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Factors Associated with Newly Diagnosed Children with Diabetic Ketoacidosis

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Abstract

Background: Diabetes mellitus type 1 is one of the most prevalent endocrine diseases in pediatrics. Diabetic ketoacidosis is considered as one of the most threatening clinical pictures of DM1, especially if occurred as the first presentation of DM1 in children.
Objectives: The current study aimed to identify factors which may play a role in DKA onset in children.
Methods: This case-control study included all patients under 18 years old who referred to department of pediatrics endocrinology at Mashhad University Hospital (Imam Reza) from January 2013 to December 2015 as newly diagnosed patients with DM1. Patients who fulfilled DKA criteria at diagnosis were considered as DKA group and those who referred with other presentations were considered as control group (non-DKA group). Data were analyzed by SPSS software ver. 16.
Results: During the study period, 97 (39.2% male) newly diagnosed patients were included as DKA group. Accordingly 97 gender- and age-matched patients were added as non-DKA group. The most prevalent symptoms in both groups were polyuria (91.88%) and polydipsia (88.66%). Fever and cold symptoms were significantly higher in the DKA group ($P < 0.001$ and $P = 0.005$, respectively). Hemoglobin A1c level was significantly higher in the DKA group ($P = 0.001$), while body mass index was significantly lower in the DKA group ($P = 0.045$). Fever and father's education level were the most important risk and protective factors in the DKA onset in newly diagnosed patients with DM1 (adjusted OR = 10.1, 95% CI = 2.9-35.3; $P < 0.001$ and adjusted OR = 0.5, 95% CI = 0.3 - 0.9 and $P = 0.019$, respectively).
Conclusions: In conclusion, a recent febrile illness was found as the strongest risk factor and father's education level as the main protective factor in the DKA to diagnose children with DM1. The study findings suggested that DKA is a severe form of DM1 instead of a neglected or misdiagnosed disease.

Keywords: Children, Diabetic Ketoacidosis, Diabetes Mellitus Type 1

1. Background

Diabetes mellitus is one of the most common metabolic diseases with the principal characteristic of chronic hyperglycemia due to impaired secretion of insulin, insulin action, or both (1). Diabetes mellitus type 1 (DM1) is an autoimmune disease resulted from chronic destruction of the pancreatic beta cells which subsequently lead to a marked decline in insulin secretion capacity (2).

It is estimated that incidence rate of DM1 among children under 15 years old is elevated 3% annually worldwide (3, 4). The incidence of DM1 in the Islamic Republic of Iran is estimated about 3.7 in 100,000 per year, which is lower compared to most European and North American countries such as the United Kingdom with 26/100,000 per year. However incidence rate in some Asian countries is even lower than IR Iran with 0.7, 1.4-2.2, and 0.1-2.3 per 100,000 per year in Pakistan, Japan, and China, respectively (5).

Diabetic ketoacidosis (DKA) is considered as the most common cause of mortality and morbidity in children with DM1 (2). Unfortunately, the first presentation of 10% to 70% of newly diagnosed children with DM1 is DKA (6). Also, these children encounter more problems than those newly diagnosed with DM1 including lower remission rate and poorer glycemic control (7, 8).

Although it is proposed that DKA awareness programs partly reduce the rate of DKA presentation in children with DM1 in some European countries, its incidence rate is still high. Therefore it is unclear whether DKA at presentation is a result of a delayed diagnosis and/or treatment or a more severe form of DM (6).

2. Objectives

The current study aimed to evaluate the demographic, socioeconomic, familial history, diagnostic errors and serobiologic factors associated with the risk of DKA in children diagnosed with DM1.

3. Methods

The current case-control study evaluated all children who were newly diagnosed with DM1 and DKA was their first presentation in Mashhad, IR Iran. All patients who referred to the department of pediatrics endocrinology at Mashhad University Hospital (Imam Reza) from January 2013 to December 2015 were included. The study protocol was approved by the local ethics committee. The gender- and age-matched patients newly diagnosed with DM1 who presented symptoms other than DKA were included as the control group. Sample size was calculated by the prevalence of DKA at diagnosis through PASS ver. 12 with a 95% confidence interval (CI) and a sample error of 10% which was 100 patients in each group.

In all cases, diagnosis of DM1 was made by ISPD 2014 criteria. All children under 18 years old who presented: 1) Fasting blood sugar (FBS) over 125 mg/dL or 2) Random blood sugar over 200 mg/dL plus polyuria or polydipsia or 3) Oral glucose tolerance test (OGTT) over 200 mg/dL were diagnosed as patients with DM1.

Among these newly diagnosed patients, children who met the DKA criteria were classified as DKA group and the remaining patients were considered as the control group. The DKA criteria included: 1) pH < 7.3 and serum bicarbonate level over 15 mEq/L, 2) Blood sugar over 11 mM/L and 3) Ketonemia and ketonuria (9). Patients who presented comorbidities were excluded from the study.

Upon diagnosis of DM1, data obtained from each patient included: demographic characteristics, parents' educational status, familial history of DM1 in the first and second degree relatives, family income level, insurance status, family structure and laboratory findings including hemoglobin A1c (HbA1c), glutamic acid decarboxylase (GAD65), c-peptide, internal carotid artery (ICA), IA and level of insulin. Weight and height were measured in kilograms and centimeters, respectively. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). According to center for disease control (CDC) charts of BMI-for-age in children 2-20 years (separate charts for boys and girls), the patients were classified into three groups. Patients with BMI under 5 percentile were underweight; patients with BMI above 85 percentile were overweight and the remaining patients were the normal group.

Additionally four questions were addressed by parents including: 1) Was the time interval between early symptoms onset and DM diagnosis more than 24 hours?; 2) Was patient's primary diagnosis correct?; 3) Was there a recent febrile disease? and 4) Were any medical visits made a week prior to diagnosis (how many times)?

Factors studied in the article were mainly based upon a recent systematic review of Usher-Smith et al.,6 which the authors had a long experience in the only tertiary health center for pediatric eccrinology in North-East of IR Iran.

The results were expressed as mean ± SD. Data were analyzed by SPSS ver. 16.0 using Pearson correlation, binary logistic regression, one-way ANOVA, Student T-test and Mann-Whitney U (nonparametric) test. A P-value of < 0.05 was considered significant. The odds ratio was determined for all studied factors by binary logistic regression. Accordingly all factors with $P < 0.1$ in the related subgroups were adjusted by forward: LR method in logistic regression. Three subgroups were considered including: 1) Socioeconomic factors, 2) Patient's signs and symptoms and 3) Health-care system factors. Consequently we added all significant factors found in subgroups were added to a logistic regression model.

4. Results

Ninety-seven children with DM1 who presented DKA were included in the DKA group and 97 children with DM1 who did not present DKA at the time of admission were included in the non-DKA group. Thirty-eight and forty-eight children in DKA and non-DKA groups were male, respectively (P = 0.193). The mean age at diagnosis was 8.72 ± 3.34 and 8.84 ± 3.94 years in DKA and non-DKA groups, respectively (P = 0.824).

Although no significant difference was observed in weight or height between the case and control groups, children in DKA group had significantly lower BMI in comparison to those of the non-DKA group (P = 0.045) (Table 1). Additionally, a significant difference was found between underweight and normal groups (P = 0.02, unadjusted OR = 2.2 (1.1-4.4).

The most prevalent symptoms in both groups were polyuria (91.88%) and other symptoms in order of prevalence were polydipsia (88.66%), increased appetite (26.8%), fever (14.4%) and cold (13.4%) (Table 2). A significant relationship was found between onset of fever and cold and presentation of DKA in patients with DM ($P < 0.001$ and P = 0.005, respectively). Fever was also found as the most important risk factor in DKA presentation in newly diagnosed patients with DM1 (unadjusted OR = 10.595, 95% CI = 3.073-36.533).

Table 1. Symptoms Before Diagnosis Among Newly Diagnosed Patients With Diabetes Mellitus Type 1

Symptoms, No. (%)	DKA (n = 97)	Non-DKA (n = 97)	P Value
Polyuria	92 (96.84)	89 (96.74)	1.0
Polydipsia	88 (92.63)	84 (91.30)	0.793
Increased appetite	29 (30.52)	23 (25.0)	0.419
Fever	25 (26.32)	3 (3.26)	< 0.001
Cold	20 (21.05)	6 (6.52)	0.005

Abbreviation: DKA, diabetic ketoacidosis.

Table 2. Comparisons of Patients With and Without Diabetic Ketoacidosis

Variable	DKA (Mean ± SD)	Non-DKA (Mean ± SD)	P Value
Age (year)	8.72±3.34	8.84±3.94	0.824
Gender (Male); n, (%)	38 (39.17)	48 (49.48)	0.193
Weight (kg)	25.64±9.82	28.30±13.60	0.120
Height (cm)	127.18±19.32	128.48±22.23	0.666
BMI (kg/m^2)	15.34±2.69	16.22±3.34	0.045
HbA1c (%)	10.15±1.68	9.41±1.42	0.001
Anti-GAD65 (U/L)	139.85±81.68	132.01±84.82	0.515
Anti-ICA (U/lit)	7.94±35.24	4.78±2.53	0.127
History of DM in the first degree relatives, n (%)	12 (12.37)	19 (19.58)	0.239
History of DM in the second degree relatives, n (%)	28 (28.87)	36 (37.11)	0.285
Divorced parents, n (%)	12 (12.37)	9 (9.28)	0.645
Monthly income; $US	8575.1±4413.6	10778.4±6020.4	0.001
Healthcare insurance, n (%)	88 (90.72)	95 (97.94)	0.058
Drug consumption history, n (%)	5 (5.15)	6 (6.19)	1.0
Sign of delayed diagnosis delay (days)	15.43±13.81	16.14±17.76	0.863
Number of visits in last week	2.15±1.40	1.46±0.66	<0.001
Diagnosis to treatment delay (hours)	9.14±21.04	24.54±54.82	0.001
Diagnosis in first visit, n (%)	43 (44.33)	58 (59.79)	0.044

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; GAD65, glutamic acid decarboxylase; ICA, internal carotid artery; DM, diabetes mellitus.

Among laboratory findings, HbA1c level was significantly higher in DKA group (P = 0.001) compared to that of the non-DKA group. Anti-GAD65 and anti-ICA were not significantly different between the groups (P = 0.515 and P = 0.127, respectively) (Table 1).

Lower patients in DKA group were diagnosed correctly in their first visit than Non-DKA group (44.33% vs. 59.79%, respectively; P = 0.044). A correct diagnosis at first visit was a protective factor from presenting patients with DKA (unadjusted OR = 0.535, 95% CI = 0.303 - 0.947) (Table 3). There was no difference between sign onset to diagnosis between the two groups (P = 0.863). However, longer time interval between diagnosis and treatment was observed in non-DKA group (24.54 ± 54.82 vs. 9.14 ± 21.04, P = 0.001) (Table 1).

The prevalence of DKA among children who live in families with monthly income below $US 233.3 was two times higher than those who live with higher incomes (unadjusted OR = 2.053; 95% CI = 1.060 - 3.977). Benefiting from healthcare insurance was a strong protective factor for DKA onset as the first DM1 sign (unadjusted OR = 0.2; 95% CI = 0.043 - 0.979). Additionally, lack of academic education or non-completed high school diploma in fathers was a more effective risk factor than that of mothers in DKA presentation (unadjusted OR = 2.179 vs. OR = 1.847, respectively). However a history of DM in the first or second degree relatives of children with DM1 did not affect the risk of DKA onset at admission [unadjusted OR = 0.6 (0.3 - 1.3) and OR = 0.7 (0.4-1.3), respectively] (Table 3).

In three subgroups of factors, four factors in socioeconomic, three in signs and symptoms and 2 in healthcare system had P Value < 0.1; therefore, they were considered for adjustment. In socioeconomic subgroup, father's education level was adjusted for monthly income below $US 233.3, benefiting from healthcare insurance and mother's education level in a forward: LR method of binary logis-

Table 3. Evaluation of Socioeconomic Factors, Patient's Signs and Symptoms, and Healthcare System Factors Regarding the Risk of Diabetic Ketoacidosis Onset at the Diagnosis of Children with DM1

Variable	DKA Group, n (%)	Non-DKA group, n (%)	Unadjusted Odds Ratio (95%CI)	P Value
First degree FH of DM	38.7	52.1	0.6 (0.3-1.3)	0.239
Second degree FH of DM	43.8	53.1	0.7 (0.4-1.3)	0.285
Drugs Hx	45.5	50.3	0.8 (0.2-2.8)	1.0
Divorced parents	57.1	49.1	1.4 (0.6-3.4)	0.645
No healthcare insurance	81.8	48.1	4.9 (1.0-23.1)	0.058
Wrong Dx In First Visit	58.1	42.6	1.9 (1.1-3.3)	0.044
Polydipsia	51.2	46.7	1.2 (0.4-3.4)	0.793
Polyuria	50.8	50	1.0 (0.2-5.3)	1.0
Increased appetite	55.8	48.9	1.3 (0.7-2.5)	0.419
Fever	89.3	44.0	10.6 (3.1-36.5)	< 0.001
Cold	76.9	46.6	3.8 (1.5-10.0)	0.005
Monthly income: < $US 233.2	62	44.3	2.1 (1.1-4.0)	0.034
Mother's education: non-completed high school diploma	56.9	41.7	1.8 (1.0-3.3)	0.042
Father's education: non-completed high school diploma	59.2	40	2.2 (1.2-3.9)	0.009
Sign to Dx: < 10 days	55.1	47.2	1.4 (0.8-2.5)	0.368
Female gender	44.2	54.6	1.5 (0.9-2.7)	0.193
BMI < 5%	64	44.2	2.2 (1.1-4.4)	0.02

Abbreviations: DM1, diabetes mellitus type 1; DKA, diabetic ketoacidosis; FH, family history; drug Hx, drug consumption history; BMI, body mass index

tic regression; only father's education level was still significant (P = 0.004; OR = 0.4, 95% CI = 0.2 - 0.8).

In signs and symptoms subgroup, cold factor was removed in adjustment studies as it was closely related to fever factor. Therefore, fever was adjusted for BMI groups and only fever was found a significant factor in DKA onset at DM1 diagnosis (P < 0.001; OR = 11.2, 95% CI = 3.2 - 38.6).

Also, in the healthcare system subgroup, number of visits prior to diagnosis was removed since it was closely related to diagnosis in the first visit and the latter was selected for final model.

In the final model, all significant factors in the three subgroups were added to assess their effect on the main outcome, which was DKA onset in children with DM1. Therefore, father's education level, fever and diagnosis in the first visit were added and fever was found as a strong risk factor (P < 0.001; OR = 10.1, 95% CI = 2.9 - 35.3) and father's education level of high school diploma (i e, successfully completing at least twelve years of schooling or higher school certificate) and more was a protective factor (P = 0.019; OR = 0.5, 95% CI = 0.3 - 0.9) in DKA onset at diagnosis. The impact of diagnosis in the first visit was not significant when adjusted in the mentioned model (Table 4).

The correlations between BMI and age with HbA1c, anti-GAD65 and anti-ICA were evaluated. There was a significant positive correlation between anti-GAD65 and BMI in non-DKA group (r = 0.22, P = 0.032). Also, a significant positive correlation was observed between age and HbA1c in both DKA (r = 0.224, P = 0.029) and non-DKA (r = 0.364, P < 0.001) groups.

5. Discussion

In the literature, it was mentioned that younger age was consistently associated with increased risk of DKA at onset in numerous studies (2, 9-11). In some studies, up to 50% of newly diagnosed DM1 patients with DKA were under two years old (12). It may be due to lower potency to control metabolic deteriorations in younger children (13) and/or low speech ability in expressing their problems (6). But only 5 (5.1%) patients in DKA group were two years old or younger. No difference was observed between under and above five -year old patients in risk of presentation with DKA in the study (unadjusted OR = 0.635, 95% CI = 0.294-1.372).

In the developed countries, the frequency of DKA onset at DM1 diagnosis in children is estimated up to 54.2% and is significantly related to income inequality (r = 0.629, P = 0.001). However, it seems that this relationship does not exist among children with DM1 who live in the developing countries (14). According to the current study results, family monthly income level below $US 233.3 was observed with DKA onset more than two times than in the other patients. But after adjustment for other socioeconomic factors, it was not significant anymore (P = 0.142).

Table 4. Adjustment of Significant Factors Found in Three Subgroups

Variable	Adjusted for	OR (95%CI)	P Value
Father's education level (diploma and above)	- Monthly income (below $US 233.3)	0.4 (0.2-0.8)	0.004
	- Healthcare insurance status		
	- Mother's education level (diploma and above)		
	- Fever	0.5 (0.3-0.9)	0.019
	- Diagnosis in the first visit		
Fever	- BMI (underweight)	11.2 (3.2-38.6)	< 0.001
	- Father's education level (diploma and above)	10.1 (2.9-35.3)	< 0.001
	- Diagnosis in the first visit		

Abbreviation: OR, odds ratio.

From a wider point of view, nations with lower gross domestic product (GDP) could not spend a huge amount of budget on health and hygiene issues. As a result, these nations face larger burden of morbidity and mortality. On the other hand, it was shown that DM1 incidence is directly correlated with national health status and GDP.

In previous studies, a history of DM1 in the first and/or second degree families was reported as a protective factor from DKA onset. Veijola et al. and Abdul-Rasoul et al. showed a history of DM1 in the first degree relatives had 0.60 and 0.15 odds ratios, respectively (15, 16). Additionally, Rosenbauer et al. expressed that the history of DM1 or DM2 in the first and second degree relatives had 0.58 odds ratio in DKA onset (17). It may be due to an increased awareness about diabetes symptoms in their families and also the physicians noticing familial history as a diagnostic clue. However, no such a relationship was found in the study. It was not clear why history of DM in relatives could not make the families aware of possible incidence of DM1 in their children. Additionally, no relationship was found between history of DM1 and parents' education, income level or insurance status.

Some authors believe that weight loss before DM1 diagnosis is an alarming sign which may indicate a metabolic deterioration and correlated with higher rate of DKA occurrence at diagnosis (18). Although no significant difference was found in weight between the two groups and only 8.25% of DKA-group patients complained of weight loss prior to diagnosis. BMI was significantly lower in DKA group (P = 0.045). This difference was more obvious in children of five to nine years old where BMI was 14.5 and 15.3 in DKA and non-DKA groups, respectively (P = 0.043). Hekkala et al. found significant lower BMI in children with DM1 and DKA onset at diagnosis (19). However they declared that BMI difference in five to nine year old children was not statistically significant (P = 0.065). When the children were classified to underweight, overweight and normal on the basis of BMI, unadjusted OR was 2.2 (95% CI = 1.1-4.4) for underweight group in relation to normal group (P = 0.02). However, when BMI was adjusted for fever, it was no more significant in DKA onset risk (P = 0.09).

As mentioned earlier, better knowledge and awareness of diabetes sign and symptoms was associated with lower risk of DKA presentation. Accordingly, high amount of effort is expended by hygiene centers to increase parents' knowledge about diabetes symptoms in their children. The results were hopeful at first and decreased DKA onset rate in children with DM1 in some regions. The environmental determinants of diabetes in the young (TEDDY) study emphasized on regular monitoring of signs and symptoms and parental education as protective measures against DKA onset at children with DM1 diagnosis (20). However, even in the developed countries, rate of DM1 presentation with DKA at diagnosis is still high. Patients who had mother with higher than secondary education in Sadauskaite-Kuehne et al. study in Lithuania, was considered as a protective factor (OR = 0.4 95% CI = 0.2-0.79) (21). Even having one parent with an academic degree decreased the risk of DKA onset at diagnosis as mentioned in the study by Komulainen et al. in Finland (OR = 0.64, 95% CI = 0.43 - 0.94) (10). Father's education level was a significant protective factor, even when it was adjusted for other socioeconomic and healthcare system factors and fever (P = 0.019; OR = 0.5, 95% CI = 0.3-0.9).

Quinn et al. observed no significant difference in the number of medical consultations before diagnosis between the children with and without DKA (P = 0.30) (22). However, Bui et al. reported that 38.8% and 34.4% of patients with and without DKA had one or more medical visits in the week before diagnosis (P = 0.026) (23); 57.7% and 30% of patients in DKA group and 38.1% and 7.2% of patients in non-DKA group had >1 and >3 medical visits in the last week prior to diagnosis, respectively. This obvious difference in the number of visits might be partly due to diag-

nostic errors by physicians. Increasing the number of visits in DKA group patients in the current study was positively correlated with the sign in the diagnosis time (r = 0.283, P = 0.005). However when wrong diagnosis in the first visit was adjusted with fever and father's education level, it was not a risk factor for DKA onset any more (P = 0.11). It seems that even a precise diagnosis of DM1 could not stop DKA presentation at onset. This finding is in accordance to the hypotheses which emphasize that DKA is a more severe form of DM1 disease.

Levy-Marchal et al. reported that only in 6.4% of patients with DM1 and DKA, treatment delayed more than a day (18). In contrast, 10.6% of patients with non-DKA presentation had more than 24 hours delay in treatment after diagnosis (P = 0.047). Similarly, mean diagnosis of treatment delay time in non-DKA group compared to DKA group, was about three folds in the current study.

A history of recent febrile illness or cold were correlated with about ten- and four-time increase in the number of children with DM1 and DKA at diagnosis. It was also significant when adjusted for other significant factors and fever can be confidently named the most important risk factor of DKA onset at DM1 diagnosis. Similar results were observed in the study by Bober et al. where they declared that a history of infection or febrile illness could increase the risk of DKA more than six-times (24). Such results were repeated by Xin et al. and they found a febrile illness history that elevated DKA risk about two folds (25). Fever in children with DM1 might be a consequence of an infection which could cause insulin resistance by itself through cytokine release and deteriorate the metabolic condition and lead to DKA. On the other hand, fever can be occurred secondary to initiating metabolic disorders (26). Usher-Smith et al. presumed that presence of fever or an infection in children with DM1 may even make the diagnosis harder and in this way, increase the rate of DKA onset in children (6). However, the current study found no significant diagnosis delay in DKA group when presenting cold or fever.

However it should be mentioned that there is no regular program to improve knowledge and awareness of DM1 in the society. Of course a better understanding of mentioned factors could be achieved after a regular program. Moreover it is of utmost importance that whether fever is the consequence of DKA or a preceding infection makes patients with DM1 vulnerable to DKA. More studies on patients with febrile DKA may clarify this dilemma.

5.1. Conclusion

In summary, it is still unclear whether DKA onset at diagnosis is a consequence of delayed diagnosis, medical faults and hygiene status of community, or these patients have a more severe form of disease or even a combination of them. In this case-control study when logistic regression models were used for significant factors only recent febrile illness or cold were the strongest risk factors which increased the risk of DKA onset. On the other hand, father's education level of high school diploma and higher was the main protective factor. These findings were in accordance with the conception that DKA is the most severe form of DM1 disease.

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Footnotes

Authors' Contribution: Raheleh Mirsadraee: acquisition of data and administrative, technical and material support; Mohamad Khajedaluee: analysis and interpretation of data; Rahim Vakili: critical revision of the manuscript for important intellectual content; Azam Hasanabade: study concept and design and administrative, technical and material support; Zahra Saeedrezaee: statistical analysis and study supervision.

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