Revisiting the annual incidence of Type 1 Diabetes Mellitus in children from the
Southeastern Anatolian Region of Turkey: A Regional report

Özalkak Ş et al. Incidence of Type 1 Diabetes Mellitus in children: A Regional report

What is already known on this topic? Type 1 Diabetes mellitus incidence in children has an increasing trend with a variable rate depending on region and ethnicity.

What this study adds? The present study 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 0-18 age T1D in Diyarbakır.

Abstract

Objective: Type 1 Diabetes mellitus (T1D) incidence in children has an increasing trend with a variable rate depending on region and ethnicity. Our group had firstly reported T1D incidence in Diyarbakır in the year 2011. The present study aims to evaluate the current incidence rate of pediatric T1D in Diyarbakır, and compare the incidence, clinical and presenting characteristics of the cases with those reported in our first report.

Methods: Hospital records of the patients under 18 years old and diagnosed with T1D in Diyarbakır city between 1st January 2020 and 31st December 2020 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 of diagnosis was 9.5±3.9 (0.8-17.9). According to the data obtained from TSI, the population between the ages of 0-18 was found to be 709803. T1D incidence was calculated as 9.14/10^5 in the 0-14 age group and 8.03/10^5 in the 0-18 age group. 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 DKA was 64.9%.

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

Şervan Özalkak MD, Diyarbakir Gazi Yasargil Training and Research Hospital, Pediatric Endocrinology
drservanoz@gmail.com
0000-0002-1557-6040
21.10.2021
15.12.2021
Published: 11.01.2022

Introduction

Type 1 diabetes mellitus (T1D) is one of the most common chronic autoimmune diseases in children which is characterized by damage in insulin-producing pancreatic β cells (1). The incidence of T1D in children is heterogenous all over the world, with a highest incidence rate in the Western countries to the lowest incidence rate in Eastern countries. For instance, the incidence rate has been reported as 64.9 / 10^5(2) in Finland and 1.9 / 10^5(3) in China. The incidence of T1D in the pediatric population has an increasing trend worldwide. The rate of change in T1D incidence varies depending on the ethnic origin, geographical region and industrialization status (4-18).

In the first and single study reporting the nationwide incidence of pediatric T1D in Turkey, the incidence rate was reported 11.3/10^5 for 0-14 and 10.8/10^5 for 0-18 age groups (19). In addition, other regional studies evaluating the incidence rate (20,21) and a regional study assessing the trend of the incidence rate have been published in Turkey (22).

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 (20). The present study aimed 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.

**Patients and 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 3 centres. Hospital files of all T1DM 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 (ADA) and ISPAD guidelines (23,24). Blood glucose level, insulin, c-peptide level, blood pH, HCO3 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 the diagnosis were evaluated. Patients with venous blood pH of <7.3 or HCO3 level < 15 mEq / L with concomitant ketosis (positive blood/urine ketones) were considered to have diabetic ketoacidosis (DKA). Based on the pH and HCO3 values at presentation, DKA was classified as mild (pH: 7.2-7.3 and HCO3: 10-15 mEq/l), moderate (pH: 7.1-7.2 and HCO3: 5-10 mEq/l), and severe (pH: <7.1 and HCO3: <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 (date: 29.5.2021 and ethics approval number: 765). Patients were included in the study following a consent form signed by parents.

**Statistical analysis**

Statistical analysis was performed with IBM SPSS Statistics for Windows Version 20 (IBM Corp., Armonk, NY, USA). Incidence of T1DM was calculated using the numbers of patients reported for each year by 0-4, 5-9, 10-14 and 15-18 years aged and gender groups (girls and boys). Annual numbers for the age groups in the Diyarbakır city were used as denominators, and incidence (per 100,000 per year) was calculated with 95% CIs, assuming. The population sizes were obtained from the Turkish census data of 2020 from the address-based population registration system of the Turkish Statistics Institute. 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 ± SD. A p-value of under 0.05 was considered statistically significant.

**Results**

Overall, 57 children and adolescents in the age group of 0-18 were diagnosed with T1D between the 1st of January 2020 – 31st of December 2020. According to data of TSI, the overall population in Diyarbakır in 2020 was 1783431, and the population within the 0-14 age group was 579460, and within 0-18 age group was 709803. 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 of 1.47. The mean age of the diagnosis was 9.5±3.9 in the whole cohort, while 9.5±4 years in females and 9.4±3.8 years in males ($p=0.91$). Regarding the pubertal status, n=18 (52.9%) of females and n=8 (34.8%) of male subjects, and 26 cases (44.6%) in total was at 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 ages of 10-14 was 23 (40.3%), while 22 patients (38.5%) was between the ages of 5-9, 8 patients (14%) between the ages of 0-4, and 4 patients (7%) between the ages of 15-18 (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 40.1% in the winter season.

In total, 37 (64.9%) of T1D cases was presented with DKA. The highest frequency for the presentation with DKA was in the 5-9 age groups (n=17/22, 77.3%) which was followed by 0-4 age group (n=5/8, 62.5%), and 10-14 age group (n=14/23; 60.9%). Of those, 15 out of 57 (26.3%) cases was presented with severe DKA, which was most prevalent in the 0-4 age group (n=3/8; 37.5%). Presentation with severe DKA has been observed in 27.3% (6/22) of cases in 5-9 age groups 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%) was presented with ketosis, and six cases (10.5%) with hyperglycemia. Mean c peptide levels were significantly lower in cases presented with DKA than those presented with no DKA ($p=0.001$) (Table 3).

Anti GAD antibody was positive in 40 cases and the anti-islet cell antibody in 29 cases, while 16 cases had positive results for both antibodies. Four cases were negative for both antibodies. Of these, two had presented with DKA, one with ketosis and one with hyperglycemia. Their HbA1c levels were ranged from 9% to 17.9%, c peptide levels 0.12 to 1 ng/ml and, glucose 365 to 622 mg/dl. Their insulin requirement continued with persistent low c-peptide (<0.8 ng/ml) during follow up. Anti tissue transglutaminase IgA (anti-TTG IgA ) serology investigated for the Celiac disease was found to be positive in 10 (17.5%) cases. One case was diagnosed with Celiac disease before diabetes. In addition to the cases with the previous 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. The diagnosis of Celiac disease was confirmed in these cases using endoscopic biopsy. All of the six cases which have a diagnosis of celiac disease were presented with DKA. In the three cases who were asymptomatic and had Anti-TTG IgA levels of 1.5 - 4 fold higher than the upper limit of reference. These cases are on clinical observation with no biopsy performed. Thyroid function tests were normal in all cases. Anti-TPO was positive in 2 cases, and anti-Tg antibody was positive in the other 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 all over the world. The lowest incidence rates have been reported from the Asian populations, such as 1-3 per 100000 in China (3,4). A gradual increase has been observed from the South European countries where the incidence rate vary between 10-20 per 100000, to the USA and Scandinavian countries where the incidence rate reaches up to 30-60 per 100000 (5,13). The incidence studies performed in Turkey have shown that the incidence rate of pediatric T1D ($7.2-10.8/10^5$) falls in between Asia and South European populations, corresponding to its geographical location (19,20,21).

Globally, within the last three decades, T1D incidence has been reported to increase by 3-4% per year (4,5,18). In various studies, this increase was found to be more marked in countries with a relatively lower incidence at the baseline (4,5).

There are a few studies carried out in Turkey on the incidence of T1D in children (19, 20, 21, 22). In the first nationwide study based on the records of the national Social Security Institution, Yeşilkaya et al. (19) have 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. (19), Turkey was divided into five regions according to incidence rates, and it was observed that the incidence rate of T1D is 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 (21).

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 (20). In the present study, we found T1D incidence in the 0-14 age group as $9.14/10^5$, 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 corresponds to the trend of increase in regions with low incidence. In the ten years elapsing after our first study, no population movement, migration, climate changes, or industrial changes have occurred in Diyarbakır(20). Therefore, the increase in the incidence rate can be attributed to the natural increasing trend of T1D in children. However, the covid-19 pandemic experienced in 2020 when we carried out the present study might have contributed to the rise in T1D incidence.

In the study of Poyrazoglu et al. (21), 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 a bimodal distribution according to the age group, with the highest incidence rate occurred in 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 obtained in the present study. Yet, incidence rates in the West and North regions of Turkey are high compared to our region (19). In the study of Esen et al. (22), in which the 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 $24.1/10^5$ within the 10 years period. Annual incidence rise of 7.8% was demonstrated particularly in 5-9 age group and boys. These incidence and increase rates are the highest ever reported in Turkey (22).

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%) (20). Indeed, as within the last 10 years after the first study, substantial national and regional organisations have been undertaken to improve the public awareness of diabetes, such as training on diabetes at school, public advertisements, and increase in the number of diabetes care professionals in the Diyarbakir city, easier access to health facilities. Delay in referring to the hospital due to Covid 19 may have played part in the lack of decrease in DKA as presenting symptom.

There is a bimodal distribution for the age of peak incidence of T1DM. The peak incidence of T1D in Diyarbakıır 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 J. et al. (3).

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 (4). 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. (21), 1.02 in the study of Yeşilkaya et al. (19) and 0.93 in the study of Esen et al. (22) of which all were reported a higher 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.

Limitations of the study: The study period overlapped with the Covid 19 pandemic, which may affect both the incidence rate and presenting characteristics such as a high rate of presentation with DKA. Another limitation is that we calculated the incidence rate crossectional for a one-year period. Therefore, a long-term prospective analysis of incidence rate consecutively may estimate the most accurate incidence of pediatric T1D in our region.
In conclusion, we have shown the annual incidence of pediatric T1D in Diyarbakır city increased from $7.2 \times 10^5$ to $9.14 \times 10^5$ within the last decade. The rate of annual increase was 2.7%, with a predominance in male subjects and the 10-14 age group. Although was consistent with our previous study, the high rate of presentation with DKA, despite several initiatives conducted to increase the awareness of diabetes over the last decade, can be attributed to the Covid 19 situations, which might be associated with delay in the admission of patients to the health centres. Nevertheless, it is yet paramount to develop new strategies targeting an increase in the awareness of pediatric T1D to alleviate the risk of presentation with DKA.

References


Table 1. Distribution of the number of cases with T1DM, population number and calculated incidence rate according to sex and age groups
<table>
<thead>
<tr>
<th>Gender (years)</th>
<th>Number of T1DM Patients; n (%)</th>
<th>Child Population</th>
<th>Incidence (Per 100000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>5 (14.7)</td>
<td>96708</td>
<td>5.2</td>
</tr>
<tr>
<td>5-9</td>
<td>13 (38.2)</td>
<td>96666</td>
<td>13.4</td>
</tr>
<tr>
<td>10-14</td>
<td>14 (41.1)</td>
<td>89011</td>
<td>15.7</td>
</tr>
<tr>
<td>15-18</td>
<td>2 (5.8)</td>
<td>63775</td>
<td>3.1</td>
</tr>
<tr>
<td>0-14</td>
<td>32 (94.1)</td>
<td>282385</td>
<td>11.3</td>
</tr>
<tr>
<td>0-18</td>
<td>34 (100)</td>
<td>346160</td>
<td>9.8</td>
</tr>
<tr>
<td><strong>Male (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>3 (13.0)</td>
<td>102333</td>
<td>2.9</td>
</tr>
<tr>
<td>5-9</td>
<td>9 (39.1)</td>
<td>101534</td>
<td>8.8</td>
</tr>
<tr>
<td>10-14</td>
<td>9 (39.1)</td>
<td>93208</td>
<td>9.6</td>
</tr>
<tr>
<td>15-18</td>
<td>2 (8.6)</td>
<td>66568</td>
<td>3.0</td>
</tr>
<tr>
<td>0-14</td>
<td>21 (91.3)</td>
<td>297075</td>
<td>7.1</td>
</tr>
<tr>
<td>0-18</td>
<td>23 (100)</td>
<td>363643</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Overall (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>8 (14.0)</td>
<td>199041</td>
<td>4.0</td>
</tr>
<tr>
<td>5-9</td>
<td>22 (38.5)</td>
<td>198200</td>
<td>11.1</td>
</tr>
<tr>
<td>10-14</td>
<td>23 (40.3)</td>
<td>182219</td>
<td>12.6</td>
</tr>
<tr>
<td>15-18</td>
<td>4 (7.0)</td>
<td>130343</td>
<td>3.1</td>
</tr>
<tr>
<td>0-14</td>
<td>53 (92.9)</td>
<td>579460</td>
<td>9.14</td>
</tr>
<tr>
<td>0-18</td>
<td>57 (100)</td>
<td>709803</td>
<td>8.03</td>
</tr>
</tbody>
</table>

*Table 2. Presentation characteristics of the pediatric T1DM patients*

*p-value <0.05 statistically significant difference.*
Table 3. Evaluation of cases according to presenting symptoms.

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

<table>
<thead>
<tr>
<th></th>
<th>No DKA</th>
<th>DKA</th>
<th>Moderate DKA</th>
<th>Severe DKA</th>
<th>P *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>6</td>
<td>14</td>
<td>15</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Age (year)</td>
<td>8.1 ±2.7</td>
<td>11.1 ±4.3</td>
<td>9.1 ±3</td>
<td>9.9 ±4.3</td>
<td>8.6 ±4.5</td>
</tr>
<tr>
<td>Pubertal stage≥2</td>
<td>4/6</td>
<td>8/14</td>
<td>4/15</td>
<td>4/7</td>
<td>6/15</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>457.0±161</td>
<td>474.0±194</td>
<td>487.0±201</td>
<td>598.0±81</td>
<td>499±98</td>
</tr>
<tr>
<td>C peptide (ng/ml)</td>
<td>1.16±0.9</td>
<td>0.77±0.44</td>
<td>0.53±0.3</td>
<td>0.54±0.32</td>
<td>0.34±0.2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>10.6 ±3.1</td>
<td>14.4 ±2.5</td>
<td>13 ±2.28</td>
<td>14.2 ±3.2</td>
<td>11.3±2.0</td>
</tr>
</tbody>
</table>
Figure 1: Annual incidence of T1DM 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.