Trend in initial presenting features of type 1 diabetes mellitus over a 24 year period in Turkey: a retrospective analysis of 814 cases

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ABSTRACT

Background. The study aim was to examine changes in trends of presenting features during the diagnosis of patients followed up with newly diagnosed Type 1 diabetes mellitus (T1DM) over the past 24 years.

Methods. The study was retrospective. Patients with a diagnosis of T1D between the years of 1996–2019 were included. Patients diagnosed in the first half of the period comprised Period I, and those from the second half comprised Period II. Patient data were extracted from medical records and included gender distribution, year of diagnosis, age at diagnosis, duration of symptoms, type of admission, frequency of diabetic ketoacidosis (DKA) and biochemical parameters. Subsequently, temporal changes in trends of these parameters were sought.

Results. For the whole cohort the gender distribution was equal; 404 (49.6%) were girls and 410 (50.4%) were boys. Mean age at diagnosis was 8.5±4.2 years and age groupings at presentation were: 23.2% (n = 189) aged 0-4; 39.2% (n = 319) aged 5-9; 27.5% (n = 224) aged 10-13; 10.1% (n= 82) aged 14-18. At presentation 72 (12.7%) had hyperglycemia, 230 (40.6%) had diabetic ketosis, and 264 (46.6%) had DKA. In those with DKA, mild DKA was found in 103 (39.0%), moderate DKA in 81 (30.6%), and severe DKA in 80 (30.3%). While the frequency of DKA was 54.9% between 1996 and 2007 (Period I), this significantly decreased to 44.4% between 2008 and 2019 (Period II). Girls and boys had a similar rate of T1DM, and this did not change over time. Three peak ages of diagnosis were evident; 5-7, 8-10, 12-14 years of age.

Conclusions. The frequency of DKA decreased and the frequency of admission with hyperglycemia and ketosis increased during the study period, which may have repercussions for mortality and morbidity rates and aid in improved treatment outcomes.

Key words: type I diabetes, diabetic ketoacidosis, childhood, trend.

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that is usually diagnosed in childhood. T1DM is due to insulin deficiency caused by damage to pancreatic beta cells.[1] Insulin deficiency will severely impair normal mechanisms of cellular glucose import. This results in a change in energy metabolism to lipid catabolism that may give rise to diabetic ketoacidosis. Several international registries have documented increasing rates of T1DM including DIAMOND, EURODIAB and SEARCH, with an annual increase in incidence of 2.8%, 3.5%, and 2.72%, respectively.[2-4] The incidence of T1DM ranges from 0.7 to 40 per 100 thousand worldwide and has been shown to differ between communities and regions and within the same community in different ethnic groups.[5] T1DM accounts for about 10% of all diabetes cases at any age.[6] T1DM is more common in two periods, between the ages of 5-7 years, when school starts and the child may encounter novel infectious agents, and between

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the ages of 10-14 years when sex hormone concentrations increase during puberty which is accompanied by increased growth hormone concentrations and emotional stress is high.[7,8]

Diabetic ketoacidosis (DKA) is an acute complication of T1DM that usually occurs at the time of diagnosis, is life-threatening but rarely causes mortality. It has been reported that the frequency of DKA in patients with newly diagnosed T1DM varies widely from 15 to 80%.[9-11] Although there are Turkish national programs to decrease the frequency of DKA by increasing awareness of diabetes, it has been reported that there has been no significant decrease in the frequency of DKA at the time of diagnosis of T1DM cases in Turkey.[12-14] The aim of this study was to evaluate the clinical and laboratory features of patients with newly diagnosed T1DM presenting to Inonu University Medical Faculty Hospital and Malatya Training and Research Hospital between the years of 1996-2019, and to investigate the trend of frequency of DKA over the years.

Material and Methods

Patient data were available from hospital records, which has been a source of reliable information about all diagnoses of pediatric T1DM since 1996. In Malatya, all children and young people (up to the age of 18 years) suspected of having newly diagnosed T1DM are seen at one of the two referral centers by specialists in pediatric endocrinology and diabetes. Each confirmed new case of T1DM is subsequently added to the registry. In addition, Syrian refugees residing in this region were also included in the study. Exclusion criteria included cases with syndromic diabetes, Type 2 diabetes (T2DM), maturity onset diabetes of youth (MODY), secondary causes of diabetes such as cystic fibrosis, steroid use and lipodystrophy, or those with missing data. As a result, a total of 814 T1DM cases diagnosed according to World Health Organization (WHO) criteria were included in the study.

Patients were categorized according to age: <5, 5-9, 10-13 and 14-18 years old. Patients with a diagnosis of T1DM between the years 1996–2019 were included. Patients diagnosed in the first half of the period comprised Period I, and those from the second half comprised Period II. Hyperglycemia was defined as plasma glucose (PG) ≥200 mg/dL. Confirmation of the diagnosis of T1DM was dependent on the presence of hyperglycemia, reliance on continued insulin treatment and presence of typical symptoms of T1DM at presentation. DKA was defined as hyperglycemia concurrent with acidosis (venous blood pH 7.30 and/or serum bicarbonate 15 mmol/L), ketonemia, and/or ketonuria. In addition presenting characteristics were divided into three clinical categories: 1) hyperglycemia without ketosis or acidosis; 2), hyperglycemia with ketosis but without acidosis; and 3) ketoacidosis. For the purposes of this study, ketosis assessment was performed by measuring urinary ketone semi-quantitatively. Thus ketonuria was present when urine ketone was ≥2+. Urinary ketone measurements were performed by an automated analyzer which used sodium nitroprusside reaction as a test principle (BT URICELL 1280-1600 devices (BT products, İzmir, Turkey) in each voiding. DKA severity was classified according to the Lawson Wilkins Pediatric Endocrine Society Consensus Statement[15], as follows: severe DKA (venous pH: <7.10; serum bicarbonate <5 mmol/L), moderate DKA (venous pH: 7.10 – 7.19; serum bicarbonate between 5 and 10 mmol/L), and mild DKA (venous pH: 7.20 – 7.29; serum bicarbonate between 10 and 15 mmol/L). Demographic and clinical features at the time of diagnosis, including gender, birth date, diagnosis date, the season at presentation, duration of symptoms prior to diagnosis, and type of presentation (DKA, hyperglycemia with ketosis or hyperglycemia only) were collected. In addition, laboratory results including venous blood glucose concentration, c-peptide concentration, hemoglobin A1c (HbA1c) percentage and the presence of T1DM-associated autoantibodies such as anti-glutamic

acid decarboxyase antibody (GAD), insulin antibody (IAA) and islet cell antibody (ICA) were recorded from patient files. ICA, IAA, and GADA levels were measured using an enzyme-linked immunosorbent assays based on antigen-antibody detection with the Isletest commercial kit in the Seac Brio 410499 model instrument. The HbA1c level was measured by high performance liquid chromatography using an Agilent 1100 model instrument at our hospital. Ethics Committee Approval was obtained from the Malatya Training and Research Hospital Ethics Committee for the study (approval date: 18.11.2019; approval number: 23536505-604.02).

Statistical analysis

The data are presented as mean±standard deviation (SD) values. Data analysis was performed using SPSS for Windows statistical software, version 17.0 (SPSS, Chicago, IL, USA). Student's two-tailed t-test was used for comparisons between independent variables with a normal distribution. Mann-Whitney U-test was used for variables showing uneven distribution. Distribution was analyzed by cross-tabulation and Chi-square statistics. A p-value of < 0.05 is considered to be statistically significant.

Results

The cohort consisted of 814 patients between the ages of 0.4-18 years. Four hundred and four were female (49.6%) and 410 were male. Across the whole cohort the mean age at diagnosis was 8.5±4.2 years with a range of 0.37-17.52 years. When patients were divided into four groups by age of diagnosis there were 189 patients (23.2%) between 0-4 years old, 319 patients (39.2%) between 5-9 years old, 224 patients (27.5%) between 10-13 years old and 82 patients (10.1%) between 14-18 years old. There were three peak ages at diagnosis, between the ages of 5-7, 8-10 and 12-14 years. When seasonality of diagnosis was examined 28.4% of the patients were diagnosed in winter, 26.7% in autumn, 24.2% in spring and 20.8% in summer.

The mean duration of symptoms prior to diagnosis (polyuria, polydipsia, nocturia) was 18.7±18 days (range 2-90). At the time of diagnosis, mean blood glucose concentration was 478±187 mg/dL (range: 128-1173), mean C-peptide was 0.6±0.5 (0.1-3.8) ng/mL and mean HbA1c was 12.4±2.7% (range: 6.0-22.4%). At diagnosis autoantibodies were assessed in 513 (63%) cases. The antibody test records of the remaining 301 patients were not available. Serum autoantibody levels of 87 patients in Period I and 426 patients in Period II were evaluated. GAD (62.40%) being most common followed by ICA (45.2%) and IAA (29.7%). Although at least one of the three antibodies was positive in 438 (85.4%) of these cases, none of the three antibodies was detected in 75 (14.6%) of the cases. Frequency of autoantibody positivity changed between Period I and Period II; ICA positivity increased from 20.7 to 50.0% (p<0.001) and IAA decreased from 44.8 to 26.5% (p<0.001) in Period I and Period II, respectively (Table I).

In 566 cases, clinical presentation at diagnosis was evaluated (122 patients in Period I and 444 patients in Period II). The records of the remaining 248 patients were not available. Of the 566 patients for whom data was available, 72 cases (12.7%) presented with hyperglycemia, 230 cases (40.6%) hyperglycemia with ketosis, and 264 cases (46.6%) with DKA. Of those with DKA 103 (39.0%) had mild DKA, 81 (30.6%) had moderate DKA and 80 (30.3%) had severe DKA. Key features of presentation were compared between Period I and Period II. In Period I 54.9% of patients presented with DKA. In Period II this dropped and plateaued at 44.4% after 2007. Over the years, the rate of presentation with DKA has declined (Fig. 1). The frequency of DKA subgroups did not change between periods. Further comparisons between Period I and Period II were made (Table I). Clinical characteristics of our cases according to age groups are shown in Table II.

Table I. Comparison of clinical and laboratory findings in type 1 diabetes by year of presentation.

	Period 1 (1996-2007)	Period 2 (2008-2019)	*p* value
Number of the patients	234	580	
Age (years)	7.6±3.7	8.9±4.28	<0.05
Gender n, (%)			
Female	122 (52.1)	282 (48.6)	NS
Male	112 (47.9)	298 (51.4)	NS
Age Groups n, (%)			
Ages of 0-4 years	67 (28.6)	122 (21.0)	0.020
Ages of 5-9 years	95 (40.6)	224 (38.6)	NS
Ages of 10-13 years	63 (26.9)	161 (27.8)	NS
Ages of 14-18 years	9 (3.85)	73 (12.7)	<0.001
Duration of symptoms before diagnosis (days)	18.9±16.4	18.6±18.7	NS
Glucose (mg/dL)	465.6±193	483±185	NS
C-peptide (ng/mL)	0.6±0.4	0.6±0.5	NS
HgA1C (%)	13.3±3.5	12.0±2.4	<0.001
Main presenting feature			
Hyperglycemia n, (%)	11 (9.0)	61 (13.7)	NS
Ketosis n, (%)	44 (36.1)	186 (41.9)	NS
Ketoacidosis n, (%)	67 (54.9)	197 (44.4)	0.039
DKA			
Mild DKA n, (%)	22 (32.8)	81 (41.1)	NS
Moderate DKA n, (%)	20 (29.9)	61 (31.0)	NS
Severe DKA n, (%)	25 (37.3)	55 (27.9)	NS
Autoantibody positivity			
Anti-GAD positivity n, (%)	56 (64.4)	262 (61.5)	NS
ICA positivity n, (%)	18 (20.7)	213 (50.0)	<0.001
IAA positivity n, (%)	39 (44.8)	113 (26.5)	<0.001

GAD: Glutamic acid decarboxylase antibody, IAA: Insulin antibody, ICA: Islet cell antibody,
HgA1C: Glycosylated hemoglobin, DKA: Diabetic ketoacidosis
NS: Not significant.
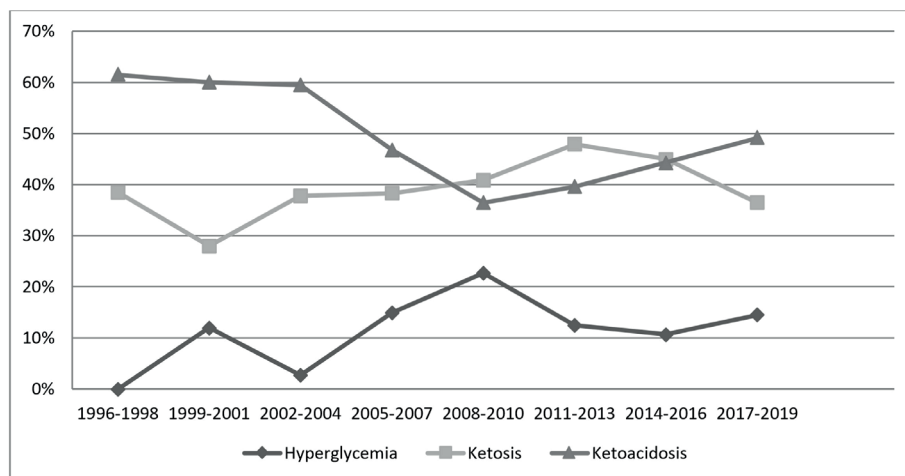
Fig. 1. Change of admission characteristics of patients with type 1 diabetes mellitus over the years.

Table II. Clinical characteristics of cases according to age groups.

Age group (years)	0-4	5-9	10-13	14-18	Total (0-18)
Main presenting feature (n=566)					
Hyperglycemia n, (%)	9 (7.0)	24 (11.7)	30 (18.4)	9 (12.9)	72 (12.7)
Ketosis n, (%)	59 (46.1)	78 (38.0)	58 (35.6)	35 (50.0)	230 (40.6)
Ketoacidosis n, (%)	60 (46.9)	103 (50.2)	75 (46.0)	26 (37.1)	264 (46.6)
Severity of DKA (n=264)					
Mild DKA n, (%)	27 (45.0)	44 (42.7)	23 (30.6)	9 (34.6)	103 (39.0)
Moderate DKA n, (%)	10 (16.6)	31 (30.0)	31 (41.4)	9 (34.6)	81 (30.6)
Severe DKA n, (%)	23 (38.3)	28 (27.3)	21 (28.0)	8 (30.7)	80 (30.3)

DKA: Diabetic ketoacidosis

Discussion

Incidence of T1D is increasing all over the world.[2-4] T1DM is one of the most common chronic endocrine diseases of childhood and adolescence and its incidence has been reported to vary with age, ethnicity, geographical region and season.[16] When the gender distribution of our diabetic patients was examined, the female/male ratio was 0.98 with no significant gender bias (*p*=0.64). Although autoimmune diseases tend to be more common in girls compared to boys, there is no gender difference in children and adolescent T1DM cases[17], in keeping with our findings. The mean age of diagnosis in our cohort was found to be 8.5±4.1 years. Poyrazoğlu et al.[18] in a study of T1DM patients aged <18 years reported a mean age of diagnosis of 9.2 years. Ardicli et al.[14] conducted a study between the years 1969-1991 and the average age of diagnosis was found to be 9.5 years. In our study, the average age of diagnosis between 2008 and 2019 had increased significantly to 8.9 years. The reason for this may be that the oldest age group (14-18 years) only made up 3.8% of all diagnoses in the earlier period of our study but this increased three-fold (12.7%) in the period between 2008-2019. Similarly, in the present study, diagnosis of cases in the youngest age group (0-4 years) fell from 28.6% in the earlier period to 21% between 2008 and 2019.

T1DM is generally reported to exhibit a bimodal distribution in age of diagnosis, with peaks at the age of 5-7 years and puberty. The first peak is thought to occur due to common infections, and the second peak occurring during puberty is due to stress and increased concentrations of circulating gonadal hormones.[19,20] In a multicenter study conducted by the European Diabetes Study Group[21] on 15,000 diabetics, when patients were divided into three groups (0-4 years, 5-9 years, and 10-14 years) the frequency of diabetes was 24%, 35%, and 41%, respectively, increasing with age. Demir et al.[12] reported that T1DM was seen in two separate age groups, most frequently between the ages of 6-8 and the second most frequently between 11-12. In our study group, the frequencies of diabetes in 0-4, 5-9, 10-13, 14-18 age groups were 23.2%, 39.2%, 27.5% and 10.1%, respectively. In addition, the frequency of the occurrence of T1DM in our study was found to peak in three different age groups, 5-7, 8-10 and 12-14 years old. While the first peak was detected in early childhood, the second peak was detected in early puberty and the third peak in late puberty.

First presentation with T1DM has been reported to be seasonal. Seasonal variations in onset of T1DM were reported in many population-based studies.[22,23] Similarly, in our study, it was observed that most presentations occurred in winter and the lowest number was in summer. The increasing frequency of viral infections in winter is thought to trigger the emergence of diabetes by increasing the need for insulin. The average symptom duration prior to diagnosis has been reported as 14 days from studies in Australia and Sweden[24,25] in patients with new diagnosis T1DM. In our study this was found to

be slightly longer at 17.8 days. In our opinion this stems from the relatively poorer socioeconomic level of our region, more difficult accessibility to health institutions, cultural differences and geographical factors.

In T1DM, the destruction of pancreatic islet beta cells occurs through T cell-mediated cellular mechanisms in 80-90% of patients. However, autoantibodies are present at diagnosis in a significant proportion of patients. Kong et al.[26] detected at least one of three antibodies in 71.4% of patients during the diagnosis of type 1 diabetic patients, including GAD in 66.2%, ICA in 54.1% and IAA in 35.6% in patients who were antibody positive. Demir et al.[12] found GAD (70%) antibodies to be most common, then ICA (44.4%) and IAA (42.6%), respectively, in patients with T1DM. In our study at least one of these three antibodies were positive in 85.4% of the cases, with GAD (62.40%) being most common followed by ICA (45.2%) and IAA (29.7%). When the rates of antibody positivity were compared between Period I and Period II there was no difference in GAD positivity while ICA positivity significantly increased from 20.7% to 50.0% and, at the same time, the IAA decreased significantly from 44.8% to 26.5%. The reason for this change has not been fully explained.

The first clinical presentation of patients with T1DM might range from hyperglycemia to diabetic coma. Demirbilek et al.[13] reported the frequency of DKA at first presentation to be 65.0% in their study between the years 2010-2011. Ardicli et al.[14] reported the frequency of diagnosis with DKA to be 50.5% between 1990-2000 and 51.0% between 2000-2010. Acar et al.[27] found the incidence of DKA to be 43.2% in patients with a new diagnosis of T1DM between 1999 and 2014. In our cohort the overall rate of DKA presentation was 46.6%, which is consistent with earlier Turkish reports. The frequency of DKA is lower in countries where T1DM is more frequent, such as Finland (22.0%), Sweden (14.0%), and Canada (18.6%), whereas T1DM prevalence is higher in countries with low prevalence including the

Arab peninsula (80.0%), Romania (67.0%), and Taiwan (65.0%).[11] It was reported that rates of DKA ranged between 26 and 67% in a 24-center study of the European Diabetes Study Group[28], covering 1260 cases. In the same study, it was highlighted that the incidence of DKA was higher in patients aged under 5 years of age compared to previous years. In New Zealand, Jackson et al.[29] reported that the frequency of DKA, which they monitored over an eight-year period, decreased from 63 to 42%, and that the blood glucose and HbA1c values in the newly diagnosed patient group were significantly lower compared to previous years. As a result of our 24-year follow-up it was found that the frequency of DKA decreased, and the frequency of admissions with hyperglycemia and ketosis increased. In Period I the frequency of presentation with DKA was 54.9%, which decreased to 44.4% in Period II. There is a need to increase both public awareness and to ensure that physicians are alert to the possibility of T1DM, even in young patients.

The severity of DKA at presentation has been previously investigated. Acar et al.[27] found severe DKA in 22.1%, moderate in 32.8% and mild in 45.1% at the time of first presentation. In a study from Germany[30], the majority of these cases (63.8%) had no ketoacidosis, while 16.6% had mild, 12.1% moderate, and 4% severe ketoacidosis at the time of diagnosis. These rates in our cohort were 30.3%, 30.6% and 39.0% for severe, moderate and mild DKA, respectively. In addition, the frequency of severe DKA was higher in the 0-4 years-old age group. The frequency of presentation with severe DKA was higher in the earlier period compared to the later period, 34.8% vs 26.3%.

The decrease in frequency of first presentation with both DKA and severe DKA was interpreted as a positive development towards likely decreased mortality and morbidity. However, in Turkey, evidence from multiple studies have shown that the frequency of DKA at first presentation is still high and has variable outcome. We recommend multicentre studies to clearly determine the national frequency

of DKA. This will provide the foundation for development of measures, involving pediatric endocrinologists, pediatricians and family physicians, in order to increase general public awareness of the first signs and symptoms of diabetes and improve the duration between first signs and presentation to a suitable specialist for assessment. For this purpose, joint seminars, public meetings, and training days in schools can be organized. In addition, social media, which is both ubiquitous and an effective communication tool, should be used. Furthermore, improved accessibility to health centers and increased socioeconomic opportunities will encourage more rapid patient presentation.

This study has some limitations. In this retrospective study, a number of factors which may have affected our results were not assessed. These included family socio-economic status and parental education level, the status of refugees, the ease of availability of health care, the number of presentations before definite diagnosis, the type of hospital used for first presentation, the status of the pediatric endocrinology centers in the region, and the number of pediatricians involved.

The rate of first presentation with DKA in T1DM cases decreased at our city between the years 1996-2019. The proportion of patients presenting with severe DKA did not change. Interestingly and in contrast to most reports, the proportion of patients presenting in the earliest age group, 0-4 years also decreased while the proportion of patients presenting in late adolescence increased. This resulted in the average age of diagnosis increasing and, as younger patients are more likely to present with DKA, may have influenced the decreasing rate of DKA at presentation. There were three peak ages of diagnosis evident in our cohort; at the ages of 5-7, 8-10, and 12-14 years. It is suggested that the rate of DKA at presentation remains a problem in Turkey, as has previously been shown by several studies.

Ethical approval

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: İD, NÇ, AA, EÇ; data collection: İD, NÇ; analysis and interpretation of results: İD, NÇ, AA, EÇ, LK, ÖN; draft manuscript preparation: İD, NÇ, AA, EÇ, LK, ÖN. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

Conflict of interest

The authors declare that there is no conflict of interest.

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