

Revisiting the Annual Incidence of Type 1 Diabetes Mellitus in Children from the Southeastern Anatolian Region of Turkey: A Regional Report

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What is already known on this topic?

The incidence of type 1 diabetes mellitus (T1D) in children has an increasing trend with a variable rate, depending on region and ethnicity.

What this study adds?

This is the first report examining the change in the incidence rate of pediatric T1D and the clinical and presentation characteristics of cases in Diyarbakır over a ten-year period. It is also the first study to report the incidence of T1D in the 0-18 age group in Diyarbakır.

Abstract

Objective: The incidence of type 1 diabetes mellitus (T1D) in children has an increasing trend globally, with a variable rate depending on region and ethnicity. Our group first reported T1D incidence in Diyarbakır in 2011. The aim of this study was to evaluate the current incidence rate of pediatric T1D in Diyarbakır, and compare the incidence, and clinical and presenting characteristics of more recent cases with those reported in our first report.

Methods: Hospital records of patients diagnosed with T1D in Diyarbakır city between 1st January 2020 and 31st December 2020 and aged under 18 years old were retrieved, and their medical data was extracted. Demographic population data were obtained from address-based census records of the Turkish Statistical Institution (TSI).

Results: Fifty-seven children and adolescents were diagnosed with T1D. Of those, 34 were female (59.6%), indicating a male/female ratio of 1.47. The mean age at diagnosis was 9.5 ± 3.9 years (0.8-17.9). TSI data indicated a population count of 709,803 for the 0-18 years age group. Thus the T1D incidence was $8.03/10^5$ in the 0-18 age group and was higher in the 0-14 age group at $9.14/10^5$. The cumulative increase in the incidence of T1D in the 0-14 age group was 26.9% suggesting an increasing rate of 2.7% per year. The frequency of presentation with diabetic ketoacidosis was 64.9%.

Conclusion: The annual incidence of pediatric T1D in Diyarbakır city increased from $7.2/10^5$ to $9.14/10^5$ within the last decade. The rate of annual increase was 2.7% in the 0-14 age group comparing this study with our earlier report, with a predominance in male subjects and a shift of peak incidence from the 5-9 year age group in the first study to the 10-14 year age group in this one.

Keywords: Type 1 diabetes mellitus, annual incidence, Southeastern Anatolian



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Introduction

Type 1 diabetes mellitus (T1D) is one of the most common chronic autoimmune diseases in children which is characterized by damage to insulin-producing pancreatic β cells (1). The incidence of T1D in children is globally heterogeneous, with the highest incidence rate in European countries and Middle-East and North Africa region and the lowest incidence rate in Eastern countries (2). For instance, the incidence rate has been reported as $52.2/10^5$ in Finland, $41.7/10^5$ in Kuwait and $1.9/10^5$ in China (2,3,4). The incidence of T1D in the pediatric population has an increasing trend worldwide. The rate of change in T1D incidence varies depending on ethnic origin, geographical region and industrialization status (5-19).

In the first and single study reporting the nationwide incidence of pediatric T1D in Turkey, the incidence rate was reported as $11.3/10^5$ for 0-14 and $10.8/10^5$ for 0-18 age groups (20). In addition, other regional studies evaluating the incidence rate (21,22) and a regional study assessing the trend of the incidence rate have been published in Turkey (23).

Our group published the first regional report on the incidence of T1D in Diyarbakır city, where the incidence rate was found to be $7.2/10^5$ (21). The aim of this study was to determine the current incidence and the change in the incidence rate of pediatric T1D and compare the clinical and demographic characteristics of pediatric T1D in the Diyarbakır city, a city of Southeastern Anatolian region of Turkey.

Methods

There are three tertiary pediatric endocrinology centres in Diyarbakır, a city in the Southeastern Anatolian region of Turkey. In Diyarbakır, all 0-18 years old patients diagnosed with T1D are referred to one of these three centres. Hospital files of all T1D patients diagnosed and referred to these three centres between 1st January 2020 and 31st December 2020 were retrieved. T1D diagnosis was made according to the criteria of the American Diabetes Association and International Society for Pediatric and Adolescent Diabetes guidelines (24,25). Blood glucose level, insulin, c-peptide level, blood pH, HCO_3^- level, glycosylated haemoglobin (HbA1c) value, anti-islet cell, anti-insulin and anti-glutamic acid decarboxylase (anti-GAD) antibodies, coeliac serology, and thyroid function tests performed at the time of diagnosis were evaluated. Patients with venous blood pH of <7.3 or HCO_3^- level <15 mEq/L with concomitant ketosis (positive blood/urine ketones) were considered to have diabetic

ketoacidosis (DKA). Based on the pH and HCO_3^- values at presentation, DKA was classified as mild (pH 7.2-7.3 and HCO_3^- 10-15 mEq/L), moderate (pH 7.1-7.2 and HCO_3^- 5-10 mEq/L), and severe (pH <7.1 and HCO_3^- <5 mEq/L). Season and month at the time of the diagnosis, anthropometric data and pubertal status were recorded from patient files. Demographic data were obtained from address-based census records of the Turkish Statistics Institution (TSI). The study was approved by the Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital Ethical Committee (ethics approval number: 765, date: 29.5.2021). Patients were included in the study after parental consent was obtained.

Statistical Analysis

Statistical analysis was performed with IBM Statistical Package for the Social Sciences Statistics for Windows, version 20 (IBM Corp., Armonk, NY, USA). Incidence of T1D was calculated using the numbers of patients reported for each year by gender and in the following age groupings: 0-4, 5-9, 10-14 and 15-18 years at time of diagnosis. Annual numbers for the age groups in Diyarbakır city were used as denominators, and incidence (per 100,000 per year) was calculated with 95% confidence intervals. The population sizes were obtained from the Turkish census data from 2020 from the address-based population registration system of the TSI. In order to assess the significance of the differences between the groups, normality of variables was tested by Kolmogorov-Smirnov test. Mann-Whitney U and chi-square tests were used. Results are reported as means \pm standard deviation. A p value <0.05 was considered statistically significant.

Results

Overall, 57 children and adolescents aged between 0-18 years were diagnosed with T1D between the 1st of January 2020-31st of December 2020. According to TSI data, the overall population in Diyarbakır in 2020 was 1,783,431 and the population within the 0-14 age group was 579,460, and within 0-18 age group was 709,803. T1D incidence was calculated as $9.14/10^5$ and $8.03/10^5$ in 0-14 and 0-18 age groups. The age and sex distribution of cases diagnosed with T1D are illustrated in Table 1.

Of 57 children and adolescents diagnosed with T1D in 2020, 34 (59.6%) were female, and the female/male ratio was 1.47. The mean age at diagnosis was 9.5 ± 3.9 years in the whole cohort, and did not differ between girls (9.5 ± 4 years) and boys (9.4 ± 3.8 years) ($p=0.91$). Regarding pubertal status, $n=18$ (52.9%) of females and $n=8$ (34.8%) of male subjects, and 26 cases (44.6%) in total were in the

pubertal period (Tanner stage ≥ 2). In the 15-18 age group, the incidence rate was similar between males and females, while a female predominance was observed in the other age groups. At the time of the diagnosis, mean serum glucose, HbA1c, and mean c-peptide levels are shown in Table 2.

The number of cases diagnosed between the ages of 10-14 was 23 (40.3%), while 22 patients (38.5%) were aged between 5-9 years, eight patients (14%) between 0-4 years, and four patients (7%) between 15-18 years (Table 1). The

peak incidence rate of T1D was observed in the 10-14 age group, both in females and males. Overall, the diagnosis was 40.4% in the winter season.

In total, 37 (64.9%) of the cases with T1D presented with DKA. The highest frequency for presentation with DKA was in the 5-9 age groups ($n = 17/22$; 77.3%), followed by the 0-4 age group ($n = 5/8$; 62.5%), and 10-14 age group ($n = 14/23$; 60.9%). Of these, 15 of 57 (26.3%) cases presented with severe DKA, which was most prevalent in the 0-4 age group ($n = 3/8$; 37.5%). Presentation with severe DKA was observed in 27.3% (6/22) of cases in the 5-9 age group and 26.1% (6/23) of cases in the 10-14 age group. There was no severe DKA in the 15-18 age group. Fourteen cases (24.6%) presented with ketosis, and six cases (10.5%) with hyperglycemia. Mean c-peptide levels were significantly lower in cases presenting with DKA compared to those presenting without DKA ($p = 0.001$) (Table 3).

Anti-GAD antibody was positive in 40 cases and anti-islet cell antibody in 29 cases, including 16 cases positive for both antibodies. Four cases were negative for both antibodies. Of these, two presented with DKA, one with ketosis and one with hyperglycemia. In the antibody-negative patients HbA1c levels ranged from 9% to 17.9%, c-peptide levels from 0.12 to 1 ng/mL and, blood glucose from 365 to 622 mg/dL. Furthermore, insulin requirement continued with persistent low c-peptide (< 0.8 ng/mL) during follow up.

Anti tissue transglutaminase IgA (anti-TTG IgA) serology was investigated for celiac disease and was positive in 10 (17.5%) cases. One case was diagnosed with celiac disease before diabetes. In addition to the case with a first diagnosis of celiac disease, in six cases, anti-TTG IgA levels were 10 fold or more higher than the upper limit of the lab-specific reference range, and all six presented with DKA. The diagnosis of celiac disease was confirmed in these cases using endoscopic biopsy. In the remaining three cases the anti-TTG IgA levels were 1.5-4 fold higher than the upper limit of reference and the patients were asymptomatic.

Table 1. Distribution of the number of cases with T1D, population number and calculated incidence rate according to sex and age groups

	Number of T1D patients; n (%)	Child population, n	Incidence (per 100,000)
Female (years)			
0-4	5 (14.7)	96,708	5.2
5-9	13 (38.2)	96,666	13.4
10-14	14 (41.1)	89,011	15.7
15-18	2 (5.8)	63,775	3.1
0-14	32 (94.1)	282,385	11.3
0-18	34 (100)	346,160	9.8
Male (years)			
0-4	3 (13.0)	102,333	2.9
5-9	9 (39.1)	101,534	8.8
10-14	9 (39.1)	93,208	9.6
15-18	2 (8.6)	66,568	3.0
0-14	21 (91.3)	297,075	7.1
0-18	23(100)	363,643	6.3
Overall (years)			
0-4	8 (14.0)	199,041	4.0
5-9	22 (38.5)	198,200	11.1
10-14	23 (40.3)	182,219	12.6
15-18	4 (7.0)	130,343	3.1
0-14	53 (92.9)	579,460	9.14
0-18	57 (100)	709,803	8.03

T1D: type 1 diabetes mellitus

Table 2. Presentation characteristics of pediatric T1D patients

	Female (n = 34)	Male (n = 23)	Total (n = 57)	p
Mean age (years)	9.54 \pm 4.09	9.42 \pm 3.8	9.49 \pm 3.9	0.910
BMI SDS	-0.79 \pm 1.49	-1.4 \pm 1.5	-1.02 \pm 1.5	0.162
Pubertal stage ≥ 2	18 (52.9%)	8 (34.8%)	26 (45.6%)	0.183
DKA	21 (61.8%)	16 (69.6%)	37 (64.9%)	0.553
Severe DKA	11 (32.4%)	4 (17.4%)	15 (26%)	0.198
Glucose (mg/dL)	462.0 \pm 143	557.0 \pm 169	500.0 \pm 159	0.038*
HbA1c %	12.9 \pm 2.85	12.6 \pm 2.3	12.8 \pm 2.6	0.694
C peptide (ng/mL)	0.7 \pm 0.54	0.46 \pm 0.3	0.61 \pm 0.47	0.064

*p value < 0.05 significant

BMI: body mass index, T1D: type 1 diabetes mellitus, DKA: diabetic ketoacidosis

These cases are under clinical observation with no biopsy performed. Thyroid function tests were normal in all cases. Anti-TPO was positive in two cases, and anti-Tg antibody was positive in another two cases.

Discussion

In the present study investigating the incidence of T1D in children between the ages of 0-18 years in Diyarbakır, a city of Southeastern Anatolian in Turkey, the incidence of T1D was found to be $9.14/10^5$ in 0-14 age group and $8.03/10^5$ in 0-18 age group.

Incidence of T1D in children varies across the world. The lowest incidence rates have been reported from the Asian populations, such as 1-3 per 100000 in China (3,4,5). A gradual increase has been observed from the South European countries where the incidence rate varies between 10-20 per 100000, to the USA and Scandinavian countries where the incidence rate has been reported to vary between 30 and 60 per 100000 (6,14). The incidence studies performed in Turkey have shown that the incidence rate of pediatric T1D ($7.2-10.8/10^5$) falls between those reported from Asia and South European populations, corresponding to its geographical location (20,21,22).

Globally, within the last three decades, T1D incidence has been reported to increase by 3-4% per year (5,6,19). In various studies, this increase was found to be more marked in countries with a relatively lower incidence at the baseline (5,6).

There are a few studies from Turkey on the incidence of T1D in children (20,21,22,23). In the first nationwide study based on the records of the national Social Security Institution, Yeşilkaya et al (20) reported the incidence of T1D as $11.3/10^5$ in 0-14 age group and $10.8/10^5$ in 0-18 age group. These rates are higher than those we found in the 0-14 and 0-18 age groups in Diyarbakır. The difference might be due to variations in population density, industrialization, climate and ethnicity between different regions of Turkey. Indeed, in

the study of Yeşilkaya et al (20), Turkey was divided into five regions according to incidence rates, and it was observed that the incidence rate of T1D was lower in the East and Southeastern regions of Turkey, including Diyarbakır, than in other regions. The peak incidence was reported in the 10-14 age group ($15.4/10^5$), consistent with our findings (22).

In the first incidence study we carried out (in 2011) in Diyarbakır, the incidence of T1D was calculated as $7.2/10^5$ in 0-14 age children (21). In the present study, we found T1D incidence in the 0-14 age group to be $9.14/10^5$ indicating a 26.9% increase within the last decade, suggesting an average annual increase rate of 2.7%. This increase in the incidence was more pronounced in females (from 8.7 to $11.3/10^5$) and 10-14 age group (from 8.4 to $12.6/10^5$). This is consistent with the reported trend of increase in regions with low incidence. In the ten years that have elapsed since our first study, no population movement, migration, climate changes, or industrial changes have occurred in Diyarbakır (21). Therefore, the increase in the incidence rate can be attributed to the natural increasing trend of T1D in children. However, the Coronavirus disease-2019 (COVID-19) pandemic experienced in 2020 when we carried out the present study might have contributed to the rise in T1D incidence. It has shown that the risk of DKA, especially severe DKA, increases significantly during the COVID-19 pandemic (26).

In the study of Poyrazoglu et al (22), covering the period of 2013-2015 in the Northwest region of Turkey, the incidence of T1D was reported to be $9.82/10^5$ in the 0-14 age group and $8.99/10^5$ in 0-17 age group. The peak incidence was shown to have a bi-modal distribution according to the age group, with the highest incidence rate occurring in the 5-9 ($11.68/10^5$) and 10-14 age groups ($11.7/10^5$). The lowest incidence was reported in the 15-17 age group ($5.04/10^5$). Their incidence rates are similar to those found in the present study. However, incidence rates in the West and North regions of Turkey are high compared to our region (20). In the study of Esen and Okdemir (23), in which the

Table 3. Evaluation of cases according to presenting symptoms

	No DKA		DKA			p*
	Hyperglycemia	Ketosis	Mild DKA	Moderate DKA	Severe DKA	
Number of cases	6	14	15	7	15	
Age (years)	8.1 ± 2.7	11.1 ± 4.3	9.1 ± 3	9.9 ± 4.3	8.6 ± 4.5	0.328
Pubertal stage ≥ 2	4/6	8/14	4/15	4/7	6/15	0.113
Glucose (mg/dL)	457.0 ± 161	474.0 ± 194	487.0 ± 201	598.0 ± 81	499 ± 98	0.334
C-peptide (ng/mL)	1.16 ± 0.9	0.77 ± 0.44	0.53 ± 0.3	0.54 ± 0.32	0.34 ± 0.2	0.001*
HbA1c (%)	10.6 ± 3.1	14.4 ± 2.5	13 ± 2.28	14.2 ± 3.2	11.3 ± 2.0	0.418

*p values indicate the comparison of values for patients with and without DKA at presentation.

DKA: diabetic ketoacidosis, HbA1c: glycosylated haemoglobin

T1D incidence trend was evaluated in children under the age of 15, between year 2009 and 2019, the incidence rate was reported to increase from $10.2/10^5$ to $24.1/10^5$ over the 10 years period. An annual incidence rise of 7.8% was demonstrated, particularly in the 5-9 age group and in boys. These incidence and increase rates are the highest ever reported in Turkey (23).

Regarding the presenting characteristics of the cases, presentation with DKA was highly prevalent (64.9%) and similar to those we detected in the first report (65.9%) (21). Indeed, in the 10 years since our first study, substantial national and regional changes have been made to improve public awareness of diabetes, such as training about diabetes for school staff, public advertisements, and increase in the number of diabetes care professionals in Diyarbakır city, and easier access to health facilities. Delay in referring to the hospital due to COVID-19 may have played a part in the negligible decrease in DKA as a presenting symptom.

There is a bimodal distribution for the age of peak incidence of T1D. The peak incidence of T1D in Diyarbakır has shown a slight shift from the 5-9 years (in the first study) to the 10-14 years group in the current study, while the distribution of the incidence revealed the highest incidence rate in these age groups, which is similar to those reported by Weng et al (Figure 1) (4).

Regarding the sex-specific disease frequency, the regions with high incidence rates have been reported to have a male-predominant incidence, while in the populations with low incidence, a female predominance has been reported (5). Indeed, a female predominance has been observed in our first (female/male ratio 1.4) and current study (female/

male ratio 1.47) (22). However, there was a lack of gender discrepancy in the other epidemiological studies reported from our country with a female/male ratio of 0.9 in the study of Poyrazoglu et al (22), 1.02 in the study of Yeşilkaya et al (20) and 0.93 in the study of Esen and Okdemir (23) all of which reported a higher overall incidence rate compared to our results.

At the time of diagnosis, in 10 (17.5%) cases, anti-TTG IgA was positive. One of these cases was diagnosed with coeliac disease before diabetes. In 6 patients with an anti-TTG IgA level 10 or more times higher than the upper limit of the reference range, a diagnosis of biopsy-proven celiac disease was considered. All cases with biopsy-proven celiac disease was presented with DKA at a mean age of 9.2 ± 3.9 . In the studies of Unal et al, (27) the frequency of biopsy-proven celiac disease was found to be 6.9% and the mean age at diagnosis was 7.58.

Study Limitations

There are limitations of this study. The study period overlapped with the first year of the COVID-19 pandemic, which may have affected both the incidence rate and presenting characteristics, such as the high rate of presentation with DKA. Another limitation is that we calculated the incidence rate cross-sectional for a one-year period. Therefore, a long-term prospective analysis of the incidence rate consecutively may estimate the most accurate incidence of pediatric T1D in our region.

Conclusion

In conclusion, the annual incidence of pediatric T1D in Diyarbakır city increased from $7.2/10^5$ to $9.14/10^5$ within the last decade. The rate of annual increase was 2.7% in the 0-14 age group comparing this study with our earlier report, with a predominance in male subjects and a shift of peak incidence from the 5-9 year age group in the first study to the 10-14 year age group in this one. Although consistent with our previous study, the high rate of presentation with DKA, despite several initiatives conducted to increase diabetes awareness of over the last decade, can be attributed to the changes in behaviour due to COVID-19, The pandemic might be associated with a delay in the admission of patients to health centres. Nevertheless, it remains paramount that new strategies are developed to increase awareness of pediatric T1D to alleviate the risk of presentation with DKA.

Ethics

Ethics Committee Approval: The study was approved by the Health Sciences University Diyarbakır Gazi Yaşargil

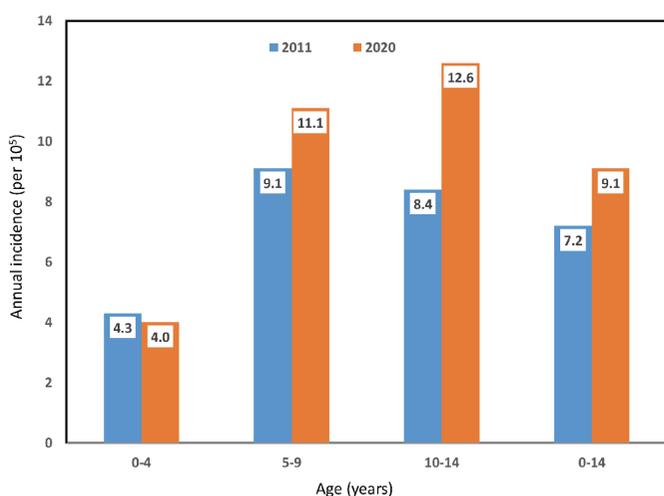


Figure 1. Annual incidence of T1D observed in the first (2011) and current (2020) regional reports conducted in Diyarbakır city revealed a 26.9% increase in the peak incidence and a shift from the 5-9 year age group to the 10-14 years

Training and Research Hospital Ethical Committee (ethics approval number: 765, date: 29.5.2021).

Informed Consent: Patients were included in the study after parental consent was obtained.

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Authorship Contributions

Surgical and Medical Practices: Şervan Özalkak, Ruken Yıldırım, Selma Tunç, Edip Ünal, Funda Feryal Taş, Mehmet Nuri Özbek, Concept: Şervan Özalkak, Hüseyin Demirbilek, Mehmet Nuri Özbek, Design: Şervan Özalkak, Hüseyin Demirbilek, Mehmet Nuri Özbek, Data Collection or Processing: Şervan Özalkak, Ruken Yıldırım, Selma Tunç, Edip Ünal, Funda Feryal Taş, Mehmet Nuri Özbek, Analysis or Interpretation: Şervan Özalkak, Hüseyin Demirbilek, Mehmet Nuri Özbek, Literature Search: Şervan Özalkak, Mehmet Nuri Özbek, Writing: Şervan Özalkak, Hüseyin Demirbilek, Mehmet Nuri Özbek.

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