2 high positive patients). The most common complication was retinopathy (n = 5 patients), followed by peripheral neuropathy (n = 4), nephropathy (n = 4), and gastroparesis (n = 1), with some patients having multiple types.
[3]18 patients had at least one DKA admission (6 negative, 5 low positive, and 7 high positive patients).
[4]13 patients had at least one type of autoimmune disease (3 negative, 2 low positive, and 8 high positive patients). The most common type was thyroid disease (n = 8 patients), followed by celiac disease (n = 4), and other type (n = 2). Only 1 patient had multiple additional autoimmune diseases (thyroid disease and celiac disease).
AI: autoimmune, DKA: diabetic ketoacidosis, CI: confidence interval, pos.: positive, neg.: negative

years of age with a gradual decrease in rates after 10 years of age, which was in agreement with two other studies (8,22,23). In contrast, Salonen et al. (19) and Elmaoğulları et al. (2) found that rates of DKA at diagnosis were lower in ZnT8-Ab positive patients (23). We did not find a significant difference in the rate of DKA at diagnosis when comparing our 3 groups (negative, low titer or high titer ZnT8-Ab).

It has been well established that patients with poor glycemic control are at a higher risk of episodes of DKA and longstanding hyperglycemia can lead to vascular complications (24). The frequency of vascular complications in our cohort was low, which likely contributed to the lack of statistical significance. Of the 10 patients with vascular complications, 6 were in the ZnT8-Ab negative group (60%), 2 in the low ZnT8-Ab titer group (20%), and 2 in the high ZnT8-Ab titer group (20%), possibly suggesting a trend towards more vascular complications in the ZnT8 Ab negative group (Table 2, footnote 2).

We found some differences in the clinical course between the different ZnT8-Ab groups, although the clinical significance of these differences is unclear. There was a statistically higher AUC HbA1c >6% in those with lower ZnT8-Ab titers compared to those with higher titers. However, there was no difference between the low titer vs. negative groups and high titer vs. negative groups. There was a trend towards higher rates of additional AI disease in the high titer ZnT8-Ab group, but no difference between the negative and low titer groups.

We had 7 subjects whose diagnosis of additional AI disease preceded their diagnosis of T1DM. The prevalence of pre-existing AI conditions was no different between the ZnT8-Ab(+) and ZnT8-Ab(-) groups. Thirteen patients developed another AI disease following their diagnosis. Thyroid disease was the most common, developing in 8 patients, 5 of whom had high ZnT8-Ab titers (62.5%), 2 low titers and 1 was ZnT8-Ab negative. Rydzewska et al. (25) evaluated the status of diabetes associated autoantibodies in children and adolescents with AI thyroid disease. When looking at AI thyroid disease only (without a diagnosis of diabetes), they found that 9.1% of patients with Grave's disease and 9.2% of patients with Hashimoto's thyroiditis were found to have positive ZnT8-Ab. When they evaluated patients with T1DM ± AI thyroid disease, they found that 53% of those with T1DM + AI thyroid disease had ZnT8-Ab and 67% of those with T1DM without AI thyroid disease had ZnT8-Ab. Even though our findings were not statistically significant, there appeared to be a tendency towards a higher occurrence of thyroid disease in those with higher ZnT8-Ab titers, however, larger numbers are needed to validate this finding.

Study Limitations

Limitations exist due to the nature of this study being a retrospective analysis. In the past, it was not common practice to obtain a type 1 diabetes autoantibody panel at the time of diagnosis. Patients with T1DM may seroconvert to negative status over time. Fabris et al. (4) reported a significant seroconversion rate for ZnT8-Ab over a 5 year time period. They showed that the percentage of patients with positive ZnT8-Ab was 61.1% at diabetes diagnosis, but only 33.8% of patients were found to have positive ZnT8-Ab if it was analyzed ≥5 years from diagnosis. Wenzlau et al. (26) found that only 6.7% remained positive for ZnT8-Ab after 25 years.

We only included patients in this study whose autoantibody profiles were obtained within 1 year from diabetes diagnosis to mitigate this issue. There was no difference in time from diagnosis to antibody testing between any of the groups (antibody negative, low titer or high titer).

Conclusion

Our study analyzed if ZnT8-Ab status positivity and ZnT8-Ab titer concentrations resulted in a difference in key patient characteristics at diabetes diagnosis and in the subsequent disease course. Our study is novel as we evaluated the predictive value of ZnT8-Ab titer concentrations along with having a longer follow-up period than previously cited in the literature. At diabetes diagnosis, we did not find a difference in ZnT8-Ab status by age at diagnosis, BMI z-score, rate of DKA, or HbA1c.

During diabetes follow-up, there were no statistically significant differences in admissions for DKA, glycemic control, vascular complications or the development of additional AI disease between those with and those without ZnT8-Ab. Some slight differences were seen between those with high vs. low titer and those with lower titer having a higher AUC for HbA1c >6%.

Our findings add further to the limited literature on the predictive value of the presence of ZnT8-Ab in patients with diabetes and further studies with larger numbers and longer follow-ups are warranted.

Ethics

Ethics Committee Approval: The study was approved by the Mayo Clinic of Institutional Review Board (study: 08-006647, date: 15.07.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Amanda R. Dahl, Siobhan T. Pittock, Concept: Amanda R. Dahl, Siobhan T. Pittock, Design: Amanda R. Dahl, Siobhan T. Pittock, Sean J. Pittock, Data Collection or Processing: Amanda R. Dahl, Sean J. Pittock, Analysis or Interpretation: Amanda R. Dahl, Sarah Jenkins M., Siobhan T. Pittock, Sean J. Pittock, Literature Search: Amanda R. Dahl, Siobhan T. Pittock, Writing: Amanda R. Dahl, Sarah Jenkins M., Siobhan T. Pittock, Sean J. Pittock.

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