Risk Factors for Diabetic Ketoacidosis among Type 1 Diabetic Children Registered at "Heraa Diabetes Center" in Makkah Al-Mokarramah City, Saudi Arabia

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Abstract

Aim of Study: To assess risk factors associated with DKA among T1DM children registered at "Heraa Diabetes Center", Makkah Al-Mokarramah City, Saudi Arabia.

Patients and Methods: A retrospective hospital-based, case-control research design was followed and included 375 diabetic patients aged less than 15 years. The "Study Group" included 125 children who had a past history of diabetic ketoacidosis (DKA Group), while the "Control Group" comprised 250 diabetic children who did not have past history of DKA. A data collection sheet was designed by the researchers.

Results: There was significantly more positive family history in the DKA group than the control group (78.4% and 68%, respectively, p=0.036). The mothers were the main person who injects the child. Differences between both study groups according to the person who injects the child was statistically significant (p=0.029). DKA occurred more than once in 59.2% of diabetic children, and in 46.4% of children with over-activity. The main presenting symptoms of DKA were polyuria, thirst and vomiting. The main causes and triggering factors were eating too many sweets (65.6%), missing blood sugar monitoring (57.6%), omitting the insulin dose (22.4%), or infection (12.8%). Children in the control group were significantly more compliant than those in the DKA group regarding daily measurement of blood sugar (82.8% and 71.2%, respectively, p=0.009), timely receiving treatment (96% and 82.4%, respectively, p<0.001), following a healthy diet (79.6% and 65.6%, respectively, p=0.003), and receiving health education (95.2% and 88%, respectively, p=0.011).

Conclusions: Risk factors for DKA include positive family history of diabetes, and less educated or employed mothers, but its incidence is lower among children of parents with health-related jobs. It can be triggered by over-activity. It is caused by eating too many sweets, missing blood sugar monitoring, omitting the insulin dose, or infection. Noncompliance is associated with higher incidence of DKA.
Recommendations: All parents of diabetic children should receive health education and be trained about management of diabetes, compliance to diabetes management, continuous monitoring of glucose levels, and early manifestations of DKA.

Key Words: Diabetic ketoacidosis, Type 1 diabetes, Children, Risk factors, Compliance, Saudi Arabia.

Introduction

Type 1 diabetes mellitus (T1DM) is the most common endocrine-metabolic disorder during childhood and adolescence (1), with increasing prevalence worldwide (2). One of its serious acute complications, ketoacidosis (DKA) accounts for most hospitalizations in cases of severe insulin deficiency (3). It comprises the biochemical triad of ketonemia, hyperglycemia and acidemia (4).

Although major advances have been achieved in the fields of care for diabetic patients, the incidence of DKA is still increasing (5), and it continues as a significant cause for morbidity and mortality (6). Frequently, it is the main presenting symptom for new-onset cases in 25-30% of T1DM cases (7).

Several risk factors for DKA have been reported. In Al-Baha, Saudi Arabia, Satti et al. (1) noted that the 74% of their admitted children with DKA had positive family history of diabetes. Vakharia et al. (8) noted that awareness that a positive family history of DM is associated with a higher risk for recurrence of DKA among diabetic children will allow for improved identification of patients who may be at risk for DKA recurrence and the education of their parents to prevent complications of DKA.

Pulungan et al. (9) emphasized that lack of parental knowledge on management of type 1 diabetes is significantly associated with non-compliance, and causes omission of insulin and failure of insulin dose adjustment. Acute infections, especially pneumonia and urinary tract infections, constitute the most common precipitating factor for DKA (10). In Jeddah, Saudi Arabia, Qari (11) showed that poor compliance was the most common precipitating factor for DKA (54.4%), followed by infections (28%).

Generally, clinical presentations of DKA develop rapidly, usually within a period of less than 24 hours. A few days before its development, certain symptoms may develop, such as polydipsia, polyuria, and rapid loss of weight. Moreover, abdominal pain and severe vomiting may occur (12).

Physical examination of a patient with DKA shows signs of dehydration, e.g., loss of skin turgor, dry mucous membranes, tachycardia, and hypotension. Mental status can vary from full alertness to loss of consciousness. Most patients are normothermic or even hypothermic at presentation. However, fever may be associated with infections. Acetone on breath and labored Kussmaul respiration may also be present on admission, particularly in patients with severe metabolic acidosis (13).

Although the diagnosis of DKA can be suspected on clinical grounds, confirmation is usually based on laboratory tests. The most widely used diagnostic criteria for DKA were blood glucose levels more than 250 mg/dL, a moderate degree of ketonemia, serum bicarbonate less than 15 mEq/l, arterial pH less than 7.3, and an increased anion gap metabolic acidosis (13). The assessment of ketonemia is usually performed by the nitroprusside reaction. Direct measurement of β-hydroxybutyrate is currently available by finger stick method, which is a more accurate indicator of DKA (14).

The primary fatal complication of DKA is cerebral edema. Moreover, vascular, musculoskeletal, pulmonary, gastrointestinal, and cognitive complications of DKA may rarely occur, but can result in acute and long-term morbidity (15).

The prevention of DKA can be successfully done by better access to medical care, proper health education, and effective communication with a health care provider during an intercurrent illness. Involvement of family members should be encouraged. They need to be educated on insulin regimen and how to perform measurements of blood glucose. Also, a written care plan should be provided to the patient and/or caregiver, as this enhances understanding and emphasizes the importance of self-management of diabetes (16). Moreover, advances in technology have provided more efficient means of monitoring and maintaining glycemic control in an outpatient setting (17-18).

Study rationale

DKA is the most severe health problem among diabetic children (19). It is typically caused by treatment non-compliance, (e.g., shortage of insulin), and may be precipitated by other factors, (e.g., infections). Although it can be a life-threatening event for T1DM children, it is a preventable condition (20). Despite the severity of DKA, research examining this event is still limited in the empirical literature (21). Therefore, the identification of magnitude of DKA and its associated risk factors is a pressing necessity.

Aim of Study

To assess risk factors associated with DKA among T1DM children registered at “Heraa Diabetes Center”, Makkah Al-Mokarramah City, Saudi Arabia.

Study Objectives

- To identify the pattern of DKA among T1DM children registered at Heraa Diabetes Center, Makkah Al-Mokarramah City, Saudi Arabia.
- To assess risk factors associated with DKA among T1DM children registered at Heraa Diabetes Center, Makkah Al-Mokarramah City, Saudi Arabia.
- To explore the association between compliance of T1DM children with occurrence of DKA.

Patients and Methods

A retrospective hospital-based, case-control research design was followed at "Heraa Diabetes Center", Makkah Al-Mokarramah City, Saudi Arabia. The study population included children with T1DM (ICD-10: E10.9), aged less than 15 years, who were registered at the study setting.

Based on patients' records, the "Study Group" (i.e., DKA Group) comprised T1DM patients who had past history of being hospitalized at least once for DKA, while the "Control Group" comprised T1DM patients who have not been previously hospitalized for DKA.

The minimum sample size for this study was decided according to Dahiru et al. (22), as follows:

$$n = \frac{Z\alpha^2 \text{ X } P \text{ X } Q}{D^2}$$

where:

- n: Calculated sample size
- $Z\alpha$: The z-value for the selected level of confidence $(1-\alpha) = 1.96$.

P: The estimated proportion of T1DM children with a history of DKA (assumed to be 0.3).

- Q: (1 – P), i.e., 0.7.
- D: The maximum acceptable error = 0.05.

$$n = \frac{(1.96)^2 \text{ X } 0.3 \text{ X } 0.7}{(0.05)^2} = 323$$

Therefore, the calculated minimum sample size was 323 T1DM children. However, the study sample included a total of 375 T1DM children, 125 in the "DKA Group" and 250 in the "Control Group", i.e., 1:2 ratio.

Study tool

Based on relevant literature, a data collection sheet was designed by the researchers. It included the following parts:

• Parent's personal data (independent variables): Age, educational level, occupation, family monthly income, and family history of diabetes.

• Diabetic child's data (independent variables): Age, gender, nationality, duration of diabetes, daily blood sugar monitoring, compliance to diet, treatment and healthcare visits, and receiving health education.

• Risk factors for DKA and previous hospitalization data (dependent variables): Frequency of hospitalization, precipitating and risk factors for DKA, symptoms of DKA, and home management of DKA.

The face validity of the data collection tool was verified by two Family Medicine consultants and one Diabetology consultant. Construct and content were validated using statistical analysis of the pilot study results (using Principal Components Analysis).

Pilot study

A pilot was conducted on data from files of 30 T1DM children at the study setting. The objective of the pilot study was to test the availability of the independent and dependent variables within the patients' record files. Internal consistency of the study questionnaire was assessed by Cronbach's alpha coefficient (α=0.79). Data collected within the pilot study was not included in the main study.

Data collection

During the period from January to April 2021, the researchers paid daily visits to Heraa Diabetes Center. Patients' files of T1DM children were consecutively reviewed by the researchers. All relevant data were recorded into the data collection sheet. The data of the most recent 125 T1DM children with previous history of DKA were included in the "DKA group". For each T1DM child with past history of DKA included in the DKA Group, two control children (with no history of DKA) were included in the "Control Group". Therefore, the total study sample included 375 children with T1DM, 125 with a past history of DKA and 250 with no past history of DKA.

Statistical analysis

Collected data were verified prior to computerized data entry and analysis using the Statistical Package for Social Sciences (IBM, SPSS version 25). Descriptive statistics were applied (frequency and percentage). The $\chi 2$-test was to compare the study groups and to identify potential risk factors for DKA. P-values less than 0.05 were considered as statistically significant.

Ethical and administrative considerations

All necessary official approvals were secured by the researchers prior to data collection. Collected data were kept confidential.

Funding and Budget

This study was completely self-funded.

Results

Table (1) shows that most type 1 diabetic children in the control and DKA groups were aged 5-10 years (58.4% and 60.8%, respectively). There was no significant difference between both study groups according to their age. Females were significantly more among the cases group than the control group (58.4% and 47.2%, respectively, p=0.041). The educational level of about half of fathers of type 1 diabetic children in the control and DKA groups was university level (44% and 53.6%, respectively). There was no significant difference between both study groups according to their father's education. The educational level of mothers in the control group was higher than the DKA group with more university educated mothers in the control group than the DKA group (52% and 39.2%, respectively, p=0.023). There were significantly more fathers with health-related jobs among the control group than the DKA group (20% and 17.6%, respectively, p<0.001). Similarly, there were significantly more mothers with health-related

jobs among the control group than the DKA group (23.2% and 20.8%, respectively, p=0.014). The monthly family income of almost half of type 1 diabetic children in the control and DKA groups was <10,000 SR (47.2% and 48.8%, respectively). There was no significant difference between both study groups according to their family monthly income.

Table (2) shows that the duration of diabetes among type 1 diabetic children in both control and DKA groups, was mainly 1-5 years, (62.4% and 60%, respectively). There was no significant difference between both study groups according to their duration of diabetes. There was significantly more positive family history in the DKA group than the control group (78.4% and 68%, respectively, p=0.036). Regarding the person who injects insulin to the diabetic child, almost half of the children in the control group received insulin injection from their mothers (48.8%), compared with 39.2% in the DKA group. Moreover, 14.8% of children in the control group used to inject themselves, compared with 27.2% in the DKA group. Differences between both study groups according to the person who injects the child was statistically significant (p=0.029).

Table (3) shows that DKA occurred more than once in 59.2% of type 1 diabetic children in the DKA group. DKA occurred in almost half of children (46.4%) with over-activity (e.g., after running or playing). The main presenting symptoms associated with DKA were polyuria, thirst and vomiting (36.8%, 23.2%, and 20.8%, respectively). Before going to hospital, 24% of children with DKA received their medication, 35.2% drank much water, while 40.8% received nothing. The main causes and triggering factors for DKA were eating too many sweets (65.6%), missing blood sugar monitoring (57.6%), omitting the insulin dose (22.4%), or infection (12.8%).

Table (4) shows that children in the control group were significantly more compliant than those in the DKA group regarding daily measurement of blood sugar (82.8% and 71.2%, respectively, p=0.009), their timely receiving of treatment (96% and 82.4%, respectively, p<0.001), following a healthy diet (79.6% and 65.6%, respectively, p=0.003), and receiving health education (95.2% and 88%, respectively, p=0.011). However, there was no significant difference between both study groups regarding regular visits to the diabetes clinic.

Table 1: Demographic characteristics of diabetic children

Characteristics	Control (n=250)		DKA (n=125)		P-value
	No.	%	No.	%	
Age of child					
• <5 years	67	26.8	38	30.4	
• 5-10 years	146	58.4	76	60.8	
• >10 years	37	14.8	11	8.8	0.245
Gender					
• Male	132	52.8	52	41.6	
• Female	118	47.2	73	58.4	0.041
Nationality					
• Saudi	220	88.0	108	86.4	
• Non-Saudi	30	12.0	17	13.6	0.659
Father's education level					
• Primary/Intermediate	20	8.0	7	5.6	
• Secondary	120	48.0	51	40.8	
• University	110	44.0	67	53.6	0.198
Mother's education level					
• Primary/Intermediate	30	12.0	26	20.8	
• Secondary	90	36.0	50	40.0	
• University	130	52.0	49	39.2	0.023
Current father's job					
• Healthcare-related	50	20.0	22	17.6	
• Not healthcare-related	190	76.0	82	65.6	
• Retired	10	4.0	21	16.8	<0.001
Current mother's employment					
• Healthcare-related	58	23.2	26	20.8	
• Not healthcare-related	71	28.4	54	43.2	
• Housewife	121	48.4	45	36.0	0.014
Family monthly income					
• <10,000 SR	118	47.2	61	48.8	
• 10,000-20,000 SAR	102	40.8	54	43.2	
• >20,000 SAR	30	12.0	10	8.0	0.173

Table 2: Clinical characteristics of patients in the control and DKA groups

Characteristics	Control (n=250)		DKA (n=125)		P value
	No.	%	No.	%	
Duration of diabetes					
• < One year	21	8.4	13	10.4	
• 1-5 year	73	62.4	75	60.0	
• >5 years	73	29.2	37	29.6	0.798
Family history of diabetes					
• Yes	170	68.0	98	78.4	
• No	80	32.0	27	21.6	0.036
Who injects insulin to the child‡					
• The mother	122	48.8	49	39.2	
• The father	68	27.2	30	24.0	
• The diabetic child	37	14.8	34	27.2	
• Someone else	38	15.2	16	12.8	0.029

‡ More than one person can be stated

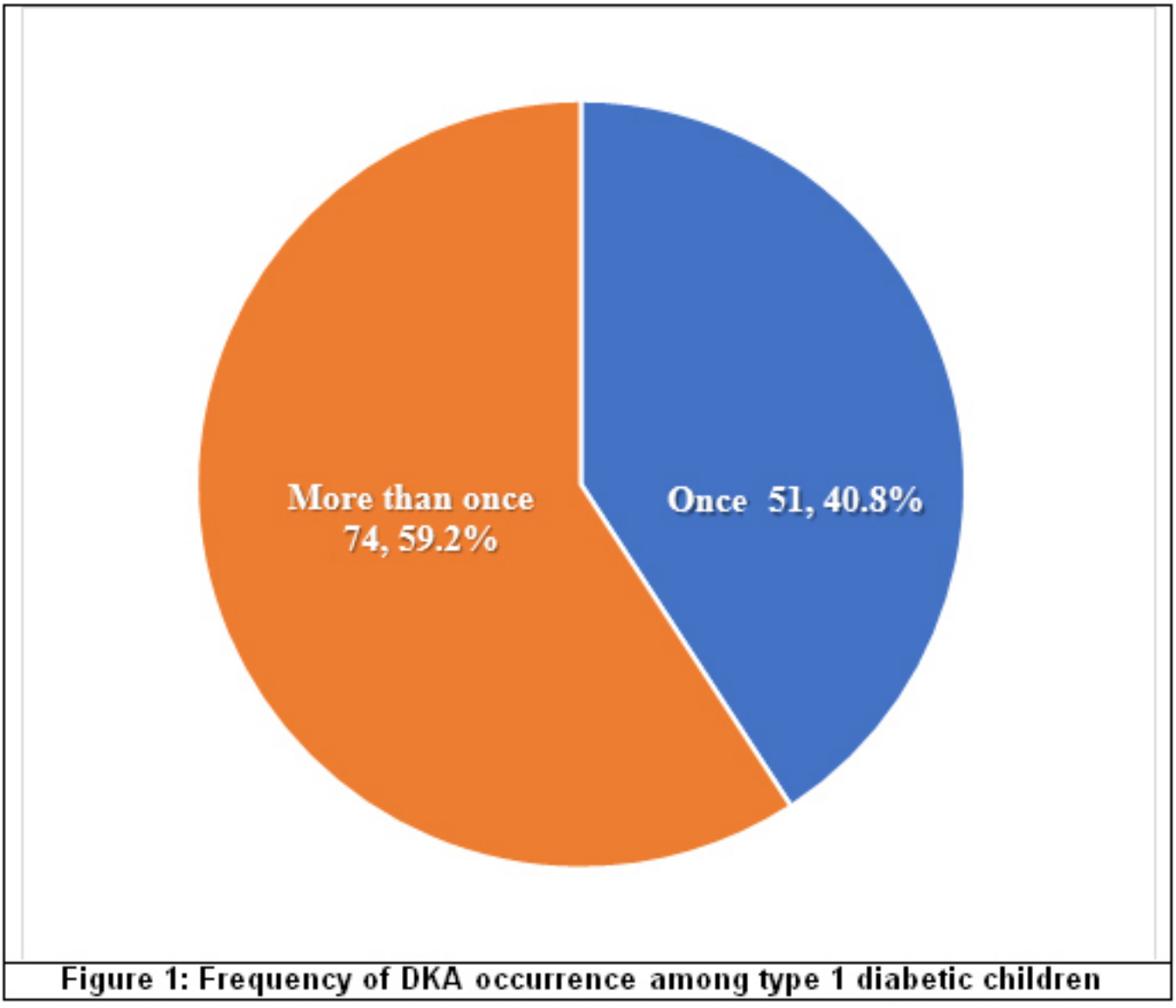

Figure 1: Frequency of DKA occurrence among type 1 diabetic children

Table 3: Characteristics of ketoacidosis among DKA group (n=125)

Characteristics	No.	%
First presentation of diabetes	13	10.4
Frequency of DKA episodes		
• Once	51	40.8
• More than once	74	59.2
Child's level of activity before DKA		
• Sleeping	33	26.4
• Sitting	34	27.2
• Overactivity (e.g., Running/Playing)	58	46.4
Main presenting symptoms associated with DKA		
• Polyuria	46	36.8
• Excessive thirst	29	23.2
• Persistent vomiting	26	20.8
• Colic	16	12.8
• Fever	16	12.8
• Others	13	10.4
Pre-hospital home management		
• Giving medications	30	24.0
• Drinking much water	44	35.2
• Nothing	51	40.8
Causes and triggering factors for DKA		
• Receiving sweets	82	65.6
• Missing blood sugar daily monitoring	72	57.6
• Omission of insulin injection	28	22.4
• Infection	16	12.8

Table 4: Compliance of type 1 diabetic children in the control and DKA groups

Characteristics	Control (n=250)		DKA (n=125)		P-value
	No.	%	No.	%	
Daily measurement of blood sugar					
• Yes	207	82.8	89	71.2	
• No	43	17.2	36	28.8	0.009
Timely receiving treatment					
• Yes	240	96.0	103	82.4	
• No	10	4.0	22	17.6	<0.001
Regular visits to diabetes clinic					
• Yes	220	88.0	102	81.6	
• No	30	12.0	23	18.4	0.094
Following a healthy diet					
• Yes	199	79.6	82	65.6	
• No	51	20.4	43	34.4	0.003
Receiving health education					
• Yes	238	95.2	110	88.0	
• No	12	4.8	15	12.0	0.011

Discussion

Findings of the present study revealed that in the DKA Group, DKA was the first presentation of their diabetes in 10.4% of children. In addition, more than half of children (59.2%) experienced several DKA episodes.

Incidence of a DKA episode as the first presentation of T1DM in our study is less than that reported by Szypowska et al. (23) in Poland, and Jefferies et al. (24), in New Zealand, who found that about one-quarter of T1DM children presented with DKA at their first diagnosis. A much higher incidence of DKA episodes was reported by Onyiriuka and Ifebi (25) in Nigeria, where about three-quarterss of diabetics presented with DKA.

Differences in reported incidence of DKA as the first presentation of T1DM may reflect variable awareness levels among parents and primary care physicians about early monitory symptoms for recognition of T1DM. Therefore, a higher incidence of DKA at first diagnosis of T1DM reflects poorer awareness and less consciousness about early diagnosis of T1DM among children.

In agreement with our findings, Al-Hayek et al. (26) reported that 45.6% of T1DM Saudi adolescents in Riyadh City had several DKA episodes. Fazeli Farsani et al. (27) noted that worldwide incidence of DKA ranges from 8 to 51.3 cases/1000 patient-years. However, Li et al. (28) in China, reported a higher incidence rate (i.e., 263/1,000 patient-years).

The variation in incidence rates of DKA has been explained by differences in national health care systems, with limited access to routine health care for T1DM and the infrequent self-monitoring of blood glucose (27). Several epidemiological studies have reported that hospitalization for DKA has increased worldwide (29), probably due to increased admissions for mild DKA cases (30).

Therefore, in order to minimize the incidence of DKA, it is important to raise parents' awareness regarding premonitory symptoms and signs for diabetes and DKA and the pressing need to facilitate prompt access to health care.

Our study revealed that significant risk factors for DKA among T1DM children included being a girl, in addition to mothers' lower educational level, an employed mother and a positive family history of diabetes. On the other hand, having a parent with a healthcare-related job and the mother being the one who injects insulin to her child proved to be a prophylactic factor.

In agreement with our findings, Neu et al. (31), in Germany, reported that DKA is frequently higher among girls than boys. In Saudi Arabia, several studies reported similar results. In Al-Madina Region, Hamed (32), reported a higher incidence of DKA among females than males (58.7% and 41.3%, respectively). Satti et al. (1), in Al-Baha, reported a female:male ratio of 1.22:1. Also Zahib et al. (33), in Abha City, reported higher DKA incidence among females than males, but the difference was not statistically significant.

In Korea, Lee et al. (34) reported that low parental education is a significant factor for DKA severity. Similarly, in Iraq, Al-Obaidi et al. (35) noted that higher educational levels of parents were associated with lower frequency of DKA among their children with T1DM.

Parents' educational status, especially that of the mother, seems to be positively associated with having better awareness regarding diabetes and its complications among their children. This can be reflected in earlier diagnosis and management of T1DM and better watchful, preventive and nursing care, e.g., timely injecting of insulin. This may explain why children of busy employed mothers have higher incidence of DKA¸ and T1DM children of parents with jobs related to healthcare have less incidence of DKA.

In agreement with our findings, several studies confirmed the significant association between occurrence of DKA and the positive family history of diabetes. Alhomood et al. (36), in Abha, Saudi Arabia, reported that 18.7% of T1DM children had a diabetic relative. Similarly, in Finland, Parkkola et al. (37) reported that 12.2% of the children with newly diagnosed T1DM had at least one affected first-degree relative. Also Sipetić et al. (38), in Bilgrade, Serbia, reported that risk of T1DM is significantly associated with a positive family history.

Gender difference in DKA has been explained by several factors. The first one is attributed to puberty-associated hormonal changes, especially the raising in the serum levels of some counter-regulatory hormones, e.g., estrogen, which is, by far, higher in girls than boys at puberty. The second factor is related to body-image psychiatric problems, including eating problems, since adolescent diabetic girls often miss insulin injections for the sake of losing weight. Moreover, girls with DKA may have more behavioral problems, lower social competence, and higher levels of family struggle (25; 39).

Our study demonstrated that DKA was triggered among T1DM overactive children (e.g., after running or playing), while the main causes for DKA were excessive eating of sweets, omitting the insulin dose, missing the daily blood sugar monitoring, or infection. Moreover, the most common symptoms associated with DKA were polyuria, thirst, vomiting, colic and fever.

In Karachi, Pakistan, Shahid et al. (40) reported that the most common clinical symptoms for DKA among diabetic patients were nausea and vomiting (57.7%), colic (42.2%) and polyuria (28.1%). Various precipitating factors of DKA were reported, especially missed insulin dose and an ongoing infection.

Children in the DKA Group were significantly more non-compliant than those in the Control Group regarding daily measurement of blood sugar, timely receiving insulin, following a healthy diet, and receiving health education.

Moreover, home management of children with DKA included receiving medication and hydration, but mostly children received nothing before going to hospital.

Therefore, for management of T1DM and prevention of DKA, it has been recommended to use recent technological advances to obtain continuous and efficient diabetes monitoring and to maintain glycemia at home. Real-time continuous glucose monitoring can significantly control hemoglobin A1c, and provides warning for early detection of glucose abnormalities and prompt intervention (17-18).

Wallace and Matthews (41) stressed that, at-home use of ketone meters that detect blood β-hydroxybutyrate has shown to aid in early detection and management of ketosis, which may decrease the need for specialized care. Short-acting insulin can be administered with fluids early on to prevent DKA. Atkilt et al. (42) added that the odds of developing DKA in newly diagnosed T1DM children is 49% lower for children whose parents knew its signs and symptoms than parents' who did not know, since parents who know its signs and symptoms can seek health care very early before their children develop DKA.

Precipitating factors for DKA are particularly important, as both infection and non-compliance are common in diabetic patients. The greater incidence of infection in diabetic patients is due to several factors including damage to neutrophil function, impairment of humoral immune system, and neuropathies (43). In Pakistan, Shams et al. (44) reported that 62% of diabetics are non-compliant to their treatment regime.

Conclusions

Results of the present study indicated that DKA may be the first presentation of T1DM, with higher incidence among girls than boys, and high tendency for recurrent episodes. Risk factors for DKA include positive family history of diabetes, less educated or employed mothers, but its incidence is lower among children of parents with health-related jobs. DKA can be triggered by child's over-activity. Its main presenting symptoms include polyuria, thirst and vomiting, while it is caused by eating many sweets, missing blood sugar monitoring, omitting the insulin dose or infection. Non-compliance regarding "daily measurement of blood sugar, timely receiving treatment, following a healthy diet or receiving health education" is associated with higher incidence of DKA.

Recommendations

All parents of T1DM children should receive health education and to be trained about management of diabetes, compliance to diabetes management, continuous monitoring of glucose level, and early manifestations of DKA.

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