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The effect of autoimmunity on the development time of microvascular complications in patients with type 1 diabetes mellitus

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Background: Type 1 diabetes mellitus (DM) is an autoimmune disease with chronic complications that is becoming more frequent as life expectancy of diabetics has increased owing to improved methods of detection and better management. In this study, we investigated whether the presence of autoimmunity can be used in predicting the development time of microvascular complications.

Material/Methods: Our study included 52 patients with type 1 diabetes mellitus (DM). The subjects had developed microvascular complications and they had been tested for anti-GAD (glutamic acid decarboxylase) antibodies and/or islet-cell antibodies (ICA). In the assessment of microvascular complications, we used ocular fundus examination, electromyography (EMG), and 24-h urine microalbuminuria tests.

Results: Of the patients included in the study, 30 were female and 22 were male. Of all patients characterized for the existence of diabetic complications, 36 of 52 had both diabetic retinopathy and diabetic nephropathy, 5 patients had diabetic neuropathy, and 11 patients had diabetic retinopathy only. At the diagnosis of diabetes, 20 in 52 patients tested negative for autoantibodies (anti-GAD and anti-ICA), while 32 of 52 tested positive for anti-GAD and/or anti-ICA. The mean HbA1C level of autoantibody-negative patients was 7.7%, while antibody-positive patients had slightly higher HbA1c levels (7.9%). However, this difference was not statistically significant ($p>0.05$). The mean development time of microvascular complications in autoantibody-positive patients was calculated as 11: 40±6.46 years, and in patients with negative autoimmunity results it was 10.91±6.70 years.

Conclusions: The presence of diabetes-related autoantibodies (DRAs) in patients with type 1 diabetes mellitus does not have a significant effect on the development time of diabetic microvascular complications.

MeSH Keywords: Autoantibodies • Diabetes Complications • Diabetes Mellitus, Type 1

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Background

Diabetes mellitus (DM) is a chronic progressive disease characterized by hyperglycemia with disturbances of carbohydrate, protein, and lipid metabolism. DM is the most common endocrine disorder, with an increasing prevalence all over the world [1]. According to data from the U.S. Centers for Disease Control and Prevention, the prevalence of type 1 DM is 0.017% in the United States and about 13 000 Americans are diagnosed with type 1 diabetes mellitus every year [2].

The onset of the disease occurs when the immune system attacks and destroys insulin-producing beta cells found in the pancreas. In this stage, antigen-induced T-lymphocytes and macrophages constantly attack the beta cells [3–6]. From the pathological standpoint, this autoimmune attack on pancreatic beta cells is a process called insulitis. The basic indicators of insulitis are circulating islet cell antibodies (ICA), insulin antibodies (IAA), protein tyrosine phosphatase antibodies (IA-2), and glutamic acid decarboxylase (GAD) antibodies. It is widely accepted that type 1 DM is associated with a genetically determined modification in immunity, which leads to the destruction of pancreatic beta cells.

Today, the number of elderly diabetic patients is increasing, mostly because of increased longevity of the diabetic population. Thus, the incidence of microvascular complications (neuropathy, retinopathy, and nephropathy) increases with the duration of diabetes, which calls for a solution effective in reducing the incidence of diabetic complications.

The purpose of this study was to determine to what extent the presence of autoimmunity can be used in predicting the development time of microvascular complications.

Material and Methods

We included 52 patients with type 1 DM (based on the American Diabetes Association's (ADA) diagnostic and classification criteria [7] issued in 2007) attending the Outpatient Diabetes Clinic of the Ministry of Health Okmeydanı Training and Research Hospital between January 2009 and September 2009. The subjects had developed microvascular complications (diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy) and they had been tested for anti-GAD (glutamic acid decarboxylase) antibodies and/or islet-cell antibodies (ICA). Measurement of anti-glutamic acid decarboxylase antibody (anti-GAD) in serum was conducted by IRMA (immunoradiometric assay) method and the reference range was accepted as 0–1 U/ml. Islet cell antibody (ICA) measurements in serum were done by IF (indirect immunofluorescence) method with a reference range considered negative.

We recorded patient details such as age, sex, age at disease onset, treatments received for diabetes, as well as other treatments for additional diseases and accompanying diseases (retinopathy, nephropathy, and neuropathy). Development time of microvascular complications was also measured, and patients were compared in terms of autoantibody positivity and development time of microvascular complications.

We measured hemoglobin A1c values by high-performance liquid chromatography (HPLC) method using a Tosoh Automated Glycohemoglobin Analyzer with Tosoh HbA1c kits and we established the reference range as 4.6–5.2%.

In the evaluation of nephropathy, 24-h urine samples were studied by immunoturbidimetric method using Beckman Coulter microalbuminuria kits on a Beckman Coulter Syncron Lx device. Albumin excretion rates below 30 mg/24-h were considered normoalbuminuria, while levels between 30 and 300 mg/24-h were considered microalbuminuria, and values above 300 mg/24-h were considered macroalbuminuria. The subjects whose test results showed 30 mg/24-h and higher values at least twice within a 6-month period were defined as microalbuminuric patients.

In the evaluation of neuropathy, we used an electromyography device (EMG) – the Nihon Kohden-Neuropack MEB-5504K – and neurologic consultations were obtained. We used direct fundus examination findings for assessment of diabetic retinopathy following ocular consultations.

In the evaluation of retinopathy, ocular fundus examination findings were used and ophthalmology consultations were obtained.

Statistical analysis

Data was classified as sex, autoantibody existence, microvascular complication development, development time of microvascular complications, and HbA1C values. The data obtained during the study were compared by using Student's t-test analysis, because there was no normal distribution. For all tests, we considered $p<0.05$ to be statistically significant.

Results

The study included 52 patients with type 1 DM who developed microvascular complications: 30 females (57.7%) and 22 males (42.3%). Comparison of mean values within each sex group revealed no statistically significant differences between males and females ($p>0.05$). The mean age of the patients was calculated as 33.94±8: 45.

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Table 1. Analysis of development times of microvascular complications based on the presence of autoimmunity by Student's t-test.

Autoimmunity n/%	Time to development of microvascular complication (in years) mean ±SD (standard deviation)	p
Negative 20/(%38.5)	11.4±6.46	0.794
Positive 32/(%61.5)	10.91±6.70	

At the diagnosis of diabetes, 20 patients (38.5% of the sample) tested negative for autoantibodies (anti-GAD and anti-ICA), while 32 (61.5%) of patients tested positive for anti-GAD and/or anti-ICA. Thirty-six patients (69.2%) had developed diabetic nephropathy and diabetic retinopathy, 11 patients (21.2%) had diabetic retinopathy, and 5 patients (9.6%) had diabetic neuropathy.

In autoantibody-negative patients, the mean HbA1C level was 7.7%, while antibody-positive patients had slightly higher HbA1c levels (7.9%), but this difference was not considered statistically significant (p>0.05).

Patients were compared in terms of autoantibody positivity and development time of microvascular complications. The mean time to onset of diabetes-related microvascular complications in patients with positive autoimmune markers was 11: 40±6.46 years. The mean time to development of microvascular complications in patients with negative autoimmunity was calculated as 10.91±6.70 years. When the results of both autoimmunity positive and negative groups were analyzed by Student's t-test, no statistically significant difference between the 2 groups was found with respect to the time to development of microvascular complications (p>0.05) (Table 1).

Discussion

Patients with diabetes mellitus may develop chronic hyperglycemia and capillary membrane changes resulting from other metabolic disorders, as well as accelerated atherosclerosis and microvascular and macrovascular complications during the clinical follow-up period [8–14]. Today, the longer life expectancy of the diabetic population has significantly increased the incidence and prevalence of diabetes-related chronic complications. Therefore, identifying and addressing the risk factors associated with microvascular complications in type 1 DM and eliminating or reducing the known risks in these patients is crucial [13,14]. For this reason, in our study, we focused on the microvascular complications of type 1 DM and examined the role of autoantibodies in patients with type 1 DM on the development time of microvascular complications. We also aimed to determine whether the presence of autoantibodies is a potentially useful prognostic marker. There are only a limited number of studies examining the prognostic significance of positivity for autoantibodies [15–19].

Roll et al. examined the prevalence of GAD-ab and ICAs in 146 insulin-dependent diabetes DM with different disease duration (2–52 years, median 13.2 years), and they detected anti-GAD positivity as 37% (54 of 146) and ICA positivity as 22% (32 of 146), thus concluding that the presence of autoantibodies is not related to the development time of diabetic complications [15]. Zanone et al. reported that autoantibodies to GAD were present in 56% of diabetic patients with neuropathy, 57% of long-standing patients without complications, 69% of the short-duration diabetic patients with no complications, 78% of the recently diagnosed diabetic patients, and 13% of the non-diabetic neuropathic patients [16]. In parallel with these results, they found that there is no correlation between anti-GAD antibody positivity and the presence of diabetic neuropathy [16]. Ko et al. examined the relationship between antibodies to GAD and diabetic microangiopathic complications in diabetic patients, dividing them into 2 separate groups as anti-GAD-positive and anti-GAD-negative patients, and they reported that both groups had similar prevalence of microangiopathic complications [17]. Glastras et al. demonstrated that the presence of diabetes-associated autoantibodies did not predict the development of microvascular complications [18]. In our study, we found similar results to those reported in these studies, suggesting that the presence of autoimmunity has no significant effect on the development of microvascular complications in patients with type 1 DM.

Szepietowska et al. evaluated the presence of late complications in 41 hospitalized subjects with latent autoimmune diabetes (LADA) by measuring anti-GAD, anti-ICA, and anti-IA-2 (protein tyrosine phosphatase antibodies) levels, and found a higher incidence of microangiopathy in the autoantibody-positive patients [19]. Their results differ from our findings and from those reported by several of the studies mentioned above.

Our study has some limitations. We did not record and classify the blood pressure, creatinine, antihypertensive therapy, antidiabetic therapy, or body mass index data of the patients. More accurate results would have been obtained by performing statistical analysis to define more detailed differences between these parameters with positive and negative autoimmunity.

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Conclusions

Based on our study findings, we can suggest that positivity for autoantibodies associated with type 1 DM plays no significant role in the development time of microvascular complications. Further studies in this field are needed to confirm these findings before a definitive conclusion can be reached.

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