Frequency of Ketoacidosis and Associated Risk Factors at the Onset of Type 1 Diabetes Mellitus in Children and Adolescents

Nadia Sattay Hassoon*, Najla I. Ayoub**

ABSTRACT:

BACKGROUND:
Diabetic Ketoacidosis (DKA) is the most serious acute Complication of type 1diabetes mellitus and the leading cause of morbidity and mortality in children. It still carries high incidence rate at time of diagnosis.
Study design: Hospital-based cross-sectional observational study conducted at Children Welfare Teaching Hospital /Medical City /Baghdad; including the admitted patients in ER.

OBJECTIVE:
To identify the frequency of ketoacidosis and associated risk factors at the onset of Type 1 Diabetes Mellitus in children and adolescents.

METHODS:
The demographic, clinical manifestation, laboratory data of 69 patients presented with DKA at the disease onset out of total 144 patients who were diagnosed as Type 1Diabetes Mellitus; during a one-year period from 1st of September 2017 to 31th of August 2018. Age distribution was categorized into three groups: 1- 5 years, >5 years, >10 years. DKA was defined as blood glucose ≥200 mg/ dl; blood PH < 7.3; associated with ketonuria and glucosuria.

RESULTS:
Of 69/144 patients (47.9%) presented with diabetic ketoacidosis at disease onset; 41 patients (59.4%) were females which was significant (P value 0.045); Mean age at diagnosis was 7.5± 3.4 years: with highest frequency (43.5%) in age group >5 years but (50%) of severe DKA patients were involved in younger age group ≤ 5 years. Family history of diabetes was found in 11 (15.9%) patients. Majority of primary caregivers had a low academic achievement just14 (20.3%) of them had higher education.

CONCLUSION:
The frequency of childhood DKA at the disease onset was still high. Girls had a higher rate of occurrence. Younger age is associated with more severe DKA. Family history of diabetes and education level of the parents did not affect the frequency of DKA.

KEY WORDS:diabetes mellitus in children, Diabetic Ketoacidosis, frequency, clinical manifestations, risk factors.

INTRODUCTION:
Diabetes is one of the most frequent chronic diseases affecting children and adolescents. Diabetes is defined by WHO as a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both**.** TIDM occurs due to cellular-mediated autoimmune destruction of pancreatic β cells, causing an absolute deficiency of endogenous insulin; formerly known as insulin-dependent diabetes mellitus or juvenile-onset diabetes [1]. Prospective large international registries and studies have shown an increasing trend in the incidence of T1DM in most regions of the world over the last two decades, evidence shows that increases in incidence were highest in the younger age group [3, 4].Every year 65000 new cases ofT1DM are diagnosed worldwide, and the annual rate of increase is 3 %- 5% [5].The sex-specific pattern in incidence among children changed towards more modest differences [6]. About 10–20% of newly diagnosed childhood

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 *Pediatric Endocrinologist in Child'Central Teaching Hospital of Pediatrics.
**Professor in Pediatrics, Faculty of Medicine / Al-Mustansiriyah University.

cases of T1DM have an affected first-degree relative [6].

Clinical Manifestations of Diabetes Mellitus:
Children with type 1 diabetes (T1DM) presented with polydipsia, polyuria, polyphagia as the classical symptoms. With further β-cell loss, chronic hyperglycemia causes a more persistent diuresis, often nocturnal enuresis ensues [7].An insidious onset with lethargy, weakness, and weight loss is also quite common [8]. Another more severe manifestation is Ketoacidosis which is responsible for the initial presentation in many diabetic children [8].

Diabetic ketoacidosis (DKA):
Is one of the most serious acute complications of T1DM.It is a medical emergency that requires treatment and monitoring for multiple metabolic abnormalities and vigilance for complications. It is the common cause of death and permanent disability in children and adolescents with new onset diabetes.

By Definition: The International Society for Pediatric and Adolescent Diabetes (ISPAD) defines DKA as: Blood glucose level >11mmol/l (200 mg/dl), Venous PH < 7.3 or bicarbonate< 15mmol/L, ketonemia, and ketonuria [9].

Epidemiology and incidence
Up to 80% of these young people already have DKA when they are diagnosed with diabetes. There is a wide geographic variation in the frequency of DKA at the onset of diabetes. Geographical factors like climate may influence the number of people affected with DKA. Countries nearer to the equator have a high prevalence of DKA due to hot climates which lead to more rapid dehydration and onset of hyperglycemia particularly in young children [10].

Precipitating factors
Precipitating factors of DKA in known diabetic patients include: Infections, intercurrent illnesses, psychological stress, and noncompliance with therapy; worldwide, infection remains the most common underlying cause, occurring in 30–50% of cases [10]. Urinary tract infection and pneumonia account for the majority of infections [11]. As well as initial presentation; stress, trauma, infections, vomiting, and major psychological disturbances are considered precipitated factors [12, 13, 14].

AIMS OF THE STUDY:
To identify the frequency of diabetic ketoacidosis and associated risk factors at the onset of type 1

diabetes mellitus in children and adolescents in an emergency room of a single teaching hospital.

PATIENTS AND METHODS:
A hospital- based cross sectional observational study. This study was conducted in the emergency room at Children Welfare Teaching Hospital /Medical city / Baghdad during a one- year period from 1st of September 2017- 31th of August 2018. A total 144 patients of children and adolescents with new onset T1DM were included in the study ,69/144 patients were presented with DKA and they were managed in ER according to DKA protocol used in the hospital; then transferred to endocrinology ward after recovery from ketoacidosis for further management. The remaining 75 patients attended out-patient diabetic clinic of the hospital and admitted to endocrinology ward with classical signs and symptoms of hyperglycemia, general weakness and weight loss.

Frequency was analyzed and associated risk factors that influencing DKA occurrence and its' effect on severity at the onset of T1DM e.g. age, gender, residence, BMI, family history of diabetes, educational level of the mother, history of delayed diagnosis (through the onset and duration of symptoms), seasonal variation. Full clinical examination and medical history were done.

Laboratory investigation: random blood glucose, blood gas analysis for PH and HCO3, renal function test, general urine examination for (sugar and keton), complete blood count, HBA1c, (thyroid function test, celiac screen after stabilization).

- Inclusion criteria: **1.** Patients with new –onset DM. 2. Age from 1-15 years.
- Exclusion criteria: **1.** Known case of diabetes. 2. Age <1 year and >15 years.
- Type2 DM; and other secondary diabetes.

Statistical analysis: Analysis of data was carried out using the available statistical package of SPSS-25 (Statistical Packages for Social Sciences-version 25). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of difference of different percentages (qualitative data) was tested using Pearson Chi-square test (χ^2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P value was equal or less than 0.05.

RESULTS:

Of 69 patients out of total 144 patients (47.9%) with new onset T1DM presented with diabetic ketoacidosis; with mean age of 7.5 ± 3.4 year; ranging from 1- 15 years of age. Males comprised 28patients (40.6%) of the study and 41patients (59.4%) were females. There was statistically significant association between gender and DKA occurrence with female preponderance (P value 0.045).

Age distribution and percentage were as follows: 23 patients (33.3%) were (≤5) years of age group; 30 patients (43.5%) among >5 years of age group; 16 patients (23.2%) among >10 years of age group. The majority of patients with T1DM during the study period were in (6 – 10) year's age group.

Majority of patients' residence were in Baghdad city 46 patients (66.7%); and to the lesser extent from Baghdad periphery mostly rural 12patients (17.4%); other 11 patients (15.9%) were referred from other governorates.

The study demonstrated that 11patients (15.9%) with newly diagnosed diabetes had positive family history of T1DM in first-degree relative member; whereas 37 (53.6%) of total DKA patients had positive consanguinity between the parents. It was found that (97.9%) of total 144 patients had no history of associated autoimmune disorder. one patient had thyroid disease (hypothyroidism) prior the onset of DM; and other two patients had celiac disease,but nil in those with DKA patients.

The study demonstrated that familial level of education especially academic achievement of the mother or other home caregiver was: 4 patients(5.8%) were illiterate; 27 patients(39.1%) were primary school attendance; 24 patients(34.8%) were secondary school; and 14 patients (20.3%) had got higher education and university graduated.

Body mass index (BMI) of the patients was analyzed in terms of mean ±SD and percentile; it was found that mean BMI at 15.7± 2.6. Thirty five patients (24.3%) were <5% underweighted; 9 patients (6.3%) ≥85% overweighed; 10 patients (6.9%) were ≥95% obese; Whereas 90 patients (62.5%) were within normal distribution < 85%.

The study demonstrated increasing incidence of diabetes during autumn and winter seasons; associated with higher frequency of DKA occurrence by 34.8% and 29% in autumn and winter respectively. As shown in table (2).

Table 1: Demographic features in patients with new – onset T1DM.

Study variables		No	%
Age (years)	1---5	45	31.2
	6---10	60	41.7
	11---15	39	27.1
	Mean ± SD (Range)	7.5±3.4 (1-15)	
Gender	Male	71	49.3
	Female	73	50.7
Residence	Baghdad center	106	73.6
	Baghdad periphery	19	13.2
	Others	19	13.2
FH of T1D	Positive	21	14.6
	Negative	123	85.4
Autoimmune	No	141	97.9
	Thyroid	1	.7
	Celiac	2	1.4
	Others	-	-
Consanguinity	Yes	72	50.0
	No	72	50.0
Education	Illiterate	8	5.6
	Primary school	65	45.1
	Secondary school	46	31.9
	Higher	25	17.4
BMI for age & sex	$<5^{th}$	35	24.3
	5th----84th	90	62.5
	85th---94th	9	6.3
	$\geq95^{th}$	10	6.9
	Mean ± SD (Range)	15.7±2.6 (10.4-27.7)	

Table 2: Seasonal distribution and percentage of DKA patients at diagnosis.

Seasonal incidence	diagnosis of DM in months	No. & % of new-onset T1DM		No. & % of DKA	
		No.	%	No.	%
Winter	December	18		11	
	January	9	25%	5	29%
	February	9		4	
Spring	March	9		1	
	April	11	22%	7	17.4%
	May	12		4	
Summer	June	9		5	
	July	10	21%	4	18.8%
	August	11		4	
Autumn	September	15		9	
	October	17	32%	6	34.8%
	November	14		9	
Total		144	100%	69	100%

In comparison between DKA group and non- DKA group patients; there was no difference in mean age of diagnosis between both groups was observed, but significant difference in gender affection between them and significant weight loss in DKA patients, no differences were detected in terms of residency, BMI, family history of T1DM, associated autoimmune disorder and educational level of the family in each group.

Table 3: Demographic parameters in comparison between DKA and non- DKA groups.

Demographic parameters		DKA		Non-DKA		P value
		No	%	No	%	
Age (years)	1---5	23	33.3	22	29.3	0.597
	6---10	30	43.5	30	40.0	
	11---15	16	23.2	23	30.7	
Gender	Male	28	40.6	43	57.3	0.045*
	Female	41	59.4	32	42.7	
Residence	Baghdad center	46	66.7	60	80.0	0.183
	Periphery	12	17.4	7	9.3	
	Others	11	15.9	8	10.7	
BMI (Kg/m2)	<5	17	24.6	18	24.0	0.391
	5---84	46	66.7	44	58.7	
	≥85	2	2.9	7	9.3	
	≥95	4	5.8	6	8.0	
FH of T1D	Positive	11	15.9	10	13.3	0.658
	Negative	58	84.1	65	86.7	
Autoimmune disorders	No	69	100	72	96.0	-
	Thyroid	-	-	1	1.3	
	Celiac	-	-	2	2.7	
Consanguinity	Yes	37	53.6	35	46.7	0.404
	No	32	46.4	40	53.3	
Educational level	Illiterate	4	5.8	4	5.3	0.560
	Primary school	27	39.1	38	50.7	
	Secondary school	24	34.8	22	29.3	
	Higher	14	20.3	11	14.7	
Weight loss	Yes	53	76.8	40	53.3	0.003*
	no	16	23.2	35	46.7	

DISCUSSION:

Demographic and clinical features of children with DKA of new onset T1DM were analyzed and followed in one center. The mean age was 7.5 ± 3.4 year; which is compatible with Ardicli et al. in Turkey [15]. Age onset is variable in different parts of the world i.e. 8.3yr in Greece [16]; 9.2yr in Germany [17] and 8yr in Finland [18]. Age distribution of T1DM in the study revealed a peak in 6-10 yr (41%) which was similar to that reported by Razavi in Iran [19] and with Xin Yin china [20], but disagree with Ardicli et al. who revealed a peak age of presentation was <6 years.

Seasonal variations showed higher incidence of T1DM and frequency of DKA in cold months (autumn and winter) than other months; which was similar seasonal pattern found by Ardicli et al. study. This seasonal trend might be explained by increased frequency of viral infections in the cooler temperatures, which may support the hypothesis

that viruses trigger and enhance autoimmune destruction of pancreatic B cells [21].

The study shows positive Family history of diabetes in 14.6% of the patients which is similar to Ardicli et al. study that observed 14% had family history; while 5.8% family history was found by Waldhor T et al. in Austria [22].

DKA is one of the most serious complications of T1DM and carries a substantial risk of morbidity and mortality. Actually, the frequency of DKA at presentation varies from 15- 67 % ([14]. In the study, frequency of DKA was 47.9% of total newly diagnosed patients that agree with Ardicli et al. study (50.8%). It was recorded 55% in Saudi Arabia [23]; 37% in Austria [23]; and 37% in Finland [24]. So, the frequency of DKA at disease onset still high in comparison to western countries; and this might be explained by ascertainment bias as the study was conducted at secondary center which tend to admit patients with more severe symptoms or there is a delayed visit to the hospital after initial presentation due to decreased awareness of both parents and clinicians regarding symptoms of diabetes.

There was statistically significant association between genders with frequency of DKA; it was 59.4% females and 40.6% males (P value 0.045); This agree with Ardicli et al. study that recorded 55.6% female and 44.4% male as well as Neu et al [25], this might reflect delayed admission of health problems for girls in comparison to boys as a general trend in our population.

Although a positive family history of T1DM is considered as protective to DKA due to family awareness of symptoms of diabetes allowing timely diagnosis before DKA can develop. However, the study showed no significant association between family history and duration of symptoms prior diagnosis with frequency and severity of DKA; which was similar to that found by Hye Jin Lee et al. study [26].

There was significant association between weight loss and DKA presentation 53\69 patients (76.8%) in the current study which agree with Hye Jin Lee study. Weight loss is a typical sign of dehydration and metabolic derangement with higher risk at onset of DKA; so it is a fact that higher frequency of weight loss occur before the diagnosis of DKA.

CONCLUSION:

The frequency of childhood DKA is still high in the newly diagnosed T1DM; cooler temperature carries higher incidence of DKA; Younger ages associated with increased risk of severe DKA and Weight loss is significant feature in the presentation of DKA; Girls were found to have higher rates of DKA at the onset; Family history of T1DM and educational level of the parents did not affect the frequency of DKA.

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