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Original Article

The Frequency of Ketoacidosis and Associated Factors at the Diagnosis of Type 1 Diabetes in Turkish Children: A Single-center Experience and Literature Review

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ABSTRACT

Aim: We aimed to investigate the frequency of diabetic ketoacidosis (DKA) and the associated factors at the time of diagnosis of type 1 diabetes (T1D) in children in a tertiary health center in Turkey, and to review previous studies conducted in Turkey.

Materials and Methods: Data of 180 children with T1D (98 boys) aged 1 to 18 years were analyzed retrospectively. All children were consecutively diagnosed as having T1D at our pediatric endocrinology clinic between April 2016 and December 2019. To conduct a literature review, we screened PubMed, Google Scholar, Web of Science, and article reference lists as well as the proceedings of the national conferences organized by the Turkish Pediatric Endocrinology and Diabetes Society for the period until January 1st, 2020.

Results: DKA was detected in 81 (45.0%) children with T1D at the time of diagnosis in this cohort. An association between DKA and high glycated hemoglobin (HbA1c) levels at the time of diagnosis was determined (p=0.038). Furthermore, a relationship was also detected between severe DKA (pH<7.1 or serum bicarbonate <5 mmol/L) and children residing in rural areas, as well as mothers with education less than high school (p=0.003 and p=0.022, respectively). This study, together with a literature review of 49 other studies, identified that 4,037 (45.6%) of 8,837 children with newly diagnosed T1D presented with DKA at diagnosis between 1981 and 2019.

Conclusion: In this cohort, presentation with DKA at the time of diagnosis of T1D in children was associated with high levels of HbA1c, and presentation with severe DKA was associated with rural life as well as low education levels of mothers. Almost half of all children with T1D presented with DKA in Turkey. There should be greater effort to increase awareness among society and health professionals for the early detection of T1D in children.

Keywords: Children, frequency, ketoacidosis, type 1 diabetes

Introduction

Type 1 diabetes (T1D) is a common chronic disease with significant morbidity and notable mortality rates in children (1,2). There is an increasing trend in the incidence of T1D in children and adolescents globally, including Turkey (3,4). Diabetic ketoacidosis (DKA) is a major acute complication of T1D and has a serious risk of mortality and morbidity. DKA develops as a result of severe insulinopenia and presents symptoms of hyperglycemia, ketosis, and acidosis. DKA is commonly detected at the time of T1D diagnosis in children and it is also detected in children previously diagnosed with T1D, usually following the interruption of insulin treatment due to an intervening disease, deliberate or unintentional omission of insulin, or when the prescribed insulin dose is no longer sufficient (5).

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A systematic review investigating 46 studies from 31 countries examining more than 24,000 children with T1D reported the frequency of DKA to have six-fold variability ranging between 12.8% and 80.0% (6). Sweden, Canada, and Finland had the lowest rates, and the highest DKA frequencies were reported in the United Arab Emirates, Romania, and Saudi Arabia (6). The frequency of DKA in children and adolescents was previously reported to be 41.9% and 64.9% at a tertiary health center in Elazığ province in Turkey at two different times (7,8). This study aimed to determine the current DKA frequency and associated factors at the time of diagnosis of children with T1D at the Elazığ province and to review literature data on DKA frequency in Turkish children with T1D at the time of diagnosis.

Materials and Methods

Data of 180 children with T1D (98 boys) aged 1 to 18 years were analyzed retrospectively. All children were consecutively diagnosed as having T1D at our pediatric endocrinology clinic in Elazığ province in Turkey between April 2016 and December 2019.

The study protocol was performed according to the Declaration of Helsinki and approved by the Ethics Committee of Non-Interventional Research of Fırat University (decision number: 0010, date: 28.11.2019). The requirement for informed consent was waived due to the retrospective nature of the study.

The hospital where the study was conducted provides healthcare services especially to residents within the provincial borders of Elazığ. Additionally, this hospital also accepts patient applications from neighboring provinces. For this study, the following demographic, clinical, and laboratory data of those children with T1D were collected and evaluated: sex, age at diagnosis, the season of diagnosis, the pre-diagnostic diabetes symptoms (polyuria and polydipsia), T1D presence in the family, parental education status, place of residence, blood glucose concentration at admission, venous blood pH and bicarbonate concentration, serum C-peptide levels, and glycated hemoglobin (HbA1c) concentrations. Children and adolescents diagnosed as having diabetes other than T1D, such as type 2 diabetes, monogenic diabetes, and diabetes developing due to secondary causes, were excluded from the study. Additionally, patients with no or insufficient laboratory data (such as those diagnosed at an external center) and whose type of diabetes was not fully defined were also excluded from the study.

DKA is defined as the presence of the following laboratory test results: Blood glucose>200 mg/dL, venous pH<7.3 or serum bicarbonate <15 mmol/L, and ketonemia (blood β-hydroxybutyrate ≥3 mmol/L) or ≥ moderate ketonuria. The severity of DKA is described in three categories: Severe DKA (pH <7.1 or serum bicarbonate <5 mmol/L), moderate DKA (pH 7.1-7.2 or serum bicarbonate 5-10 mmol/L), and mild DKA (pH 7.2-7.3 or serum bicarbonate 10-15 mmol/L) (5). Those children who presented with DKA were compared with the children who presented with non-DKA at the time of diagnosis according to their residential area type (urban or rural), age groups (<5 years, 5-9 years, and >10 years), duration of diabetes symptoms (≤2 weeks or >2 weeks), and education level of parents (less than high school or high school and above). An analysis was also performed for those children who presented with severe DKA at the time of diagnosis.

A compilation from a literature review on DKA prevalence at diagnosis was made via the following sources: PubMed, Google Scholar, and Web of Science, which were screened using the date criteria December 2019 and with the keywords DKA, T1D, and Turkey in children and adolescents. Additionally, the abstract books of national meetings organized between 1996-2019 by the Turkish Pediatric Endocrinology and Diabetes Society were examined for reports on T1D-related studies. Google Scholar and Web of Science were also screened for all case series with data on the frequency of DKA at diagnosis together with study references and studies cited in them. Congress papers of the studies published as articles were excluded from the study. The following data were obtained from studies that were included in the review: (a) Year of study, (b) diagnosis period of children with T1D, (c) number of children with T1D, (d) frequency of DKA and severe DKA at diagnosis, and (e) factors associated with DKA.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS 22.0, SPSS Inc., Chicago, U.S.A.) program for Windows was used for the statistical analysis of the data. Demographic, clinical characteristics and laboratory results were evaluated using descriptive and frequency statistics. Student's t-test or the Mann-Whitney U test was used in the comparison of the averages, and the chi-square test was used to compare frequencies. Logistic regression analysis was performed for parameters with significant differences between groups. Statistical values of $p<0.05$ were considered significant. The odds ratio (OR) was calculated with 95% confidence intervals (CI) for nominal values that were found to be significant through regression analysis.

Results

In this study, we analyzed data obtained from 180 children with T1D, of whom 98 (54.4%) were boys, with a mean age of 10.1±4.2 (range: 1.1-17.9) years. DKA at diagnosis was detected in 81 (45.0%) of these children. When the patients were classified by the severity of DKA, 26 (32.1%) patients had severe DKA, 37 (45.7%) had moderate DKA, and 18 (22.2%) had mild DKA. Of the patients with DKA at diagnosis, 41 (50.6%) were male with a mean age at diagnosis of 9.7±4.2 years. The mean age was not significantly different from that of patients with no DKA at diagnosis. When compared by age groups, the number of patients in both groups was similar. Furthermore, there was no statistical difference between those patients with and those without DKA when compared according to their duration of diabetes symptoms before the diagnosis, the season in which diabetes was diagnosed, the presence of T1D in first-degree relatives, and parental education status.

When the groups were compared as per their residence area, the frequency of DKA at diagnosis was significantly higher for those living in rural areas (p=0.030). A comparison of the laboratory data at diagnosis revealed that children with DKA had higher HbA1c and lower C-peptide levels (p=0.017 and p=0.001, respectively). Those children with severe DKA had lower average C-peptide levels, a higher occurrence of rural residency, and inadequate maternal education levels (below high school) (p=0.024, p=0.003, and p=0.022, respectively). A regression analysis of children with severe DKA indicated a relationship between children living in rural areas [OR 3.95; 95% CI: (1.69-8.72); p=0.003] and having mothers with lower education levels [OR 1.34; 95% CI: (1.12-1.60); p=0.022]. High levels of HbA1c at diagnosis was found to be a risk factor for all patients with DKA (p=0.017). The comparison of clinical features by the presence of DKA and severe DKA at diagnosis in children with T1D is shown in Table I.

Table I. Comparison of clinical features by presence of DKA and severe DKA at diagnosis in children with type 1 diabetes

	DKA present	No DKA	p-value	Severe DKA present	No severe DKA	p-value
Number (%)	81 (45.0%)	99 (55.0%)		26 (14.4)	154 (85.6)	
Sex (M/F)	41/40	57/42	0.370	10/16	88/66	0.091
Age at diagnosis (years)	9.7±4.2	10.4±4.2	0.262	9.4±4.3	10.2±4.2	0.448
Diagnosis age groups (%) <5 years 5-9 years >10 years	 12 (14.8%) 33 (40.7%) 36 (44.4%)	 14 (14.1%) 32 (32.3%) 53 (53.5%)	0.442	 5 (19.2%) 10 (38.5%) 11 (42.3%)	 21 (13.6%) 55 (35.7%) 78 (50.6%)	0.657
Diabetes symptoms period (≤2 weeks/>2 weeks)	54/27	54/45	0.126	15/11	93/61	0.831
Diagnosis Season (%) Spring Summer Fall Winter	 21 (25.9%) 19 (23.5%) 18 (22.2%) 23 (28.4%)	 22 (22.2%) 24 (24.2%) 25 (25.3%) 28 (28.3%)	0.932	 8 (30.8%) 4 (15.4%) 6 (23.1%) 8 (30.8%)	 35 (22.7%) 39 (25.3%) 37 (24.0%) 43 (27.9%)	0.661
Residence Area (rural/urban)	14/67	6/93	**0.030**	8/18	12/142	**0.003***
T1D in Family (%)	4 (4.9%)	5 (5.1%)	1.000	1/25	8/146	1.000
Mother's education level (%) Lower than high school High school and above	 58 (71.6%) 23 (28.4%)	 67 (67.7%) 32 (32.3%)	0.627	 23 (88.5%) 3 (11.5%)	 102 (66.2%) 52 (33.8%)	**0.022****
Father's education level (%) Lower than high school High school and above	 47 (58.0%) 34 (42.0%)	 57 (57.6%) 44 (42.4%)	1.000	 19 (73.1%) 7 (26.9%)	 85 (55.2%) 69 (44.8%)	0.132
Glucose (mg/dL)	471±158	435±194	0.171	491±116	444±187	0.085
C-peptide (ng/mL)	0.409±0.468	0.726±1.198	**0.001**	0.324±0.217	0.629±1.023	**0.024**
HbA1c (%)	12.2±2.5	11.3±2.4	**0.017*****	12.5±2.9	11.6±2.4	0.173

Parameters with significant difference between the groups, and a significant relationship with logistic regression analysis; *p=0.001, **p=0.023, ***p=0.038
DKA: Diabetic ketoacidosis, M: Male, F: Female

The literature search performed for this study revealed 24 research articles, 18 national and seven international meeting proceedings for studies with data on the frequency of DKA at diagnosis in Turkey. These studies all together showed that 4,032 (45.6%) out of 8,837 children with T1D had DKA at the time of diagnosis between 1981 and 2019 in 24 provinces. In 18 studies evaluating severe DKA, the frequency of DKA at diagnosis was reported to be 6.0-41.5%, and the frequency of severe DKA among patients with DKA was reported to range between 12.7% and 63.0% (Table II) (7-55). Changes in the frequency of DKA and severe DKA at diagnosis according to the time intervals in which the children were diagnosed as having T1D are shown in Figure 1.

Discussion

Diagnosis of T1D in children at the stage of hyperglycemia and ketonemia before the development of DKA is critical for reducing diabetes-related mortality and morbidity levels. This study reports on the experience of a tertiary health center and data in the literature about the prevalence of DKA and DKA-associated factors at the time of diagnosis for children and adolescents with T1D in Turkey.

The initial data from our clinic on the frequency of DKA at diagnosis was reported to be 64.9% from a total of 74 children and adolescents between June 2004 and June 2007 (7). A second study conducted between June 2013 and February 2016 reported a frequency of 41.9% for DKA in a group of 93 patients (8). The results of this work indicate a significant decrease in DKA frequency compared with the first study, and a comparison with the current study on the topic indicates no change.

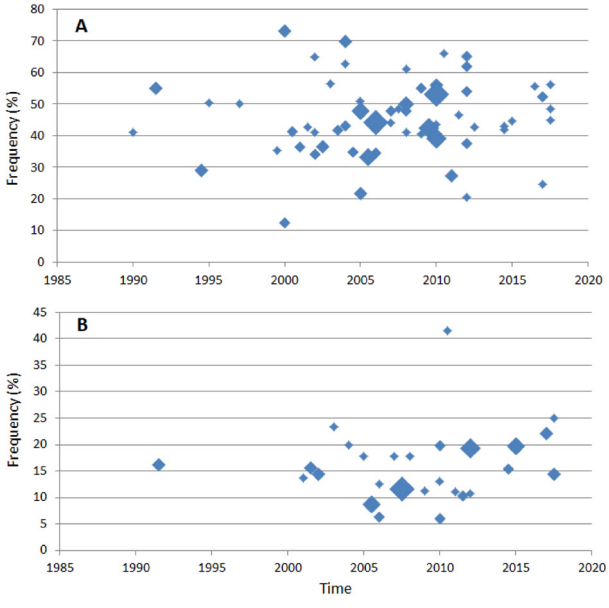

Figure 1. Reported frequencies of DKA (A) and severe DKA (B) at diagnosis of children with type 1 diabetes in Turkey. Symbols were scaled according to the sizes of case series and indicated the middle of the time periods for these case series
DKA: Diabetic ketoacidosis

A decrease in the frequency of DKA at diagnosis was reported in studies conducted at some centers in Turkey (10,15,28). However, there are also publications reporting no change (11) or an increase in its frequency (21,29,33). Fifty studies, including this one, reported DKA findings at diagnosis in approximately half of 8,837 children and adolescents with T1D in Turkey. There is an inverse correlation between T1D incidence of communities and the frequency of DKA at diagnosis (56). This can be explained by an increased awareness of T1D and its symptoms. The increase in T1D incidence in a 20-year period in Northern Finland and the decrease in DKA risk in diagnosis support this proposition (57). The fact that Turkey is listed as a country with moderate T1D incidence may be related to the relatively high incidence of DKA at diagnosis (4,38,58,59). However, despite the increase in T1D incidence in some countries that are well-organized and have good access to health systems, it has been reported that there has been no decrease in the frequency of DKA at diagnosis. For example, in a study conducted in a center in Australia, it was observed that the risk of DKA did not change in children and adolescents with newly diagnosed T1D in the period from 1998 to 2010 (60). Similarly, in Auckland, the largest city in New Zealand, the frequency of DKA at diagnosis remained unchanged between 1999 and 2013, at around 27% (61). The symptoms of diabetes in children with newly diagnosed T1D are usually noticed within a few days to a few weeks before their presentation to hospital. In the EURODIAB study conducted in 24 centers across Europe, 75% of children younger than 15 years with newly diagnosed T1D were found to have had symptoms of diabetes for at least two weeks (56). There has been no significant reduction in the frequency of DKA and severe DKA at diagnosis in children with T1D in our country for years. This strongly implies a failure in the recognition of early T1D symptoms by families and healthcare providers. In our country, a program called "Diabetes Program at School" has been carried out since 2010 to raise awareness of T1D via schools and teachers, enabling the early diagnoses of T1D and decreasing the frequency of DKA in school children. Within the scope of this program, posters about diabetes were hung in schools, a short film was broadcast on national channels, meetings were held at schools and a website was launched (62).

Table II. Studies reporting frequency of DKA at T1D diagnosis in children in Turkey

Order	Reference	Province	Time period	T1D n	DKA n	DKA frequency	Severe DKA frequency
1	Kendirci et al. (9)	Kayseri	1981-1999	190	78	41.0	
2	Demir et al. (10)	İstanbul	1985-2004	395	196	48.5	15.9
			1985-1998	NA	NA	55.0	16.2
			1999-2004	NA	NA	42.6	15.6
3	Ardicli et al. (11)	Ankara	1990-2010	354	180	50.8	
			1990-2000	105	53	50.5	
			2000-2010	249	127	51.0	
4	Demir et al. (12)	Ankara	1990-2017	621	259	41.7	
5	Bober et al. (13)	İzmir	1991-1998	62	18	29.0	
6	Şen et al. (14)	Afyonkarahisar	1993-2007	52	38	73.1	
7	Bideci et al. (15)	Ankara	1995-2004	73	30	41.0	
			1995-1999	32	16	50.0	
			2000-2004	41	14	34.1	
8	Darcan et al. (16)	İzmir	1995-2005	128	16	12.4	
9	Arı Yuca et al. (17)	Van	1995-2009	166	68	41.0	14.4
10	Kocabaş et al. (18)	Antalya	1996-2013	89	31	34.8	
11	Aktaş et al. (19)	Şanlıurfa	1998-2001	17	6	35.3	
12	Şimşek et al. (20)	Düzce	1998-2003	46	19	41.3	
13	Acar et al. (21)	İzmir	1999-2014	282	122	43.2	9.5
			1999-2003	44	16	36.4	13.7
			2004-2008	96	40	41.7	6.3
			2009-2014	142	66	46.5	10.3
14	Haliloglu et al. (22)	İstanbul	1999-2016	517	251	48.4	11.6
15	Taskin et al. (7)	Elazığ	2000-2004	74	48	64.9	
16	Karaguzel et al. (23)	Antalya	2000-2005	115	42	36.5	
17	Candemir et al. (24)	Denizli	2001-2007	53	37	69.8	
18	Karadağ et al. (25)	İstanbul	2002-2006	51	22	43.1	
19	Çayır et al. (26)	Erzurum	2002-2010	129	57	44.2	
20	Sağlam et al. (27)	Bursa	2003-2008	490	163	33.2	8.7
21	Ucar et al. (28)	İstanbul	2003-2012	401	177	44.2	
			2003	NA	17	56.5	23.3
			2004	NA	22	62.8	20.0
			2005	NA	22	47.8	17.8
			2006	NA	18	45.0	12.5
			2007	NA	22	47.8	17.8
			2008	NA	22	47.8	17.8
			2009	NA	17	40.4	11.2
			2010	NA	18	43.4	13.1

Table II. continued

			2011	NA	10	27.3	11.1
			2012	NA	9	20.4	10.7
22	Cizmecioglu et al. (29)	Kocaeli	2005-2008	95	37	38.9	11.6
			2005	23	5	21.7	
			2006	29	10	34.5	
			2007	25	11	44.0	
			2008	18	11	61.1	
23	Arıcan et al. (30)	Kayseri	2006-2013	453	192	42.4	
24	Aydın et al. (31)	Ankara	2007-2013	92	36	39.1	
25	Demir et al. (32)	İzmir and Manisa	2008	139	57	41.0	
26	Özsu et al. (33)	Kocaeli	2008-2010	124	66	53.2	16.5
			2008	NA	NA	50.0	
			2009	NA	NA	55.0	
			2010	NA	NA	56.0	
27	Dilek et al. (34)	Edirne	2006-2018	315	195	61.9	19.3
28	Esen et al. (35)	Ankara	2009-2011	111	59	53.1	19.8
29	Karamık et al. (36)	Ankara	2009-2015	115	62	53.9	
30	Demir et al. (37)	İzmir and Manisa	2010	84	34	40.5	6.0
31	Demirbilek et al. (38)	Diyarbakır	2010-2011	41	27	65.9	41.5
32	Evliyaoglu et al. (39)	İstanbul	2010-2014	184	69	37.5	
33	Demiral et al. (40)	Eskişehir	2010-2015	103	44	42.7	
34	Baran et al. (41)	Diyarbakır	2011-2013	83	54	65.1	
35	Kara et al. (42)	Ankara	2011-2013	50	27	54.0	20.0
36	Cicek et al. (43)	Kayseri	2011-2019	323	144	44.6	19.7
37	Aras et al. (44)	Diyarbakır	2013-2016	142	61	42.9	15.4
38	Esen (8)	Elazığ	2013-2016	93	39	41.9	15.1
39	Kara (45)	Bursa	2015-2018	144	80	55.6	
40	Araslı Yılmaz et al. (46)	Ankara	2016-2018	149	78	52.3	22.1
41	İşleyen and Bolu (47)	Adıyaman	2016-2018	45	11	24.5	
42	Esen and Okdemir*	Elazığ	2016-2019	180	81	45.0	14.4
43	Ersoy et al. (48)	Manisa	2017-2018	64	31	48.4	25.0
44	Yazkı et al. (49)	Adana	2017-2018	66	37	56.1	
45	Ökten et al. (50)	Trabzon	NA	33	20	60.6	
46	Şimşek et al. (51)	Ankara	NA	67	21	31.3	
47	Hatun et al. (52)	33 centers	NA	498	227	45.6	
48	Karagüzel et al. (53)	Trabzon	NA	100	54	54.0	
59	Bala et al. (54)	Van	NA	101	52	51.4	
50	Ozbek et al. (55)	Diyarbakır	NA	538	279	51.9	
				8837	4032	45.6	

*This study, NA: Not available
DKA: Diabetic ketoacidosis, T1D: Type 1 diabetes

Although a possible positive effect of this program on the frequency of DKA at the time of diagnosis was reported in one local study (28), this effect was not demonstrated by studies designed throughout the country.

Due to various factors, it can be expected that the risk of DKA at diagnosis is greater in younger children owing to the difficulty in recognizing the classic symptoms of T1D, especially in children aged <2 years, as the possibility of a diagnosis of T1D is considered less likely by physicians, and also the faster development of dehydration and acidosis in young children. Furthermore, beta-cell destruction in the T1D development process in young children may be more aggressive (6). Usher-Smith et al. (63) conducted a meta-analysis study investigating 31 studies and reported that children aged under 2 years had a 3-times greater risk of being diagnosed as having DKA than children older than 2 years (OR 3.41; 95% CI: 2.54-4.59). This risk is present for children aged up to five years, albeit to a lesser extent (OR 1.59; 95% CI: 1.38-1.84) (63). In our patient series, this age group was not evaluated in terms of DKA risk due to the small number of children aged <2 years. However, when children with and children without DKA were compared according to their average age and age groups (<5, 5-10, and 10-18 years), there was no statistically significant difference. Similarly, in some studies conducted in our country, it was reported that the risk of DKA at diagnosis was not different in children aged <5 years (10,27,37,39). On the other hand, some studies found that the incidence of DKA was higher in children aged <5 years (21,28,32,38,46). However, in only two of these studies, the relationship between DKA risk and causality of being aged under 5 years was shown through regression analysis (28,32).

Lower risk of DKA at diagnosis has been reported to be associated with having parents with high education levels and first-degree relatives with T1D (6). This reduced risk can be explained by higher awareness of T1D and familiarity with the signs and symptoms of hyperglycemia. A low frequency of DKA at diagnosis in children was associated with their mothers' high school or higher education levels in a study from Lithuania, and another study from Finland also reported a decreased frequency of DKA for children with at least one parent with an academic degree (64,65). In contrast, no relationship was detected between the level of parental education and frequency of DKA at the time of diagnosis of children with T1D in a German study. However, the same study also reported a higher risk of severe DKA (pH ≤7.2) in children with parents that had <9 years of education in comparison to parents with ≥12 years of education (OR 3.54; 95% CI: 1.10-11.35) (66). Ucar et al. (28) reported no association between parental education and the risk of DKA at the time of diagnosis in Turkish children with T1D. There was no association between the education level of the parents and the risk of DKA at diagnosis in our patient series; however, having a mother with less than high school education was associated with severe DKA.

In a meta-analysis, Usher-Smith et al. (63) evaluated five studies investigating the relationship between having a relative with diabetes and the risk of DKA at T1D diagnosis in children and concluded that having a relative with diabetes was a risk-reducing feature for DKA. In this study, it was found that having a first-degree relative with T1D made no difference in terms of either DKA risk or severe DKA risk. Ucar et al. (28) found that the frequency of DKA was lower (p=0.042) in applicants who had first and/or second-degree relatives with T1D, but no causal relationship was detected (p=0.21). Although a family history of a parent or sibling with T1D was found to be a risk factor in the first of two different studies conducted by Demir et al. (37) in İzmir and Manisa in 2008 and 2010, the second study reported that it was not a risk factor (32). Apart from these studies, two studies from our country reported that a T1D history in the family made no difference in terms of DKA risk at diagnosis (38,52). However, Ozbek et al. (55) reported that children with a family history of diabetes had a significantly lower frequency of DKA (p=0.04), although at a statistically borderline value. These different results were thought to be related to the low incidence of childhood T1D throughout the community.

This study detected that the DKA diagnosis rate was higher for those living in rural areas. Three studies, including one from our country, found that living in rural or urban areas did not affect the risk of DKA at diagnosis. There was no difference in DKA diagnosis rates between those living in villages or the countryside in comparison with those living in the city center, towns or suburbs in two different studies conducted in Finland, Sweden, and Lithuania (64,65). According to a study by Demirbilek et al. (38) conducted in the province of Diyarbakır, Turkey, there was also no difference in DKA diagnosis rates between those living in the city center, suburbs or villages. This study found that there was a causality relationship between living in villages and the frequency of severe DKA at diagnosis. This may be due to limited access to health services due to rural isolation and may be an indirect factor in the presence of DKA during diagnosis.

This study detected a weak causality relationship between the presence of DKA at diagnosis and HbA1c levels,

but no similar relationship was found with the frequency of severe DKA. In two related studies conducted in Turkey, it was reported that children with DKA had higher HbA1c levels (32-37). However, in another study, no difference was found between the groups (38). The lack of a relationship between severe DKA and high HbA1c levels in this study could be because there was a small number of children with severe DKA and the possibility of the rapid development of T1D in some children. Compared with older children, the lower C-peptide level of children aged <2 years in the diagnosis of T1D suggests that beta cell damage may be more aggressive in younger children (65). In this study, we found low levels of C-peptide in children with DKA and with severe DKA groups compared with the no DKA or non-severe DKA groups but no causal relationship was detected. Ucar et al. (28) reported that serum C-peptide ≥0.6 ng/mL was associated with a reduced risk of DKA at diagnosis (OR 0.55; 95% CI: 0.33-0.92). Furthermore, three other studies conducted in Turkey investigated the differences in C-peptide levels in children with DKA and without DKA at diagnosis of T1D; two reported that children who presented with DKA had lower levels of C-peptide than those without DKA (37,39). However, in another study, no difference was found between the groups (38).

In a meta-analysis of 21 studies, Usher-Smith et al. (63) examined the effect of sex on the frequency of DKA in the diagnosis of T1D, and 20 of these studies showed no effect of sex. A study evaluating 2,121 children aged under 15 years from Germany reported that the frequency of DKA at T1D diagnosis was higher for girls (OR 1.30; 95% CI: 1.07-1.58; p=0.008) (67). When nine studies with sufficient data for meta-analysis were evaluated together, the OR for boys was 0.93 [95% CI: (0.76-1.14); p=0.472] (63). Another study reported that female sex was not associated with an increased risk of severe DKA (pH≤7.2) [OR 0.68; 95% CI: (0.26-1.83); p=0.450] (66). In our patient series, neither risk of DKA nor risk of severe DKA at diagnosis was associated with the sex of the child with T1D. In seven studies conducted in Turkey, the effect of sex on the frequency of DKA at diagnosis was investigated, and two of these studies reported that the frequency of DKA was higher for girls. The first of these studies by Ardicli et al. (11) investigated the clinical features of 354 children with T1D diagnosed over 40 years and they found that the frequency of DKA at diagnosis was higher for girls (55.6% vs. 44.0%, p=0.008). A second study by Demir et al. (10) reported that the frequency of DKA at diagnosis was higher for girls (55.1% vs. 41.7%, p=0.042). On the other hand, five other studies reported that sex was not associated with the frequency of DKA at the time of diagnosis of T1D (27,28,32,39,55).

Difficulty in accessing health services due to a lack of health insurance, low socio-economic status, and being a minority have been reported as other factors associated with the risk of DKA presence at diagnosis (6). A relationship of the above factors with the presence of DKA in our country is probably unlikely because general health insurance provides diagnostic, treatment, and rehabilitation services for all children aged less than 18 years in Turkey. This study does not discuss the ethnic and socioeconomic characteristics of the patients and, as such, these features were not evaluated.

Study Limitations

The high number of patients in this study provides strong data on the frequency of DKA at the time of T1D diagnosis, which makes this study powerful. However, as the designs of the studies examined in this review were heterogeneous and only the abstracts of some studies were evaluated, estimating the factors associated with the presence of DKA at T1D diagnosis was limited.

Conclusion

This study researched several databases rigorously and systematically and detected that approximately half of 8,837 children with T1D presented with DKA at diagnosis, and there was no decrease in the frequency of DKA in Turkey between 1981 and 2019. Our findings indicate that for an earlier childhood T1D diagnosis across Turkey, awareness must be raised among members of society and health professionals. Also, there is a need for investigations to determine the reasons for the persistence of the high frequency of DKA at the time of T1D diagnosis in Turkey.

Ethics

Ethics Committee Approval: The study protocol was performed according to the Declaration of Helsinki and approved by the Ethics Committee of Non-Interventional Research of Fırat University (decision number: 0010/28.11.2019).

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Medical Practices: İ.E., D.Ö., Concept: İ.E., D.Ö., Design: İ.E., D.Ö., Data Collection or Processing: İ.E., D.Ö., Analysis or Interpretation: İ.E., D.Ö., Literature Search: İ.E., D.Ö., Writing: İ.E.

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