Comprehensive Evaluation of Sibling Cases with Type 1 Diabetes

Tip 1 Diyabetli Kardeş Olguların Kapsamlı Bir Şekilde Değerlendirilmesi

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ABSTRACT

Objective: Type 1 diabetes mellitus (T1DM) is a polygenic disease influenced by genetic, environmental, immunological factors.There are few studies regarding siblings with T1DM.We aimed to evaluate the presentation, diagnosis, follow-up, sociodemographic characteristics of sibling T1DM cases.

Material and Methods: We retrospectively reviewed characteristics of sibling cases followed with T1DM between January 2005 and May 2017.

Results: The prevalence of T1DM sibling diabetes in our clinic was 5.9%.We included 17 siblings (a total of 34 cases) who had diagnosis and follow-up data. One of the siblings was a twin.There were no statistically significant differences between the ages at diagnosis, presenting symptoms, duration of symptoms before diagnosis, glucose/C-peptide values at diagnosis, average HbA1c values in the first five years of follow-up, or hospitalization rates in the first five-years post-diagnosis between the first and second diagnosed siblings.Despite having a child diagnosed with T1DM, 23.6% of families had a second child diagnosed with diabetic ketoacidosis.Variations in antibody positivity were observed among siblings, there were no similarities between celiac disease, Hashimoto's thyroiditis.Vitamin D levels were significantly lower in siblings diagnosed secondarily.

Conclusion: Our study is significant for being conducted at a reference center with a high number of diabetes patients under follow-up, for filling a gap in the literature with a detailed evaluation of sibling cases with T1DM.It serves as a comprehensive pilot study examining the manner, order of diagnosis, clinical, laboratory, and follow-up data of siblings with diabetes.There is a need for prospective studies with a larger number of sibling cases to further explore this topic.

Key Words: Type 1 diabetes mellitus, Diabetic siblings, Vitamin D

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ÖZ

Amaç: Tip 1 diyabetes mellitus (T1DM) genetik, çevresel ve immünolojik nedenlere bağlı poligenik bir hastalıktır. Kardeş T1DM'ler ile ilgili az sayıda çalışma vardır. Çalışmamızda, izlemimizdeki kardeş T1DM olguların başvuru, tanı, izlem, sosyodemografik özelliklerini değerlendirmeyi, olası ortak ve farklı özellikleri tespit etmeyi amaçladık.

Gereç ve Yöntemler: Ocak 2005-Mayıs 2017 arasında T1DM tanısı ile izlemimizde olan, kardeş olguların; başvuru, klinik, laboratuar, izlem, sosyoekonomik özellikleri retrospektif olarak dosya verilerinden tarandı.

Bulgular: Kliniğimizde T1DM kardeş diyabet sıklığı %5.9'du. Tanı ve izlem verileri olan T1DM'li 17 kardeş (toplam 34 olgu) çalışmaya dahil edildi. Kardeşlerden biri ikiz idi. İlk ve ikinci tanı alan kardeşlerin tanı yaşları, başvuru yakınmaları, tanı öncesi yakınma süreleri, tanıdaki glukoz/C-peptid değerleri, takipteki ilk beş yıl ortalama HBA1c değerleri, tanı sonrası ilk beş yıllık izlemde hastaneye yatış sayıları arasında istatistiksel olarak anlamlı fark saptanmadı. Evde T1DM tanılı çocuk olmasına rağmen, ailelerin %23.6'sında ikinci çocuğun da diyabetik ketosiadoz (DKA) ile tanı aldığı, T1DM'li kardeşler arasında antikor pozitiflikleri açısından farklılıklar olduğu, tanı-takipte Çölyak hastalığı-Hashimoto tiroiditi açısından benzerlik olmadığı, ikinci tanı alan kardeşlerin D vitamin düzeylerinin ilk tanı alan kardeşlerden anlamlı düzeyde düşük olduğu saptandı.

Sonuç: Çalışmamız; takipteki diyabetli hasta sayısının oldukça yüksek olduğu referans bir merkezde yapılmış olması, literatürde kardeş T1DM'ler ile ilgili detaylı bir değerlendirmenin bulunmaması, kardeş diyabetli olguların tanı alma şekli, tanı alma sırası, klinik, laboratuar ve izlem verilerinin değerlendirildiği kapsamlı bir pilot çalışma olması nedeni ile önemlidir. Konu ile ilgili daha fazla sayıda kardeş olgu ile yapılacak prospektif çalışmalara ihtiyaç duyulmaktadır.

Anahtar Sözcükler: Tip 1 diyabetes mellitus, Diyabetli kardeş, D vitamini

INTRODUCTION

Diabetes mellitus (DM) is a widespread, chronic, endocrine, metabolic disease characterized by biochemical elevation of blood glucose levels due to insufficient insulin secretion or ineffectiveness (1). This disrupts the balance in carbohydrate, protein, fat metabolism, ultimately leading to inappropriate high blood glucose levels during fasting and after meals, resulting in DM (2). Diabetes characterized by permanent insulin deficiency due to autoimmune damage to pancreatic beta cells is the most common type of diabetes in childhood and is referred to as type 1 diabetes mellitus (T1DM) (2).

T1DM is a complex autoimmune disease arising from the interaction of genetic and environmental factors (3). However, the exact contributions of these factors to the disease process remain unclear. Studies investigating the impact of these factors have focused on twin and sibling cases (4, 5). Even siblings raised in the same environmental conditions, identical twins with the same genetic makeup, siblings with the same disease can exhibit different courses and characteristics.

The evaluation of socio-economic, clinical, laboratory, follow-up data related to T1DM, especially among sibling cases, could generate new insights. There is currently a lack of detailed evaluation in the literature specifically focusing on sibling diabetes. Factors such as the frequency of diabetes among siblings, how siblings present for diagnosis, which sibling is diagnosed first (the period of disease onset), clinical course, metabolic control during follow-up have not been thoroughly assessed in the literature to date. Addressing these aspects could lead to new understandings and potentially improve management strategies for T1DM in familial contexts.

In our study, we aimed to evaluate various aspects of siblings with T1DM under follow-up. Specifically, we aimed to assess their clinical presentation at diagnosis, the sequence of diagnosis among siblings (period of disease onset), clinical course, initial laboratory findings upon presentation, metabolic control during follow-up, the potential impact of family education level on metabolic control. Additionally, our objective was to identify common and distinct characteristics among sibling diabetes cases.

MATERIAL and METHODS

Between January 1, 2005, and April 30, 2017, siblings diagnosed and followed-up with T1DM at our clinic were retrospectively screened from medical records. This Study Dr. Sami Ulus Gynecology and Obstetrics and Gynecology Child Health and Diseases Training and Research Hospital is academically approved (5030/20.04.2016).

The demographic characteristics, symptoms and their duration prior to presentation, sequence of diagnosis among siblings, anthropometric measurements at presentation, pathological findings on physical examination, glucose, insulin, C-peptide, hemoglobin A1C(HbA1c) levels at presentation and during follow-up, insulin antibodies (IAA), antibodies to glutamic acid decarboxylase (anti-GAD), islet cell antibody (ICA) levels at diagnosis and follow-up, 25-hydroxy vitamin D levels, clinical presentation at diagnosis (hyperglycemia, hyperglycemia with ketosis, ketoacidosis, etc.), length of hospital stays, treatments used at discharge and their doses (in units/kg/day for insulin), annual average HbA1c values were recorded in the study. Cases were also evaluated for honeymoon periods, celiac serology, and autoimmune thyroid diseases. Patients' medical and family histories, socio-economic characteristics were obtained from medical records.

The annual HbA1c values were calculated by averaging HbA1c measurements taken every three months and average HBA1c <7.5% was considered as good metabolic control, 7.6-9% as

moderate metabolic control, >9% as poor metabolic control (6). The honeymoon period is defined as an insulin dose of <0.5 units/kg/day (7).

The data were analyzed using SPSS version 23.0 for Windows (IBM Corp, Armonk, NY, USA). Descriptive statistics were reported as mean and standard deviation (SD) or median (minimum-maximum) for continuous variables, and as numbers and percentages for nominal variables. For non-normally distributed data, values were presented as median and interquartile range (IQR). The chi-square test was used to examine the relationship between two categorical variables. All clinical, laboratory, and endocrinological values were defined using descriptive statistics, and comparisons between parametric and nonparametric data were conducted using Student's t-test and Mann-Whitney U test, respectively. Spearman or Pearson correlation analyses were used to evaluate relationships between parameters. A 'p' value of <0.050 was considered statistically significant.

RESULTS

The frequency of sibling diabetes among all T1DM cases was 5.9%. Of the 40 cases diagnosed with T1DM (20 siblings in total), 34 cases with diagnostic and follow-up data (17 siblings in total) were included in the study. General characteristics of siblings with T1DM were given in Table I.

The median age at diagnosis was 8.8 years (IQR 4.3-12.5 years). There was no statistically significant difference between the ages at diagnosis of the first and second diagnosed siblings (p=0.580). Among the 17 sibling pairs, the older sibling was diagnosed first in 13 cases, the younger sibling was diagnosed first in three cases, and other cases were identical twins.

The median duration of symptoms before diagnosis was 8.5 (IQR 7-30) days. There was no statistically significant difference in the duration of symptoms between the first and the second diagnosed siblings (p=0.060).

There was also no significant difference between the first and the second diagnosed siblings in terms of the distribution of hyperglycemia, hyperglycemia with ketosis, and diabetic ketoacidosis (DKA) at diagnosis (p=0.270). Furthermore, there was no significant difference between the ages of siblings diagnosed with DKA (6.5±4.4) compared to those diagnosed with hyperglycemia/hyperglycemia with ketosis (9.3±4.5) (p=0.090).

In seven (41.2%) of the sibling pairs, both siblings were diagnosed with hyperglycemia, in three (17.2%), one sibling was diagnosed with hyperglycemia and one sibling was diagnosed with ketosis, in three (17.2%), one sibling was diagnosed with hyperglycemia and one sibling was diagnosed with DKA, and in four (23.6%), both siblings were diagnosed with DKA.

It was determined that among the second diagnosed siblings, there was a higher incidence of diagnosis with hyperglycemia. Conversely, the incidence of diagnosis with DKA was found to be lower among the second diagnosed siblings compared to the first diagnosed siblings.

The most common symptoms were polyuria and polydipsia. There was no statistically significant difference between the presenting complaints among the first and second diagnosed siblings.

The median duration between the diagnoses of two siblings was 5 years (IQR 2-7.3). Among the siblings, the duration between diagnoses was ≤12 months in three (17.7%) siblings, 13 months to 5 years in eight (47%) siblings, and >5 years in six (35.3%) siblings.

Three of the patients (8.8%) had a history of prematurity, and eight (23.5%) were born by C/S. Consanguinity was present in 29.4% (n=5) of the families. There was a family history of T1DM in 2 families (11.8%) and a history of T2DM in 14 families (82.4%). There were no significant differences between the first and second diagnosed siblings in terms of prematurity, birth by cesarean section, or duration of breastfeeding.

The evaluation based on the number of siblings and birth order of the cases is presented in Table II.

There was no statistically significant difference in height SDS, weight SDS, and BMI SDS between the first and second

Table I: General characteristics of siblings with Type 1 Diabetes

	T1DM	First Diagnosed	Second Diagnosed	p
Sex, n (%) 2 male siblings 2 female siblings 1 female 1 male	9 (53) 4 (23.5) 4 (23.5)			
Median age at diagnosis (IQR)	8.8 (4.3-12.5)	7 (5.3-11.5)	8.9 (3.5-14)	0.580*
Duration of symptoms before diagnosis, days median (IQR)	8.5 (7-30)	15 (7-30)	7 (7-15)	0.060*
Mode of diagnosis, n (%) Hyperglycemia Hyperglycemia with ketosis Diabetic ketoacidosis	 20 (58.8) 3 (8.8) 11 (32.4)	 9 (53) 1 (5.9) 7 (41.1)	 11 (64.7) 2 (11.8) 4 (23.5)	0.270†

**: Student t Test, †: Chi_square Test*

Table II: Evaluation of Sibling T1DM Cases According to Number of Siblings and Sibling Order

	1st child	2nd child	3rd child	4th child	5th child	6th child
1st siblings	T1DM	T1DM	Healthy			
2nd siblings	T1DM	T1DM				
3rd siblings	Healthy	Healthy	T1DM	T1DM		
4th siblings	T1DM	Healthy	T1DM			
5th siblings	Healthy	T1DM	Healthy	T1DM		
6th siblings	T1DM	T1DM				
7th siblings	T1DM	T1DM	Healthy	Healthy		
8th siblings	T1DM	T1DM				
9th siblings	T1DM	T1DM	Healthy			
10th siblings	T1DM	Healthy	T1DM	Healthy	Healthy	Healthy
11th siblings	Healthy	T1DM	T1DM			
12th siblings	T1DM	T1DM	Healthy			
13th siblings	T1DM	T1DM				
14th siblings	T1DM	T1DM	Healthy			
15th siblings	Unknown					
16th siblings	Unknown					
17th siblings	T1DM	Healthy	T1DM			

diagnosed siblings. While there were no significant differences found in glucose and C-peptide levels at diagnosis between the first and second diagnosed siblings, the second diagnosed siblings had significantly lower levels of 25-hydroxy vitamin D and HbA1c at diagnosis. There was no statistically significant difference in insulin doses at discharge and honeymoon periods between the first and second diagnosed siblings. However, the hospitalization duration was significantly shorter for the second diagnosed siblings, whereas there was no significant difference in the number of hospitalizations during follow-up (Table III).

No significant differences were found in the average HbA1c values during the first five-years of follow-up among the siblings. When examining the annual metabolic control, no significant differences were observed between the siblings in the first three years after diagnosis. However, in the fourth and fifth years, it was found that the metabolic control of the second diagnosed siblings deteriorated compared to the first diagnosed siblings.

The cases were evaluated for diabetes autoantibodies at diagnosis, revealing that 11.8% (n=4) tested positive for anti-insulin antibodies, 35.3% (n=12) for anti-GAD antibodies, and 35.3% (n=12) for anti-islet cell antibodies. During the five-year follow-up, it was observed that one case became negative for anti-islet cell antibodies, one for anti-insulin antibodies, and one for anti-GAD antibodies, while three cases became positive for GAD antibodies and one for islet cell antibodies.

In two siblings, one was positive for anti-insulin antibodies at diagnosis while the other was negative. In eight siblings, one was positive for anti-GAD antibodies at diagnosis while the other was negative. In four siblings, one was positive for anti-islet cell antibodies at diagnosis while the other was negative. Differences were found in antibody positivity among siblings. The only pair of siblings who tested positive for all three diabetes autoantibodies were twins.

While none of the siblings were diagnosed with celiac disease at the time of diagnosis, one case was diagnosed with celiac disease during follow-up, initially showing positive tissue transglutaminase (tTG) IgA (90.6 U/ml) at the time of diagnosis. This case had negative tTG IgG and EMA but was HLA-DQ2 positive. During follow-up, 26.5% (n=9) of the cases were diagnosed with Hashimoto's thyroiditis, 88.9% (n= 8) of the cases were girl. Thyroid function tests of two of the patients with Hashimoto's thyroiditis were also abnormal at the time they were diagnosed with T1DM.

The analysis indicated no significant difference in the occurrence of DKA at diagnosis between children of parents with higher education (high school and above) and those with lower education (middle school and below) (mothers p=0.7 and fathers p=0.860). However, children of mothers with elementary school education were found to be hospitalized significantly more frequently compared to children of mothers with middle and high school education (p=0.010). There was no significant correlation found between father's education level and duration of hospital stay after diagnosis or number of hospitalizations during follow-up. Similarly, there was no significant correlation found between parental education levels and average HbA1c levels during the first, second, third, fourth, and fifth years of follow-up.

While the monthly income of 10 of the families was at or below the minimum wage, the income of four of them was above the minimum wage. Three families did not provide monthly income information. No significant correlation was detected between

Table III: Anthropometric characteristics and laboratory data of siblings with T1DM at diagnosis

	All cases	First diagnosed siblings	Second diagnosed siblings	p*
Anthropometric characteristics†				
Body weight SDS	-1.26±0.94	-1.42±0.94	-1.13±0.96	0.44
Height SDS	-0.32±1.09	-0.57±1.14	-0.11±1.05	0.29
BMI SDS	-1.36±1.23	-1.72±1.49	-1.1± 0.9	0.18
Laboratory data‡				
Glucose (mg/dl)	476.1±239.2 (109-1008)	523±235 (269-1008)	432.5±243.3 (109-847)	0.34
C peptide (ng/ml)	1.67±4.76 (0.01-21.8)	2.94±7.62 (0.01-21.8)	0.83±0.59 (0.19-2)	0.46
HbA1c (%)	10.8±2.4 (5.6-14.9)	11.8±2.2 (7.4-14.9)	9.9±2.2 (5.6-12.8)	0.04
25-OH D vit (ng/ml)	18.8±9.7 (9.4-51.2)	23.1±11.2 (10.6-51.2)	14.1±4.9 (9.4-26.2)	0.03
Duration of hospital stay, insulin dose at discharge, honeymoon period and number of hospitalizations during follow-up				
Length of hospital stay at diagnosis (days)‡	17±6.5 (3-27)	20±5 (10-27)	14.6±6.7 (3-27)	0.03
Insulin dose at discharge dozu (U/kg/day)†	0.89±0.4	0.87±0.36	0.9±0.47	0.88
Honeymoon period (months)‡	5.3±7.6 (0-24)	3.5±7.43 (0-24)	6.7±7.8 (0-24)	0.31
Number of hospitalizations during follow-up‡	1.9±1.4 (1-6)	2.3±1.7 (1-6)	1.6±0.9 (1-4)	0.18

: Student t Test, †:mean±SD, ‡:mean±SD (min-max)

family income level and average HBA1c levels in the first, second, third, fourth and fifth years.

When comparing groups where the first sibling was diagnosed with DKA and the second sibling was diagnosed with hyperglycemia, with groups where both siblings were diagnosed with DKA, similarities were found in terms of parental education levels, income status, number of children in the family, and the duration between children's diagnoses.

DISCUSSION

In our study, we evaluated all aspects of siblings with T1DM who were followed up in our clinic over a 12-year period. Although T1DM is a multifactorial disease, it is noteworthy that having a sibling with T1DM increases the risk compared to the general population (8), which led us to conduct this study in our center.

There is no detailed evaluation of sibling diabetes in the literature. In our study, we found that family education and awareness of diabetes may vary despite having a sibling with diabetes, it may be important to keep the vitamin D levels of siblings with T1DM at adequate levels, and close monitoring is required for the development of diabetes in the sibling, especially in monozygotic twin T1DM cases.

In the model developed by Mrena et al. (5) to predict the likelihood of T1DM developing in siblings of 701 children newly diagnosed with T1DM, it was reported that in a 15-year follow-up period, T1DM developed in 6.7% of the siblings. The empiric rate of T1DM when identical twin affected is %30-70 and the risk in dizygotic twins is approximately the same as in non-twin siblings (8). In our study, the frequency of sibling diabetes for T1DM was 5.9% and there was one monozygotic twin sibling.

Harjutsalo et al. reported that a young age at diagnosis in the index case, a paternal history of diabetes starting at a young age, male gender, advanced parental age at birth significantly increase the risk of T1DM in siblings (9). Mrena et al. (5) reported that besides age and family history of T1DM, information regarding autoantibody status and levels, HLA-DR-associated disease susceptibility, insulin secretion and sensitivity are effective in evaluating the time to diagnosis of T1DM in siblings of children newly diagnosed with T1DM and predicting the progression risk to T1DM in those siblings.

At the time of diagnosis, 32% of cases presented with DKA. In the SEARCH study group's analysis of the temporal trends of the prevalence of DKA in diabetes diagnosis, it was reported that the prevalence of DKA in young-onset type 1 diabetes remained stable at approximately 30% between 2002 and 2010. However, there was an observed increase in prevalence from 35.3% to 40% between 2010 and 2016 (10,11). While it was reported that the rate of diabetic ketoacidosis at the time of diagnosis in Turkey was around 50%, this rate reached up to 80% in the eastern region of Turkey (12,13). In 2010, the Turkish Society of Pediatric Endocrinology and Diabetes has implemented a School Diabetes Program to increase teacher awareness (14). Similarly, in Italy, a successful campaign that educated teachers, students, parents, and pediatricians reduced the presentation rate with DKA from 78% to 12.5% over eight years (15).

In our study, no significant difference was found in the mode of diagnosis (hyperglycemia, hyperglycemia with ketosis, or DKA) between siblings who were diagnosed first and subsequently. However, siblings diagnosed secondarily showed a higher incidence of hyperglycemia and a lower incidence of DKA compared to those diagnosed initially. This difference was attributed to the families receiving diabetes education during hospital stays and routine outpatient clinic visits for their first diagnosed children. On the other hand, the lack of significant differences in terms of duration of complaints before diagnosis among siblings suggests that despite parental education, there

may be limitations in recognizing diabetes symptoms early enough.

When comparing sibling groups where the first sibling was diagnosed with DKA and the second with hyperglycemia versus groups where both siblings were diagnosed with DKA, we found similar parental education levels, income status, number of children in the family, and time elapsed between diagnoses. Despite these similarities, the occurrence of severe conditions like DKA in both siblings could not be directly linked to these factors. This suggests that factors beyond those we examined, such as the importance placed on diabetes by the family, their ability to cope with and accept the disease, and individual sensitivities, may play crucial roles. Therefore, there is a need for studies involving more heterogeneous groups and larger numbers of siblings to further explore these factors.

Several studies have examined the relationship between parental consanguinity and the development of T1DM. In a study conducted in Saudi Arabia have reported no association between parental consanguinity and the development of T1DM (16). In a study examining the clinical characteristics of T1DM in our country, parental consanguinity was reported as 15.5% (17). In our study, the consanguinity rate was 30%.

Ardicli et al. (17) reported that 14% of T1DM cases had a family history of T1DM and this rate was %53.4 for T2DM. In our study, 12% of the cases had family members with T1DM other than their siblings.

No significant differences were found in glucose and C-peptide levels between those diagnosed first and later. However, HbA1c levels were lower in siblings diagnosed later. The development of overt diabetes clinical symptoms occurs after a certain stage of pancreatic beta-cell destruction, which explains the lack of differences in glucose and C-peptide levels. The lower HbA1c in siblings diagnosed later may be associated with increased family experience and awareness, despite no differences being found in presenting symptoms and duration of symptoms in our study.

It was found that there was no difference in the mean HbA1c values among the sibling cases during follow-up. This could be associated with siblings consuming similar foods, consistent care and sensitivity shown for the diabetic child, stability in parental controls over the years, and siblings assisting each other in diabetes monitoring. Similarly, the absence of differences in hospitalization rates among siblings during the first five-years post-diagnosis in T1DM cases may be linked to their similar glycemic control. The lack of significant metabolic control changes over the years, or at least no deterioration, may demonstrate the family's resilience in coping with chronic illness.

The serological markers of beta cell autoimmunity associated with diabetes are anti-GAD, tyrosine phosphatase-like insulinoma antigen 2 (IA2), IAA, beta cell-specific zinc transporter 8 autoantibody (ZnT8) (18). The presence of these autoantibodies indicates developing autoimmune disease and can be detected in the serum many years before diabetes manifests (18). The expression of autoantibodies is age-dependent. In children under the age of ten, expression of IAA and ZnT8 is more prevalent, whereas GAD and IA-2 are more commonly seen in older individuals. Additionally, GAD autoantibody is more prevalent in females (19). In the literature, it has been reported that anti-GAD antibodies are found in approximately 70-80% of cases at the time of diagnosis, while IA-2 antibodies are detected in about 60% of cases (8). In our study, anti-insulin antibody positivity was 11.8%, anti-GAD antibody positivity was 35.3%, and islet antibody positivity was 35.3% at the time of diagnosis. There is no study in the literature examining autoantibody positivity among siblings with diabetes and while antibody positivities could be expected to be similar in siblings, differences were observed between sibling pairs in our study.

Mrena et al. developed a model to predict the risk of developing T1DM in siblings of children newly diagnosed with T1DM, where the presence and levels of autoantibodies were reported to be effective predictors. Among 701 children newly diagnosed with T1DM, 47 siblings developed T1DM, out of which 38 initially had at least one diabetes-related autoantibody positivity. Seven siblings initially negative for autoantibodies later became positive before diagnosis (5).

In our study, we found that siblings diagnosed later had significantly lower vitamin D levels compared to those diagnosed first. However, in a study conducted in Denmark, which examined the vitamin D levels of children newly diagnosed with T1DM and their healthy siblings, no significant differences were found in the vitamin D levels between the siblings (20). Literature includes studies showing that vitamin D supplementation during infancy reduces the risk of developing T1DM (21,22). Additionally, Şahin et al. investigated polymorphisms in the vitamin D receptor and susceptibility to T1DM and reported that the BsmI BB, BsmI Bb, TaqI tt polymorphisms are associated with increased risk of T1DM, whereas the BsmI bb and TaqI TT polymorphisms have a protective effect against the development of T1DM in children (23). Literature includes studies on the relationship between autoimmunity, T1DM, vitamin D, and immunomodulation; however, there is no clear recommendation regarding maintaining adequate vitamin D levels in siblings of children with T1DM.

When the relationship between the parental education level of the cases and metabolic control was examined, contrary to expectations, no improvement in metabolic control was detected as the family education level increased. This situation was thought to be related to the fact that diabetes education in our clinic is given by paying attention to the education level of each parent. At the same time, no correlation was found between parental education level and the severity of clinical conditions (hyperglycemia, ketosis, and DKA) at the time of diagnosis. Contrary to our study, in studies conducted in Italy, it

was reported that metabolic control deteriorated as the parental education level and socio-economic status decreased (24) and that children of mothers with higher education levels had a lower probability of experiencing DKA at the time of diabetes diagnosis (25).

Many studies have shown that low socioeconomic status is associated with poor glycemic control (24,26). In our study, the monthly income of 10 families was at or below the minimum wage, there was no significant correlation between family income level and average HBA1c levels in the first five-years. This finding, which is not compatible with the literature, may be associated with the fact that our center's tailored diabetes education based on family income and living conditions, and that patients with low socioeconomic levels try to cope with diabetes with the same determination. It was thought that the determining factor in glycemic control was not socioeconomic status but individuals' ability to cope with the disease.

This study has potential limitations: Despite examining personal and family history characteristics, diabetes autoantibodies at diagnosis, and even though siblings were from large families, we did not identify a factor that would predict the development of T1DM in siblings, apart from vitamin D levels and twin status. Although our study was conducted in a large center where a substantial number of diabetic patients were followed, the limited number of sibling diabetes cases may have prevented the determination of these factors.

In conclusion, our study is important for several reasons: it was conducted in a reference center where the number of diabetic patients is significantly high, there is a lack of detailed evaluation of sibling T1DM in the literature, and it represents a comprehensive pilot study evaluating the manner of diagnosis, sequence of diagnosis, clinical, laboratory, and follow-up data of sibling diabetic cases. Consequently, there is a need for prospective studies involving a larger number of sibling cases. Our study suggests that among sibling diabetic cases, particularly noteworthy topics include the evaluation of vitamin D levels and the support system among siblings during diabetes management.

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