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The relationship between autoimmunity and HbA1c in type 1 diabetes mellitus patients

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Abstract

Indicators of increased risk for type 1 diabetes (T1DM) are specific antibodies that are mainly immune markers. Islet cell antibody (ICA), insulin autoantibody (IAA), glutamic acid decarboxylase enzyme antibody (GADA) and HgA1c are also used in the diagnosis and follow-up of patients with type 1 diabetes mellitus. ICA, IAA, GADA, HbA1c were checked at the time of diagnosis and at 6-month intervals in pediatric patients monitored with T1DM. Decreased ICA, GADA and HbA1c levels were evaluated as good blood glucose control and good clinical response. Patients aged ≤5 years had a higher rate of IAA and patients aged >5 years had a higher rate of ICA. Antibody selection according to age during diabetes screening was found to be significant in terms of cost.

Keywords: Diabetes mellitus, autoantibody, glycolyzed hemoglobin

Introduction

Type 1 diabetes (T1DM) is a chronic autoimmune disease. Unfortunately, the pathogenesis is still not fully understood [1]. Indicators of an increased risk for T1DM are mainly specific antibodies, which are immune markers. The most important of these are islet cell antibody (ICA), insulin autoantibody (IAA), and glutamic acid decarboxylase enzyme antibody (GADA). Islet cell antibodies are polyclonal antibodies that develop against different islet antigens and generally have an IgG structure. ICA is the most useful marker for determining the risk for T1DM [2]. Glutamic acid decarboxylase is an enzyme found in beta cells and the central nervous system and is thought to be the antigen that induces T1DM. Antibodies to this enzyme may be positive in the blood before a patient is diagnosed with T1DM [4]. Antibody positivity is determined at the time of diagnosis of T1DM, and antibody levels are controlled during clinical follow-up.

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Antibody positivity decreases over time, and the rate drops to 5–10% 10 years after the diagnosis. High titer islet antibodies are generally considered to be an indicator of progressive beta cell destruction, and blood titers are high before DM becomes clinically evident [3].

Antibody positivity is very strong in children <5 years with T1DM, and their blood glucose regulation is more difficult than in children with weak antibodies [5]. Antibody measurements in patients with T1DM are also helpful laboratory results for writing treatment protocols.

In this study, we compared the ICA, IAA, and GADA antibody titers at the time of diagnosis and follow-up of pediatric patients with T1DM. We also evaluated the relationship between antibody positivity and glycated hemoglobin (HbA1c) levels in these patients.

Materials and Methods

Study Design

This study was composed of type 1 diabetes patients between the ages of 1-17 at İnönü University Faculty of Medicine, Turgut Ozal Medical Center, Department of Pediatrics. The diagnosis of

T1DM was based on polyuria, polydipsia, weight loss, low insulin and c-peptide associated with blood sugar over 200 mg/dl at the time of diagnosis. These patients were diagnosed with T1DM and were positive for ICA, IAA, and GADA. Patients with negative antibody titers were excluded. Patients with HbA1c values >7% had poorly controlled blood sugar, and patients with values <7% had well controlled blood sugar [6]. Therefore, an HbA1c level of 7% was used as the threshold value. The Ethics Committee of Inonu University Faculty of Medicine approved this study (permission number 2006/12).

Data of pediatric patients with T1DM were retrospectively analyzed. T1DM children were divided into two groups according to their age. Patients aged ≤5 years were defined as group A, and patients aged >5 years were group B. The age, sex, date of diagnosis, ICA, GADA, IAA, and HbA1c results at the time of diagnosis and at 6, 12, and 18 months later were recorded for all children. The ICA, IAA, and GADA levels were measured based on antigen-antibody detection using enzyme-linked immunosorbent assays with the Isletest kit in the Seac Brio 410499 model instrument. The HbA1c level was measured by high performance liquid chromatography using an Agilent 1100 model instrument at our hospital.

Routine follow-up of patients was conducted in terms of microvascular complications of T1DM. Ocular examinations were performed for retinopathy at 6-month intervals. Microalbuminuria levels were used to examine diabetic nephropathy in 24 h urine samples. Routine neurological examinations were performed for diabetic neuropathy.

Statistical Analysis

The SPSS for Windows 13.01 package program (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Data are expressed as mean ± standard deviation and countable data are expressed as percentages. Measurable data were determined to be normally distributed according to the Shapiro–Wilk test (p >0.05). Parametric and nonparametric tests were used to statistically evaluate the data. The unpaired t-test, the paired t-test, the McNemar test, Pearson's chi-square, and Fisher's exact chi-square test were used. A p-value <0.05 was considered significant.

Results

The primary outcome is that while antibody positivity rates decrease, this is reflected in the patient's clinic as a good blood glucose control. The secondary outcome is that antibody selection can be made according to age in diagnosis.

Patient Demographics and Clinical Characteristics

Among 84 pediatric patients diagnosed with T1DM, 54 were included in the study, with one of the antibodies positive at diagnosis and regular follow-up visits. The average age of these patients was 7.81±0.5 years (1–17), 12 of whom were boys (22%) and 42 who were girls (78%). Of the 24 patients included in group A (≤5 years), 9 were male (37.5%) and 15 were female (62.5%) and their mean age was 4.25±1.18 years. In all, 3 of the 30 patients included in group B (>5 years) were male (10%), 27 were female (90%), and their mean age was 10.66±2.18 years.

HbA1c Outcome

The rate of HbA1c being above 7% tended to decrease in the first 6 months (p> 0.05). The proportion of patients with at diagnosis and at 6 months was 87% (47/54) and 74.1% (40/54), respectively. The percentage of patients with, which was examined 12 months after diagnosis, was 74.1% (40/54). Although there was a 1-year decrease in the HbA1c ratio, it was not significant (p > 0.05) (Table1, figure1). The HbA1c values in group A were 87.5%, 70.8%, 66.7%, and 45.8% at 6-month intervals. The rate of decrease in the HbA1c value between the time of diagnosis and 18 months was significant (p < 0.05). The mean HbA1c values in group A were 9.99%, 8.86%, 8.1%, and 7.8% at 6-month intervals. The changes detected at the 6-month intervals were significant except for the first 6-month change (p = 0.0001) (Table 2). HbA1c values in group B were 86.7%, 76.7%, 80%, and 63.3% at the 6-month intervals. Although the rate decreased, the change was not significant. The mean HbA1c values at 6-month intervals were 13.4%, 9.8%, 10%, and 9.29%, and these changes were significant (p = 0.0001) (Table 3).

Table 1. Tracking of antibody positivity percentages of patients with Type 1 DM and percentages of patients with HbA1c value higher than 7% at 6-month intervals.

	ICA (n=54) (%)	GADA(n=54) (%)	IAA (n=54(%)	HbA1c (%)
Diagnosis	12 (22.2)	29 (53.7)	25 (46.3)	47 (87)
6 months	7 (13)	25 (46.3)	41 (75.9)	40 (74.1)
12 months	4 (7.4)	22 (40.7)	45 (83.3)	40 (74.1)
18 months	5 (9.3)	20 (37)	47 (87)	30 (55.6)
Diagnosis-6 months	p=0.227	p=0.503	p=0.0001	p=0.143
Diagnosis-12 months	p=0.057	p=0.210	p=0.0001	p=0.143
Diagnosis-18 months	p=0.118	p=0.093	p=0.0001	p=0.002

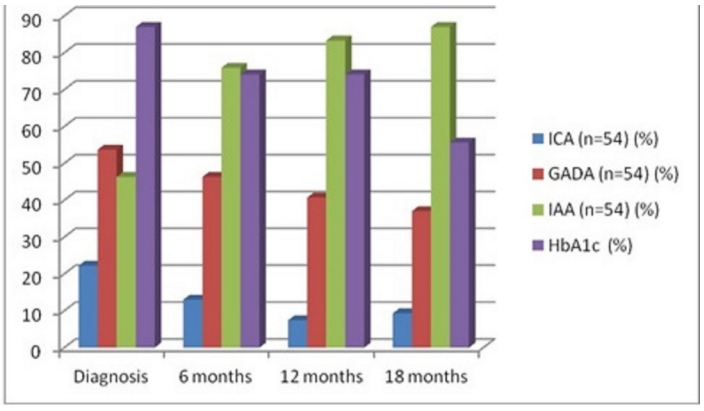

Figure 1. Change of antibodies of patients with Type 1 DM every 6 months

ICA Outcome

The ICA positivity rate at the time of diagnosis of the T1DM patients was 22.2 % (12/54), and the ICA positivity rate (7/54) at month 6 was 13%. The ICA positivity rate (4/54), which was examined 12 months after the diagnosis, was 7.4%. The ICA positivity rate at 18 months was 9.3% (5/54) (Figure 1). This change was not

significant (p>0.05) The ICA positivity rates in group A were 16.7%, 8.3%, 4.2%, and 4.2% for the 6-month intervals (Table 2). In group B, the ICA positivity rates were 26.7%, 16.7%, 10%, and 13.3%, respectively (Table 3).

GADA Outcome

The GADA positivity rate at the time of diagnosis of the T1DM patients was 53.7% (29/54), and the GADA positivity rate at month 6 was 46.3% (25/54) (p > 0.05). The GADA positivity rate (22/54) detected 12 months after diagnosis was 40.7%. The GADA positivity rate (20/54) measured at month 18 was 37% (Tablo 1, figure 1). GADA positivity rates in group A were 54.2%, 37.5%, 37.5%, and 29.2% at the 6-month intervals (Table 2). The GADA positivity rates in group B were 53.3%, 53.3%, 43.3%, and 43.3%, respectively (Table 3). While the diagnosis was negative in 12 patients, the GADA and ICA titers turned positive. Overall, 8 of these 12 patients experienced a simultaneous increase in HbA1c value.

IAA Outcome

The IAA positivity rate of patients with T1DM at the time of diagnosis was 46.3 % (25/54), and the IAA positivity rate at month 6 was 75.9 % (41/54) (p = 0.000). The IAA positivity rate examined 12 months after the diagnosis was 83.3% (45/54). The IAA positivity rate observed during month 18 was 87% (47/54) (Tablo 1, figure 1). The increase in IAA rate was statistically significant (p = 0.001). The IAA positivity rates in group A were 62.5%, 87.5%, 87.5%, and 87.5%, respectively, and those in group B were 33.3%, 66.7%, 80%, and 86.7%, respectively (Table 2 and 3).

Table 2. Tracking of antibody positivity percentages of group A patients, percentages of patients with HbA1c values higher than 7% and mean HbA1c levels at 6-month intervals

	ICA (n=24) (%)	GADA(n=24) (%)	IAA (n=24) (%)	HbA 1c(n=24) (%)	HbA1c(n=24)
Diagnosis	4 (16.7)	13 (54.2)	15 (62.5)	21 (87.5)	9.99
6 months	2 (8.3)	9 (37.5)	21 (87.5)	17 (70.8)	8.86
12 months	1 (4.2)	9 (37.5)	21 (87.5)	16 (66.7)	8.10
18 months	1 (4.2)	7 (29.2)	21 (87.5)	11 (45.8)	7.8
Diagnosis - 6 months	p=0.625	p=0.388	p=0.70	p=0.289	p=0.118
Diagnosis - 12 months	p=0.375	p=0.388	p=0.70	p=0.227	p=0.005
Diagnosis - 18 months	p=0.375	p=0.146	p=0.70	p=0.021	p=0.002

Table 3. Tracking of antibody positivity percentages of group B patients, percentages of patients with HbA1c values higher than 7% and mean HbA1c levels at 6-month intervals

	ICA (n=30) (%)	GADA(n=30) (%)	IAA (n=30) (%)	HbA 1c(n=30) (%)	HbA1c(n=30)
Diagnosis	8 (26.7)	16 (53.3)	10 (33.3)	26 (86.7)	13.4
6 months	5 (16.7)	16 (53.3)	20 (66.7)	23 (76.7)	9.8
12 months	3 (10)	13 (43.3)	24 (80)	24 (80)	10
18 months	4 (13.3)	13 (43.3)	26 (86.7)	19 (63.3)	9.29
Diagnosis - 6 months	p=0.453	p=1.000	p=0.02	p=0.508	p=0.0001
Diagnosis - 12 months	p=0.180	p=0.549	p=0.01	p=0.688	p=0.001
Diagnosis - 18 months	p=0.344	p=0.549	p=0.00	p=0.065	p=0.0001

Discussion

It is thought that people with a genetic predisposition to T1DM develop beta cell damage due to autoimmune inflammation [6–10]. Long-term follow-up of twins and first-degree relatives of patients with T1DM have revealed that humoral or cellular autoimmune activity occurs before clinical manifestations appear, indicating that beta cell destruction began years earlier [11–13]. The period of insulitis and antibody positivity may be prolonged before the clinical signs of the disease appear. The best markers for this period are autoantibodies, and the most important of these are ICA, IAA, and GADA. Autoantibodies are used to predict the onset time and pathogenesis of the disease, and to monitor beta cell function to show the autoimmune process that occurs during the early stages of pancreatic damage (9–18 months) in diabetic patients [14].

HbA1c level is used during the follow-up of diabetic patients, as it reveals the blood glucose level 2–3 months previously [15]. Microvascular complications of diabetes decrease with HbA1c level within normal limits. Therefore, HbA1c is accepted as the gold standard for diabetes control [16]. Studies have shown that by decreasing the HbA1c value to 7%, renal, retinal, and neurological complications decrease [17].

Redondo et al. found no relationship between the HbA1c level at

the end of the first year following the diagnosis and the number of positive antibodies at the time of diagnosis [18]. Hoeldtke et al. [19] studied 35 patients with DM1. They measured GADA, ICA, and HbA1c during the second year after the diagnosis. They found a weak association between ICA and HbA1c. Feeney et al. [20] evaluated 232 patients between 9 months and 14.9 years of age. Antibody titers were examined on day 14 after the diagnosis, and the ICA positivity rate was higher in patients >5 years of age. In the present study, the decrease in ICA value observed at diagnosis is consistent with the decrease in the HbA1c value. The ICA results were reevaluated according to age group. Although there was a decrease in ICA positivity rates in group A (≤5 years) and group B (>5 years) according to the results at the time of diagnosis, this change was not statistically significant. The percentage of positivity was lower at 18 months than at diagnosis. The slight increase in the percentage of antibody positivity at the end of the 18th month is thought to be due to the subsequent detection of ICA positivity in a patient in group B. The positivity rate in group B tended to be higher than in group A. In our study, the decrease in the ICA positivity rate was associated with good control of blood sugar. It was observed that the decrease in ICA antibody positivity in patients reflected to the patient clinic as a good control of blood sugar. It may be thought that this situation may cause a decrease in the complication rates that may develop in the future.

Hoeldtke et al. reported an increase in GADA titer 1 year after diagnosis that was associated with an increase in HbA1c level [19]. Zimmet et al. reported that GADA is detected at a higher frequency in European individuals than in Asian individuals [21]. Chang et al. determined that the frequency of GADA in Taiwanese DM1 patients is correlated with the age of onset; in addition, the GADA positivity rate increased with age [4]. Rodacki et al. conducted an epidemiological study and reported GADA in 45% of Brazilian patients with T1DM [22]. In that study, no significant differences were detected between age groups, as in our study. In a previous study, GADA (66.7%) was highly prevalent in a group of Italian T1DM patients diagnosed after the age of 20 years. In combination, GADA+ICA was 71.9% positive. GADA and ICA together increased the sensitivity of the tests, and this combination of antibodies was recommended for a differential diagnosis [23]. Combined islet autoantibody testing against glutamic acid decarboxylase (GADA), islet antigen 2 (ICA), and zinc transporter 8 (ZnT8) has been used in the differential diagnosis between autoimmune Type 1 diabetes and monogenic diabetes [24].

According to the results at the time of the diagnosis, a decrease in GADA positivity rates was detected in the group A. That same was found in the group B. No significant difference in positivity rates was observed between the age groups. The ability to detect GADA in the blood for many years allows it to be used during follow-up. In our study, GADA positivity rates tended to decrease in patients. The decrease in antibody titers in group A was faster than in group B. Patients with low GADA titer had good blood glucose control. Therefore, attention should be paid to irregularities in blood glucose monitoring in patients with positive GADA titer.

There was a significant increase in the IAA positivity rate evaluated in our study (p=0.001). Despite the decrease in the HbA1c value, no clinically significant relationship was observed with the increase in the IAA value. This increase in IAA, while other antibody titers decrease, is thought to be due to the use of exogenous insulin. As the age at diagnosis increased, the IAA positivity rate decreased. Antibody positivity was higher in group A patients at the time of diagnosis. A significant difference was observed in the positivity rates between the two groups separated by age (p=0.03). Accordingly, the preference of IAA in those <5 years may be more rational for selecting the diagnostic test. Since the positivity rates increase with the use of exogenous insulin, its use in follow-up is not cost effective. Borg et al. studied antibody titres in 75 children with TIDM at the time of diagnosis and 1-10 years later [3]. In that study, IAA was higher in patients <3 years of age. As in our study, the rate of positivity decreased with increasing age in that study. In another study, IAA was 90% positive in patients <5years [5]. The combination of IAA and GADA is more sensitive and that is why it is important to take age into account when deciding the antibody combination used for differential diagnosis and follow-up of first-degree relatives in a risk group. The positive rate of the combination of IAA and GADA increased to 98.2%.

Conclusion

As a result, the decrease in ICA and GADA positivity rates during the follow-up period was associated with the decrease in the HbA1c value. Therefore, decreases in ICA and GADA titers have been associated clinically with good glycemic control. The age group is important in the follow-up of first-degree relatives at risk of diabetes and in the selection of antibodies in differential diagnosis. Preference of IAA and GADA in the group ≤5 years old and ICA and GADA in patients >5 years old may decrease screening costs.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The Ethics Committee of Inonu University Faculty of Medicine approved this study (permission number 2006/12).

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