The Distribution of Different Types of Diabetes in Childhood: A Single Center Experience
Short Title: The types of diabetes in childhood

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What is already known in this topic?
Although, Type 1 diabetes (T1D) is the most common type of diabetes in childhood, a variable increase in the prevalence of type 2 diabetes (T2D) and MODY in the different multicenter studies depending on the ethnic background, the country lived and the availability of genetic tests.

What this study adds?
There is no such large data in the literature regarding the distribution of the type of diabetes in Turkish pediatric population. Also, this study compared clinical characteristics of the different types of diabetes in a tertiary pediatric diabetes center over the last 17 years.

Abstract
Background: Type 1 diabetes (T1D) is the most common cause of diabetes in childhood but type 2 diabetes (T2D) and maturity onset diabetes of the young (MODY) are emerging and noteworthy causes of diabetes in youths.
Aim: To determine the distribution, trends and clinical features of the different types of diabetes in childhood in a tertiary single-center.
**Method:** Children and adolescents aged 0-18 years who were diagnosed "diabetes/persistent hyperglycemia" between January 1999 and December 2016, were reviewed. Clinical and laboratory characteristics of the patients at the diagnosis and type of diabetes were recorded.

**Results:** The mean age of 835 patients (48.7% females) at diagnosis was 8.8±4.4 years. Eighty-four percent of the patients were diagnosed with T1D, 5.7% with T2D, 5.3% with clinical MODY and 5% with other types of diabetes. The frequency of all DKA and severe DKA in T1D were 48.4% and 11.6%, respectively. Fourteen patients (29.2%) with T2D presented with ketosis and 2 of them (4.2%) had DKA at diagnosis. Antibody positivity was 83.1% in T1D and 14.8% in T2D. A statistically significant increase in the frequency of T2D has clearly been demonstrated in recent years with a frequency of 1.9%, 2.4% and 7.9% in 1999-2004, 2005-2010 and 2011-2016, respectively (p<0.001). In MODY, genetic analysis was performed in 26 (59%) patients and \textit{HNF1A} and \textit{GCK} gene mutations were detected in 3 (11.5%) and 14 (53.8%) patients, respectively.

**Conclusion:** Although the most frequent cause of DM is T1D in childhood, a trend towards increase in the frequency of T2D in recent years is notable in our population.

**Keywords:** Type 1 diabetes, Type 2 diabetes, MODY, childhood

**Introduction**
Type 1 diabetes (T1D) is the most common type of diabetes in childhood and its incidence is still rising in various parts of the world (1). However, the increasing worldwide rates of child obesity have also been associated with a variable increase in the prevalence of type 2 diabetes (T2D), depending on the ethnic background and the country lived (2). Although, its prevalence in children with diabetes was reported 11% in USA (3), this ratio was reported to be lower in Europe (1.3% in SWEET) (4).

Childhood T2D can be confused with maturity onset diabetes of the young (MODY) due to family history, presenting features and a possible confounding factor of obesity/overweight (5,6). Furthermore, MODY, especially \textit{HNF1A} mutations can be misclassified as T1D (7).

Determining the type of diabetes is important for therapeutic considerations as well as genetic counseling (8).

The aim of the present study is to review the etiologic distribution, temporal changes in the etiology of childhood diabetes and compare clinical characteristics of the different types of diabetes in a tertiary pediatric diabetes center over the last 17 years.

**Methods**
In the present study, 927 children and adolescents aged <18 years who were diagnosed "diabetes" or "persistent hyperglycemia" and were followed-up at Marmara University, School of Medicine, Pediatric Endocrinology and Diabetes Unit, Istanbul, Turkey, between January 1999 and December 2016, were examined. Ninety-two patients with a follow up duration of less than one year were excluded, since the type of diabetes could not be specified because of insufficient data. Finally, 835 patients were included in this single-centered observational retrospective study.

The patients' gender, age of diagnosis, height (cm), weight (kg), body mass index (BMI, kg/m²), e-peptide level (ng/ml), presence of the autoantibodies (ICA, GADA, IAA), presence of ketone bodies, pH and HCO3 levels at the time of diagnosis, type of diabetes, treatment modalities (diet, oral antidiabetic drug, insulin) were recorded. The patients were classified according to the ISPAD Consensus 2014 (Table 1).

T1D was diagnosed in the presence of severe insulin deficiency, autoantibody positivity and the absence of any suggestive signs of other causes of diabetes. The diagnostic criteria for T2D were based on overweight/obesity, clinical findings of insulin resistance.
(acanthosis nigricans, hypertension, dyslipidemia), family history of T2D and good metabolic control with metformine or metformine and low dose long-acting insulin (<0.5 U/kg/d). The patients who had history of diabetes of at least two generation in one side of the family, negative autoantibodies, had no evidence of insulin resistance and good metabolic control with diet, sulphonylurea or low dose insulin were classified as clinically MODY. \textit{HNF1A}, \textit{HNF4A} and \textit{GCK} genes were analysed for clinically suspected MODY cases when available. Children with an onset of diabetes before 6 months of age were diagnosed as neonatal diabetes and relevant genetic tests were performed. All statistical data were analyzed using SPSS statistical software for Windows, version 17.0 (SPSS, Chicago, IL). Variables were summarized with descriptive statistics. Data were presented as mean ± standard deviation (SD). The statistical comparisons for means were performed using parametric test (independent t-test). Chi-square test was used for cross tables. The level of statistical significance was set at \( p=0.05 \).

\textbf{Results}

After 92/927 patients (9.9\%) were excluded, the mean age of 835 patients (48.7\% females) at diagnosis was 8.8±4.4 (median 9.0, range 0.0-18.0) years old. Seven hundred one patients were diagnosed with T1D (84\%), 48 with T2D (5.7\%), 44 with clinical MODY (5.3\%) and 42 with other types of diabetes (5\%) (Table 1). The clinical characteristics at diagnosis of T1D, T2D and MODY were shown in Table 2. In T1D, 23.7\% (n:166) of them were younger than 5 years old and 1.6\% (n:8) had BMI SDS >2. The frequency of severe DKA at diagnosis in T1D was 11.6\%. T2D was more common in girls and older children. Fourteen patients with T2D (29.2\%) presented with ketosis and 2 of them (4.2\%) had DKA at diagnosis. Diabetes autoantibody positivity was 83.1\% in T1D and 14.8\% in T2D. The patients with antibody-positive T2D were compared with those with antibody-negative T2D in terms of age, BMI SDS, the presence of DKA and use of insulin. The only statistically significant difference was age of diagnosis. The patients with antibody-positive T2D were younger than those with antibody negative (11.8±3.3 vs 13.7±1.94, \( p=0.045 \)).

A statistically significant increase in the frequency of T2D has clearly been demonstrated in recent years with a frequency of 1.9\%, 2.4\% and 7.9\% in 1999-2004, 2005-2010 and 2011-2016, respectively (\( p<0.001 \)) in our cohort (Figure). The frequency of DKA was 58.4\% and there was also a statistically significant decrease in the proportion of ketoacidosis at diagnosis in T1D after 2011 was imposed (55\% vs 44.6\%, \( p=0.022 \)). However, the decrement in the proportion of severe ketoacidosis was not statistically significant (15.1\% vs 9.7\%, \( p=0.066 \)). The mean c-peptide level at the time of diagnosis was 0.7±0.6 ng/ml in T1D, 3.2±1.5 ng/ml in T2D and 1.3±0.6 ng/ml in MODY patients (\( p<0.001 \)) (table 2).

In MODY, genetic analysis was available in 26 (59\%) patients and \textit{HNF1A} and \textit{GCK} gene mutations were detected in 3 (11.5\%) and 14 (53.8\%) patients, respectively. Seven patients had NDM and it was molecularly confirmed in 6 of 7 patients in whom \textit{KCNJ11} (n=2), \textit{6q24} (n=1), \textit{EIF2AK3} (n=1), \textit{SLC19A2} (n=1) and \textit{PTF1A enhancer} (n=1) gene mutations were identified. In 8 (2F/6M) patients with Wolfram syndrome from 5 families, 3 known homozygote/compound heterozygote mutations in \textit{WFS} gene were detected and 4 of them had optic atrophy, 1 had cataract and 1 had diabetes insipidus. Cystic fibrosis-related diabetes (CFRD) was detected in 11 patients (6F/5M, 1.3\%) and the mean age and mean BMI SDS at diagnosis were 12.7±4.1 (5.0-17.4) and -1.4±1.5 (-3.7-1.1), respectively.
The frequency of drug-induced diabetes was 0.6% (n:5) and 4 of which was due to L-asparaginase and 1 due to tacrolimus.

**Discussion**

The present study illuminated some issues concerning the frequency of the different types of diabetes in our population and allowed us to make comparisons with other societies. The overall frequency of T1D, T2D, MODY and other specific types of diabetes were 84%, 5.7%, 5.3% and 5%, respectively. T1D is still the most common cause of childhood diabetes and its frequency varies between 85-95% in different regions of the world (3,4,7). This variability originates from the number of children with T2D and MODY. The frequency of T1D, T2D and MODY were 85.6%, 10.8% and 1.2% respectively in SEARCH study (USA), whereas, these ratios were 95.5%, 1.3% and 1.5% respectively in SWEET study (Europe) (3,4,9). Also, the frequency of MODY was higher (5.5%) in a recent study from Italy (7). The variation in the frequencies could be explained by the availability of genetic testing and prevalence of obesity in that region. Misclassification of diabetes due to the lack of evidence-based clinical criteria for differential diagnosis is widespread and reported to be 7-15% (10). In the present study, the frequency of T1D, T2D and MODY were 84%, 5.7% and 5.3%. The diagnosis of MODY and T2D is more common in this study than SWEET study. The present study is not a national multicenter study, so this difference may be explained by referral of the rare types of diabetes to our tertiary center.

The most confusing factor for classification of diabetes is obesity. BMI at the time of diagnosis has less discriminatory feature for classification (10), since the increase in obesity has led to the appearance of children with obese T1D/MODY. In different studies, the frequency of obesity among patients with T1D at the time of diagnosis was 3.1-9% (11,12), but it was 1.6% in the present study. This could be due to lower obesity rates in our pediatric population (13) compared to North America and Western Europe. Although lower than these regions, obesity rates are increasing in Turkey as well which could be the reason for increase in the frequency of T2D observed in this study over the years from 1.9% to 7.9%. Similar to the literature (14), T2D was more common in girls and at pubertal ages.

The antibody positivity in T2D is reported up to 15% and these antibody-positive patients are usually younger, less overweight/obese and have higher HbA1c (15). So, several terminologies have been recommended such as double diabetes, type 1.5 diabetes and latent autoimmune diabetes of youth (LADY). In the present study, the antibody positivity was 14.8% and there was significant difference only at the age of diagnosis between antibody positive and negative subjects. Although, a few case reports described antibody positive MODY patients, the prevalence of antibody positivity in MODY is <1% (16). Therefore, the antibody positivity was used as exclusion criteria for MODY in the present study.

The frequency of DKA in T1D varied 48-66% in the different studies in Turkey (18-20). Our study shows a decrease of 10% in the rate of DKA at the time of diagnosis, albeit, the current ratio is still high. DKA at the time of diagnosis of pediatric T2D is not infrequent and is reported up to 40% of patients (15). However, it was not frequent in our study (4.2%) but nearly one-third of patients with T2D presented with ketosis without acidosis. The frequency of MODY varies between 0.83-5.5% in different studies (4,6,7,21-24). GCK mutation (up to 95%) was the most common cause in the studies that reported higher MODY frequency (6,7,23). Similarly, we detected GCK mutation in 53.8% of the clinically MODY patients who were genetically tested. This can be explained by the widespread use of random glucose measurement in general pediatric clinics in Turkey. On
the other hand, the rate of genetic analysis in the clinical MODY patients was low (59%) in the present study, as it was not possible before 2010. In 65.3% of these patients a mutation in one of the known MODY genes could be detected. This ratio varies between 27-89% in the different studies (25). This variation and failure to detect mutations may result from including criteria for genetic test, a mutation in a gene not yet identified or diagnostic overlap of different types of diabetes.

C peptide levels, although useful in long-standing diabetes cases, might not be discriminative in patients with new onset diabetes because of substantial overlap among different types of diabetes mellitus (26). Nevertheless, in addition to autoantibody positivity, c-peptide levels remains as a relatively good diagnostic parameter. In the present study, c-peptide levels at the time of diagnosis were helpful especially to differentiate between T1D and T2D.

In conclusion, the present study provides trends in the last 17 years in pediatric diabetes in a large number of patients from a single tertiary center and tries to identify distinguishing features of different types of diabetes. The frequency of T2D is in rise but still lower than that in North America. MODY is being more easily recognized in recent years owing to availability of autoantibody testing and genetic tests. Despite overlapping features such as obesity, ketosis and antibody positivity, there are demographic (age, puberty, gender, family history) as well as laboratory (autoantibody positivity, c-peptide) tools to correctly identify the type of diabetes in the pediatric population.

Acknowledgement
We would like to thank to all medical doctors, students and staffs who were worked in our institution between 1999-2016 for their efforts.

References


### Table 1: The distribution of the patients with diabetes

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1D</td>
<td>701</td>
<td>84</td>
</tr>
<tr>
<td>T2D</td>
<td>48</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Genetic defects of β-cell function

- MODY: 44 (5.3)
- NDM: 7 (0.8)
- Mitochondrial: 2 (0.2)
Genetic defects in insulin action 2 0.2
Diseases exocrine pancreas
  CFRD 11 1.3
  Pancreatectomy 1 0.1
Endocrinopathies 1 0.1
Drug-induced 5 0.6
Infections 1 0.1
Genetic syndromes
  Wolfram 8 1
  Others 4 0.5
Total 835 100

T1D: Type 1 Diabetes Mellitus, T2D: Type 2 Diabetes Mellitus, MODY: Maturity Onset Diabetes of the Young, NDM: Neonatal Diabetes Mellitus, CFRD: Cystic Fibrosis Related Diabetes

Table 2: The clinical features of the patients with T1D, T2D and MODY at diagnosis

<table>
<thead>
<tr>
<th></th>
<th>n*</th>
<th>T1D</th>
<th>T2D</th>
<th>MODY</th>
<th>p</th>
<th>T1D vs T2D</th>
<th>T1D vs MODY</th>
<th>T2D vs MODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M) (%)</td>
<td>793</td>
<td>49/51</td>
<td>71/29</td>
<td>52/68</td>
<td>0.003</td>
<td>0.028</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>793</td>
<td>8.4±4.2</td>
<td>13.2±2.5</td>
<td>10.2±3.9</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age &lt;5 years, n(%)</td>
<td>793</td>
<td>166 (23.7%)</td>
<td>0</td>
<td>5 (11.4%)</td>
<td>&lt;0.001</td>
<td>0.06</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>BMI SDS</td>
<td>560</td>
<td>-0.5±1.3</td>
<td>2.3±1.0</td>
<td>-0.4±1.1</td>
<td>&lt;0.001</td>
<td>0.91</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>BMI SDS ≥2, n(%)</td>
<td>560</td>
<td>8 (1.6%)</td>
<td>30 (69.8%)</td>
<td>0</td>
<td>&lt;0.001</td>
<td>0.46</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>C-peptide (ng/ml)</td>
<td>442</td>
<td>0.7±0.6</td>
<td>3.2±1.5</td>
<td>1.3±0.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Antibody positivity, n(%)</td>
<td>526</td>
<td>397 (78.1%)</td>
<td>4 (14.8%)</td>
<td>0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.006</td>
<td></td>
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<tr>
<td>Anti-GAD, n(%)</td>
<td>519</td>
<td>301 (64.2%)</td>
<td>2 (7.1%)</td>
<td>0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>ICA, n (%)</td>
<td>511</td>
<td>297 (64.8%)</td>
<td>1 (3.7%)</td>
<td>0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>IAA, n (%)</td>
<td>494</td>
<td>147 (33%)</td>
<td>1 (3.7%)</td>
<td>0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.37</td>
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<tr>
<td>pH</td>
<td>558</td>
<td>7.26±0.15</td>
<td>7.38±0.05</td>
<td>7.36±0.03</td>
<td>&lt;0.001</td>
<td>0.008</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>HCO3</td>
<td>547</td>
<td>15.1±7.8</td>
<td>24.6±5.2</td>
<td>22.7±3.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.057</td>
<td></td>
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<tr>
<td>DKA, n(%)</td>
<td>566</td>
<td>251 (48.4%)</td>
<td>2 (6.5%)</td>
<td>0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.29</td>
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<tr>
<td>Severe DKA, n(%)</td>
<td>566</td>
<td>60 (11.6%)</td>
<td>0</td>
<td>0</td>
<td>0.04</td>
<td>0.14</td>
<td></td>
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</tr>
</tbody>
</table>

* The n values are the number of patients who had available data. Anti-GAD: Anti-Glutamic acid decarboxylase, ICA: Islet cell antibody, IAA: Insulin autoantibody, DKA: Diabetic ketoacidosis
Figure Legends:

Figure: The frequency of the type of diabetes in a single-center according to 6 years period. * p<0.05