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Frequency of Diabetic Ketoacidosis and Severe Hypoglycemia in Children with Type 1 Diabetes

A. Homaei (MD)[1], F. Saffari (MD)[*2], E. Parsarad (MSc)[3], Z. S. Mohammadi (BS)[2]

1.Student Research Comitte, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, I.R.Iran.

2.Children Growth Research Center, Research Institute for Prevention of Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, I.R.Iran.

3.Clinical Research Development Unit, Qods Hospital, Qazvin University of Medical Science, Qazvin, I.R.Iran.

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ABSTRACT

Background and Objective: Diabetic ketoacidosis and severe hypoglycemia are common and recurrent acute complications of type 1 diabetes and are associated with high mortality and morbidity. The aim of this study was to determine the frequency of diabetic ketoacidosis and hypoglycemia in children with type 1 diabetes.

Methods: In this retrospective cross-sectional study, 480 patients with type 1 diabetes admitted to the Children Hospital in Qazvin were enrolled by census method. Demographic characteristics, season of referral, place of residence, existence of type 1 diabetes in the family, kin relationship of parents, cause of hospitalization (hyperglycemia, hypoglycemia and diabetic ketoacidosis) and length of hospital stay were extracted from the files and examined.

Findings: Most patients (62.9%) were female. 46%, 44.4% and 9.6% of patients were admitted with diabetic ketoacidosis, hyperglycemia and hypoglycemia, respectively. 47.96% of patients had severe diabetic ketoacidosis. 49.3% of patients had ketoacidosis with infection and 20% of known cases were hospitalized due to poor insulin compliance. Hospitalization days were significantly higher in patients with ketoacidosis (p=0.00).

Conclusion: According to the results of this study, the occurrence of infection and lack of adherence to insulin use were the main cause of hospitalization in patients with diabetes, which led to an increase in hospitalization days in these patients. Adequate training to regulate blood sugar reduces the rate of hospitalizations.

Keywords: *Type 1 Diabetes Mellitus, Diabetic Ketoacidosis, Hypoglycemia, Insulin, Hyperglycemia.*

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***Corresponding Author: F. Saffari (MD)**
Address: Qods Tertiary and Educational Hospital, Qods Square, Qazvin. I.R.Iran.
Tel: +98 (28) 33328709. **E-mail:** drfa_saffari@yahoo.com

Introduction

Type 1 diabetes is caused by the autoimmune destruction of insulin-producing cells by infectious or environmental factors that are often diagnosed in childhood (1, 2). Diabetic ketoacidosis (DKA) and severe hypoglycemia are common complications in patients with type 1 diabetic and may be associated with morbidity and mortality, and are more likely to recur in treated diabetic patients (3-6). Ketoacidosis can be the first manifestation of type 1 diabetes or it can occur when a person with diabetes has an increased need for insulin during illness or stress or a decrease in insulin intake (7). Psychiatric disorders, stress, female gender, non-white race, and lower socioeconomic status and elevated glycosylated hemoglobin (HbA_1C) levels increase the risk of DKA (1, 8-10).

Infection is one of the most important factors predisposing to DKA in diabetic patients. Insufficiency in insulin injection also leads these patients to ketoacidosis (11). In a significant number of patients, no cause for ketoacidosis is found (12). Diabetic ketoacidosis and its associated cerebral edema are the leading causes of hospitalization and mortality in diabetic children and adolescents. Children under 5 years of age are at high risk for developing DKA (6).

Hypoglycemia is another common complication in patients with type 1 diabetes and is caused by insulin injections and excessive increase in insulin relative to serum glucose and if not treated in time can lead to loss of consciousness, seizures and even death of the child (13, 14). Hypoglycemia is a major barrier to optimization of blood sugar control. Hypoglycemic attacks per week can range from a mild attack in people with poor control to a few attacks in those on strict diets, and the severe form occurs annually in 10-25% of patients. Age, gender, duration of diabetes, blood sugar control, insulin therapy and socioeconomic status are risk factors for hypoglycemia (15).

In the study of Li et al., the rate of DKA in diabetic patients under 18 years of age was 27.1% and the incidence of hypoglycemia was 70.9% per year. Furthermore, the prevalence of diabetes and recurrence of DKA in girls was 53.7% (4). In the study of Mejia-Otero et al., hospitalization history, high HbA_1c level, lack of health insurance, female gender and non-white race were all predisposing factors for hospitalization with acute complications of diabetes (16). Assefa et al. reported the total incidence of DKA to be 2.27 cases per 100 cases per month. Age less than 5 years, lack of drug adherence and the presence of concomitant infections were predisposing factors for DKA in these patients (17). In the study of Kao et al., the mean age of diabetes was 9.9±4.8 years and there was no gender-dependent difference in the incidence of new cases of DKA, but the risk of DKA was higher in young patients. Girls with known diabetes were more likely to develop DKA (18).

Since type 1 diabetes is one of the most common chronic endocrine-related metabolic disorders in children and leads to recurrent hospitalizations with ketoacidosis, hypoglycemia and infection, and given the impact of these complications on the quality of life of these patients, the present study was conducted to evaluate the cause of these complications in diabetic patients admitted to Qods Children's Hospital in Qazvin during 2005-2020. It is hoped that based on the results of this study, patients will be given the necessary training in better control of diabetes.

Methods

This retrospective cross-sectional study was performed after approval by the ethics committee of Qazvin University of Medical Sciences with the code IR.QUMS.REC.1399.335 by reviewing the hospital records of 480 patients with type 1 diabetes. All patients admitted with type 1 diabetes from 2005 until 2020 in

Qazvin Children's Hospital were included in the study by census. Hospitalized patients with hypoglycemia and other causes other than type 1 diabetes were excluded from the study.

In these patients, the diagnosis of diabetes was made on the basis of fasting blood sugar equal to or greater than 126 mg/dL or random blood sugar equal to or greater than 200 mg/dL with symptoms of hyperemia, binge drinking, overeating, and weight loss. Hyperglycemia with blood sugar equal to or greater than 250 mg/dL was considered (19). Diagnosis of DKA was made on the basis of general condition, presence of acidosis (arterial pH<7.3), bicarbonate less than 18 mmol/L, and ketonemia or ketonuria (20). The severity of ketoacidosis was categorized based on arterial blood pH and bicarbonate level (HCO_3): (mild: pH=7.25-7.35 and HCO_3=15-18, moderate: pH=7.15-7.25 and HCO_3=10-15, and severe: pH<10, HCO_3<7.15) and the duration of treatment was calculated from the time of admission to the time of DKA resolution. pH>7.3, absence of nausea and vomiting, serum sodium 135-145 mEq/L, and HCO_3>15 or Pco_2>16 was considered as DKA resolution (19, 21).

Predisposing factors including upper and lower respiratory tract infections, gastroenteritis, and urinary tract infections and poor compliance, which meant not injecting insulin, forgetting to inject an insulin dose, or inappropriate insulin dose for hyperglycemia, were examined (15). The presence of infections was recorded by studying the files, blood culture and urine.

Blood sugar levels between 50 and 70 mg/dL were considered as mild hypoglycemia and blood sugar less than 50 mg/dL was considered as severe hypoglycemia (15). Symptoms of hypoglycemia were neuroglycopenic symptoms such as headache, blurred vision, dizziness, irritability, speech disorder, seizures, and coma, and adrenergic symptoms due to catecholamine responses such as tremor, rapid heartbeat, paleness, sweating, anxiety, and improvement of symptoms after glucose prescription. In addition, the number of cases of acute complications in each patient was recorded.

Required information including duration and frequency of hospitalization, gender and age at hospitalization, new or known case of diabetes, kin relationship of parents, family history of type 1 diabetes, cause of hospitalization (DKA, hyperglycemia or hypoglycemia), severity and time of DKA resolution, blood glucose levels during hospitalization, severity of acidosis, season of referral, place of living, co-infection, or poor compliance to insulin were recorded. Patients' weight was measured with a German Seca scale with an accuracy of 100 g and height with a height measuring stand with an accuracy of 1 mm. Body Mass Index (BMI) was determined based on the weight in kilograms divided by the square of height in meters.

The collected data were analyzed by SPSS version 23 and the studied variables were expressed as mean, standard deviation for quantitative variables and number and percentage for qualitative variables. Chi-square was used to analyze the relationship between qualitative variables and ANOVA test was used to analyze quantitative variables in the three groups and $p \leq 0.05$ was considered significant.

Results

480 diabetic patients were evaluated in this study, of which 255 were known and 230 were new cases. The mean age of patients at diagnosis was 7.1±3.27 years and at the time of hospitalization was 8.37±3.51 years. 302 patients (62.9%) were female and 20.3%, 19.7% and 60% of patients were in the age groups under five years, 5-8 years and greater than or equal to 8 years, respectively. The minimum and maximum age at hospitalization were 2 months and 17 years, respectively. The mean height of patients was 127.64±22.97 cm, mean weight was 28.96±12.58 kg and mean BMI was 16.98±3.82 kg/m2. The relationship between patients' gender and the cause of hospitalization (hyperglycemia, hypoglycemia and diabetic ketoacidosis) was significant (p<0.001) (Table 1).

Table 1. Demographic information of hospitalized patients with type 1 diabetes

Variables	Hyperglycemia (n=213)	Hypoglycemia (n=46)	Diabetic ketoacidosis (n=221)	p-value
	Number(%)	Number(%)	Number(%)	
Age				
Less than 5 years	38(17.8)	7(15.2)	49(22.2)	
5-7 years	39(18.3)	11(23.9)	48(22.7)	0.471
Greater than or equal to 8 years	136(63.8)	28(60.9)	124(56.1)	
Gender				
Boy	100(46.9)	14(30.4)	64(29.0)	<0.001
Girl	113(53.1)	32(69.6)	157(71.0)	
Weight* (kg)	29.6±13.9	27.9±10.5	28.4±11.8	0.596
Height* (cm)	129.1±23.8	127.9±23.5	126.1±22.3	0.496
Body mass index* (kg/m2)	17.0±5.2	16.6±1.7	17.0±2.8	0.848

***Numbers are reported as Mean±SD.**

The highest number of hospitalizations was 30.4% (146 patients) in autumn. 221 patients (46%) were hospitalized with diabetic ketoacidosis. 213 patients (44.4%) were hospitalized with hyperglycemia and 45 patients (9.6%) were hospitalized with hypoglycemia. Parents of 27.7% of patients had kin relationship. 14.7% of patients had a positive family history of type 1 diabetes. Six families had two or three infected children. 303 patients (63%) were residents of Qazvin. In 141 cases (29.3%), concomitant infection was diagnosed. There were 25, 23 and 93 patients with gastroenteritis, urinary tract infection and upper or lower respiratory tract infection, respectively. The overall mean of hospitalization days in patients was 5.36±2.92. The total mean blood glucose in patients was 420.29±191.20 mg/dL. The number of hospitalizations was higher in girls compared to boys (1.9±2.53). The number and days of hospitalization were higher in the villagers compared to city dwellers. The rate of hospitalization due to DKA, hypoglycemia and hyperglycemia in known diabetic patients was 5.61%, 26.9% and 5.08% per 100 patients per year, respectively. 8.7%, 14% and 14.6% of patients were hospitalized twice or more due to hypoglycemia, DKA and hyperglycemia, respectively. Hospitalization season, disease status, concomitant infection, number of hospitalization days and blood sugar level had a significant relationship with the cause of hospitalization ($p \leq 0.05$) (Table 2).

The number of hospitalization days was significantly higher in patients with ketoacidosis (6.6±2.1) ($p<0.001$). The number of hospitalizations in girls was higher than boys (7.9±2.8) ($p<0.001$). The number and days of hospitalization were higher in the villagers than in the city dwellers ($p=0.007$). Furthermore, blood sugar level was higher in ketoacidosis patients ($p=0.001$). Regarding the severity of ketoacidosis, 65.2%, 25.3% and 9.5% of patients with ketoacidosis had severe, moderate and mild diabetes, respectively. Fifty-one cases (20%) of known diabetic patients with diabetic ketoacidosis had poor insulin compliance.

The number of hospitalized diabetic patients increased from 6 in 2005 to 69 in 2020. Hospitalization with DKA was significantly higher in new cases of diabetes ($p=0.001$). However, the old known cases were mostly hospitalized due to hyperglycemia ($p=0.001$). The mean recovery time from diabetic ketoacidosis was 31.92±20.08 hours. Mean arterial blood pH, bicarbonate level and blood glucose in patients admitted with ketoacidosis were 7.19±0.16, 11.45±7.38 mEq/L and 510.21±151.42 mg/dL, respectively.

Table 2. Factors examined in hospitalized patients with type 1 diabetes

Variables	Hyperglycemia (n=213)	Hypoglycemia (n=46)	Diabetic ketoacidosis (n=221)	p-value
	Number(%)	Number(%)	Number(%)	
Season				
Spring	66(31.0)	16(34.8)	50(22.7)	
Summer	41(19.0)	17(37.0)	46(20.9)	0.008
Autumn	60(28.2)	6(13.0)	80(36.4)	
Winter	46(21.6)	7(15.2)	44(20.0)	
Average age* (years)	8.8±3.6	8.8±3.4	7.8±3.3	0.006
Disease status				
New	85(39.9)	2(4.3)	139(62.9)	<0.001
Known	128(60.1)	44(95.7)	82(37.1)	
Kin relationship				
Related	59(34.9)	20(46.5)	54(25.6)	0.012
Non-related	110(65.1)	23(53.5)	157(74.4)	
Positive history of type 1 diabetes in the family	62(29.7)	8(17.4)	44(20.7)	0.050
Residence				
City	128(61.0)	33(71.7)	142(64.3)	0.370
Village	82(39.0)	13(28.3)	79(35.7)	
Concomitant infections	42(22.7)	6(15.8)	93(47.7)	<0.001
Days of hospitalization*	4.1±2.4	2.5±1.3	6.6±2.1	<0.001
Blood sugar* (mg/dl)	397.8±150.7	79.8±104.0	510.2±151.4	<0.001
Number of hospitalizations				
Once	182(85.4)	42(91.3)	190(86.0)	0.571
Twice or more	31(14.6)	4(8.7)	31(14.0)	

***Numbers are reported as Mean±SD.**

Discussion

The results of the present study show that acute complications of diabetes (diabetic ketoacidosis and severe hypoglycemia) are common in our patients. Most new cases of diabetes were hospitalized with severe ketoacidosis. In a large number of patients, there was concomitant infection and lack of insulin compliance. In a study by Shraga et al., the incidence of ketoacidosis in known diabetic patients was 8 cases per 100 patients per year, and recurrence of ketoacidosis was seen in 5% of patients, and female patients were at higher risk for DKA. Death rates were also higher in DKA (6). In the present study, the rate of hospitalization with DKA was 5.61 cases per 100 patients, which is higher than the above study. Furthermore, the incidence was higher in girls and 13.7% of patients developed ketoacidosis twice or more per year. In the study of Karges et al. on 31,330 diabetic patients, the mean number of hospitalizations with DKA and severe hypoglycemia was 4.81 and 1.45 per 100 patients per year, respectively, which was lower than our study. The number of hospitalizations with DKA was higher in girls, which was similar to our study. Moreover, the number of hospitalizations due to severe hypoglycemia increased with age and a history of severe hypoglycemia in previous years, but was not related to the duration of diabetes, age and gender (22). The

majority of ketoacidosis patients in our study (55.4%) were eight years or older. Differences in the rate of ketoacidosis and hypoglycemia reported in different studies can be due to differences in methods between studies or heterogeneity in patients in terms of eating habits, daily blood sugar control, insulin regimens, etc. (4).

Secondary DKA and severe hypoglycemia are relatively low in countries such as Sweden, Australia and the United States, which have a high prevalence of diabetes. Conversely, in some countries in East and Southeast Asia where diabetes is less prevalent, secondary DKA and hypoglycemia are higher. Key factors that may lead to poor blood sugar control include age at diagnosis of diabetes, place of residence, household income, daily consumption of fruits and vegetables, physical activity, insulin compliance, and use of insulin pumps. Several studies have reported an association between younger age at onset of diabetes and a longer history of diabetes with poor glycemic control (23-25).

In the study of Varadarajan et al. in India on 118 diabetic patients, 62.7% of the patients were female. The mean age at onset of DKA was 8.5 years, which was similar to our study. Comorbid infections were reported in 61 cases (56%), the most common causes being urinary tract infections, skin infections, bronchopneumonia and sepsis. 35% of new cases of diabetes had infections. The cause of ketoacidosis in known diabetic patients was reported as concomitant infection in 48%, infection and poor compliance in 14% and poor compliance in 36% of cases, respectively, and the rate of skin infection in known patients was higher than new cases. Patients with infections were in a worse condition (26).

In this study, the mean age of patients at the onset of diabetic ketoacidosis was 7.8±3.3 years. 20% of known diabetic patients had ketoacidosis due to poor insulin compliance, and 29.3% of hospitalized patients had DKA infection, and the rate of respiratory infection was higher than other infections. In the study of Cengiz et al. on 13487 diabetic patients, 49% of the patients were female. The highest number was in the age group of 13 to 18 years and the average duration of diabetes was 6 years. One seizure of hypoglycemia or more occurred in 6.2% of patients in one year and hypoglycemia was more in the age group of 2 to 6 years than other age groups (1). The recurrence rate of hypoglycemia and DKA was higher in our patients. DKA levels are high in patients with known diabetes, especially in girls. Furthermore, patients who develop diabetes at a younger age have a higher risk of developing DKA in the future. Discovering the cause of these cases requires more patient-centered research (18).

In the study of Westerberg et al. on 28770 diabetic patients, the mean age was 13.96±3.93 years and 52.1% of the patients were male. The overall incidence of diabetes was 6.29 cases per 100 patients per year. 4.85% of these cases had one episode of DKA and 1.03 cases had two or more DKA attacks. DKA and hospitalization days were higher in girls and immigrants. DKA was also more common in patients with higher age of onset of diabetes or longer duration of diabetes (3). This study was different from our study in terms of gender-based prevalence, mean age and hospitalization percentage.

In the study of Alijanpour Aghamaleki et al., 45.3% of patients were male and the incidence of ketoacidosis was high (55.5%). The mean age of patients was 8.57±3.27 years and the highest rate of hospitalization was in summer. 103 patients were new cases and 25 patients had known cases of diabetes. 25.6% of patients had a positive history of type 1 diabetes in the family. 50.7%, 29.6% and 19.7% of patients had severe, moderate and mild ketoacidosis, respectively. The cause of ketoacidosis was infection in 69.23% of patients and lack of insulin injection in 30.76% (27). In our study, the number of girls was higher and the mean age of ketoacidosis patients was 7.8±3.3 years. The highest number of referrals (29.4%) was in autumn and 10.7% of patients had a family history of type 1 diabetes. 21% of patients with known diabetes had poor insulin compliance and 42.2% of patients with ketoacidosis had an infection. Good socioeconomic status and knowledge of diabetes, easier access to resources and better adaptation to diabetes can increase

self-management and self-efficacy of patients and their parents, and motivate them to learn about proper diet and a dynamic approach for stricter control of blood sugar during illness and infection (28, 29).

In the study of Choleau et al., the mean age of patients at diagnosis was 8.2±4 years. Moreover, type 1 diabetes was present in 14.5% of family members, which was more than the present study. 43.9% of patients referred with DKA and its prevalence did not differ between the sexes but was higher in children younger than 5 years (30). In the study by Cooper et al., 48% of the patients were female and the mean age at the time of diagnosis of diabetes was 6.8 years, and 47.5% of the patients had severe hypoglycemia (15), which was much higher than in our study. Living in rural areas and low household income significantly increase the risk of poor control. Income levels are also inversely related to HbA1c. There is a linear relationship between socioeconomic status, a healthy diet, and physical activity and type 1 glycemic control. Lower household income and living in rural areas may be associated with poor self-management and possibly lack of access to medical care or the impossibility of using good health care (e.g., glucometers and insulin pumps and blood glucose test strips) (31).

In the study by Seth et al., 73.3% of patients developed an infection with diabetic ketoacidosis (7), which was higher than in our study (50%). In this study, respiratory infections with 40.9% and urinary tract infections with 27.27% were more common, respectively, which was almost consistent with our study. In the present study, most patients were eight years old or higher and most of the newly diagnosed diabetic patients referred with ketoacidosis. Hospitalization of a large number of new cases with severe ketoacidosis is because of delayed referral, which may be due to the unfamiliarity of these patients with the symptoms of diabetes and the inaccuracy of physicians in diagnosing diabetes. The number of days hospitalized with ketoacidosis is significantly higher, leading to higher occupation of hospital beds. More than a third of patients had an infection, which indicates its role in hyperglycemia and progression to ketoacidosis. The number of female patients was higher than male patients, which is probably due to the higher prevalence of autoimmune diseases in girls which requires further studies in this field. Hospitalization days were shorter in patients living in the city.

The incidence of diabetic ketoacidosis in our diabetic patients, both known and new, was high, which necessitates more education in the community and among physicians in terms of paying more attention to the symptoms of diabetes. Increasing the knowledge of patients and their parents about diabetes will improve their health and will lead to increased compliance, regular monitoring of blood sugar and regular visits to adjust the dose of insulin. Timely treatment of infections in these patients should also be considered and requires more attention and can reduce the financial burden of hospitalization and complications. The limitations of our study were the inability to perform HbA1c in the hospital, lack of quality control of these patients before hospitalization, lack of information about the patients' financial ability and the level of literacy of the parents. It is suggested that, if possible, studies be conducted in all provinces to better understand the factors related to a better control of these patients in order to make an overall decision about educating these patients based on the results.

Conflicts of Interest: The authors declare that there is no conflict of interest.

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