



Risk Factors of Recurrent Diabetic Ketoacidosis in Karbala Teaching Hospital for Children

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Abstract. Diabetic ketoacidosis (DKA) is defined as life threatening condition that happen mainly in T1DM and less frequently with T2DM in certain situation, an increase in the serum concentration of ketones greater than 3 mmol/L, a blood sugar level greater than 11mmol/L (although it is usually much higher), and a blood (usually arterial) pH less than 7.3 and it is the most frequent acute hyperglycemic emergency in persons with diabetes mellitus (DM). The main cause of morbidity and mortality in children with diabetes is DKA from both type1 DM (T1DM) and T2DM. Children with diminished metabolic control or previous episodes of DKA are at higher risk, as are prepubescent and adolescent girls, children with psychiatric disorders, such as eating disorders, and children who come from challenging families with lower socioeconomic status and inadequate health insurance as well as low general education levels.

Keywords: Children, Diabetic Ketoacidosis, Hospital, Socio-Economic

1. INTRODUCTION

Diabetic ketoacidosis (DKA) is caused by an absolute or relative lack of insulin in the bloodstream and the interaction of elevated levels of catecholamine's, glucagon, cortisol, and growth hormone, which act as counter regulatory hormones [1]. Absolute insulin insufficiency happens in cases of type 1 diabetes mellitus (T1DM) that have not yet been recognized, as well as when people who are receiving treatment forget to take their insulin, particularly the long-acting portion of a basal-bolus regimen. In situations like sepsis, trauma, or gastrointestinal disease with diarrhea and vomiting, the concentrations of counter regulatory hormones rise in reaction to stress, resulting in relative insulin insufficiency [2].

It has been established that the risk of DKA at diagnosis is higher in children when new-onset T1DM is not promptly recognized by healthcare professionals, the majority of DKA episodes in children with known T1DM are brought on by insulin omission, with a small minority of episodes also being brought on by illnesses, most frequently gastrointestinal infections with vomiting and dehydration [3].

In multiple studies, across many nations and cultures, female sex was found to be a According to a Chinese study, women and girls have a 2-times higher chance of developing DKA again (OR 2.12, 95% CI 1.50-3.04) [4].

It is important to state that children who present with ketoacidosis at the time of diagnosis are at greater long-term risk of poor glycemic control independent of concurrent socioeconomic and demographic risk factors [5]. This risk distribution may be influenced by psychosocial changes that occur throughout puberty, such as the desire for independence, the

passing of parental diabetes care duties to the teenager, or the change from pediatric to adult care [6].

The link between socioeconomic disadvantage and DKA is well established. Poor socioeconomic status (SES), area-level deprivation (a geographically based measure of SES), poor income, homelessness, and health insurance status were risk factors for several socioeconomic disadvantages [7]. Low general education levels, limited healthcare access, and low health literacy are significant risk factors. In conclusion, socioeconomic determinants are very important for DKA recurrence and tend to be more pronounced in children. These can be improved with earlier recognition and educational public health interventions [8].

Study Significance

Recurrent DKA is more common in girls and young women, and it is more common in late childhood, adolescence, and young adulthood, according to the analysis of risk variables. Social disadvantages and a history of migration are additional risk factors that are hard or impossible to alter. Prior DKA, elevated HbA1c, non-adherence, mental health issues, somatic comorbidities, drug or alcohol addiction, and inadequate diabetes management are the key modifiable risk factors that should be addressed by preventative measures [9].

The significance of identifying these risk factors that are particular to the local Iraqi children cannot be overstated because some, if not most, of the risk factors for DKA among children with T1DM are likely to vary from locality to locality and are demographic and socioeconomic in nature.

Therefore, in the present study, the clinical characteristics, socioeconomic and demographic risk factors of children with T1DM having recurrent DKA, were compared with a group of age-matched children comprising of T1DM patients with only one DKA episode or without DKA. The findings from this investigation would help with the early detection of the onset of DKA in kids with T1DM and serve as the foundation for future research into the development of targeted interventions and risk factor reduction techniques specifically for the pediatric population in Iraq.

Objectives of the Study

To evaluate the risk factors for diabetic ketoacidosis in children with insulin dependent diabetes mellitus admitted in the pediatric unit of Karbala Teaching Hospital Iraq.

Study design and setting

The present study is a cross-sectional case-control study was done in Karbala teaching hospital for children, 167 children diagnosed with T1DM their age 1-14 years at the last visit, selected cases were 83 patients presented with recurrent DKA (more than 1 attack of DKA

event) and was admitted to the hospital compared with control group 84 (patients with T1DM with history of single attack of DKA or non) were taken from endocrine center in Karbala city from January 2022 to August 2023. A list of information were taken for both groups (cases, control) after full history and clinical examination The socio-demographical data of the patients were also obtained from the children and their parents/ guardians via questionnaire-based interview, a list of information were taken regarding sex, age level of parent's education (Illiterate, Primary school, Secondary school, College), economic state of the family, types of treatment (Basal Bolus, Conventional), dose of insulin , diet control , frequency of DKA, any history of celiac disease diagnosed by serology and duodenal biopsy history of thyroid disease (thyroid function test) and the presence of lipodystrophy, both groups were sent for (HbA1c , RBS, urine for ketones, blood gas analysis, serum electrolysis, TFT, celiac screen). Blood urea, serum creatinine were sent for selected patients. The data collected were subjected to statistical analysis for evaluation and comparison of the risk factors between the study groups. Those patients diagnosed with DKA depend on presence of RBS >250 (more than 13 mmol/L), PH<7.30, Hco₃<15 mEq/L, presence of ketones in urine, HbA1c (6.5 – 15) %. (Nelson Essentials of Pediatric 9th Edition book).

Exclusion criteria

One patient with T1DM presented with infection (UTI, PNEUMONIA, GE) were excluded due to (lack of investigation and follow up). As well as patient with insulin pump was also excluded .In addition, Patients without perfect history and follow up were excluded.

Statistical analysis

Statistical analysis were preformed using SPSS Statistics (IBM SPSS Statistics for Windows, Version 20.0 Armonk, NY: IBM Corp). Frequencies and percentages were presented for categorical variables while means and standard deviations were calculated for numerical variables. For inferential statistics, the chi-squared was used to association between categorical variables, while the t-test and Chi-squared test was used to test the association between categorical and numerical variables. Statistical significant difference was set at P-value less than 0.05.

Aims of the study

This study aimed at identifying of risk factors associated with DKA in Pediatric T1DM patients. The findings of which would provide insights useful for the development of interventions aimed at improved recognition of early T1DM before development of DKA and at reducing rates of recurrent DKA in children, and reduce the severity of complication that lead to early death in T1DDM.

2. SUBJECTS AND METHODS

The present study is a cross-sectional study was done in Karbala teaching hospital for pediatric, 167 children diagnosed with T1DM, selected cases were 83 patients presented with recurrent DKA (more than 1 attack of DKA event) and was admitted to the hospital compared with control group 84 (patients with T1IDDM with history of single attack of DKA or non) were taken from endocrine center in Karbala city from January 2022 to August 2023. A list of information were taken for both groups (cases, control) after full history and clinical examination The socio-demographical data of the patients were also obtained from the children and their parents/ guardians via questionnaire-based interview. Venous blood sample was collected and was sent for investigation. The data collected were subjected to statistical analysis for evaluation and comparison of the risk factors between the study groups.

3. RESULTS

Socio-economic Characteristics and Treatment Type of the patients

A total of 167 children with T1DM were recruited in the study, which comprised of 83 patients with recurrent DKA and 84 patients with one or no DKA events (control). Table 1 details the socio-economic features as well as the treatment type of the patients.

Table 1 Distribution of the Patients with respect to Parent Socio-economic Status, Level of education and Treatment Type

Features	N	Case	Control	p-value
n (%)	167	83 (100%)	84 (100%)	
Education, n (%)				
Illiterate	24	20 (83.3)	4 (16.7)	0.001
Primary	60	31 (51.7)	29 (48.3)	
Secondary	59	27 (45.8)	32 (54.2)	
College	24	5 (20.8)	19 (79.2)	
Income, n (%)				
Low	33	25 (75.8)	8 (24.2)	0.001
Average	64	37 (57.8)	27 (42.2)	
High	70	21 (30.0)	49 (70.0)	
Treatment Type, n (%)				
Basal Bolus	128	61 (47.7)	67 (52.3)	0.33
Conventional	39	22 (56.4)	17 (43.6)	

Abbreviations: N (number).

Regarding education, majority of the illiterate parents/guardians (20 parents, representing 83.3%) had children having recurrent DKA while only 4 illiterate parents (16.7%)

had children in the control group. A 31 (51.7%) of the parents with primary level of education had children with recurrent DKA compared to 29 parents (48.3%) with children in the control group. Most parents with secondary and college education had children in the control group when compared to those with children having recurrent DKA (i.e. 32 parents (54.2%) [control] vs. 27 parents (45.8%) [recurrent DKA] and 19 parents (79.2%) [control] vs. 5 parents (20.8%) [recurrent DKA] for secondary and college education respectively). The differences between both groups with respect to education were statistically significant at $p < 0.05$.

Regarding level of income, majority of the low income parents/guardians (25 parents, representing 75.8%) had children having recurrent DKA while only 8 low income parents (24.2%) had children in the control group. A37 (57.8%) of the parents with average income had children with recurrent DKA compared to 27 parents (42.2%) with children in the control group. Most parents with high income had children in the control group when compared to those with children having recurrent DKA (i.e. 49 parents (70%) [control] vs. 21 parents (30%) [recurrent DKA]). The differences between the groups with respect to education were statistically significant at $p < 0.05$.

Regarding the type of treatment, 128 patients were treated by basal bolus; out of which 61 patients (representing 47.7%) had recurrent DKA while 67 patients (representing 52.3%) were in the control group. However, 39 patients were given conventional treatment; out of which 22 patients (representing 56.4%) had recurrent DKA while 17 patients (representing 43.6%) were in the control group. The differences between both groups with respect to treatment type were not statistically significant at $p < 0.05$.

The frequency distributions of the patients regarding their parents' socio-economic status and treatment type are also graphically presented in Figure 1.

Preparasi Ekstrak

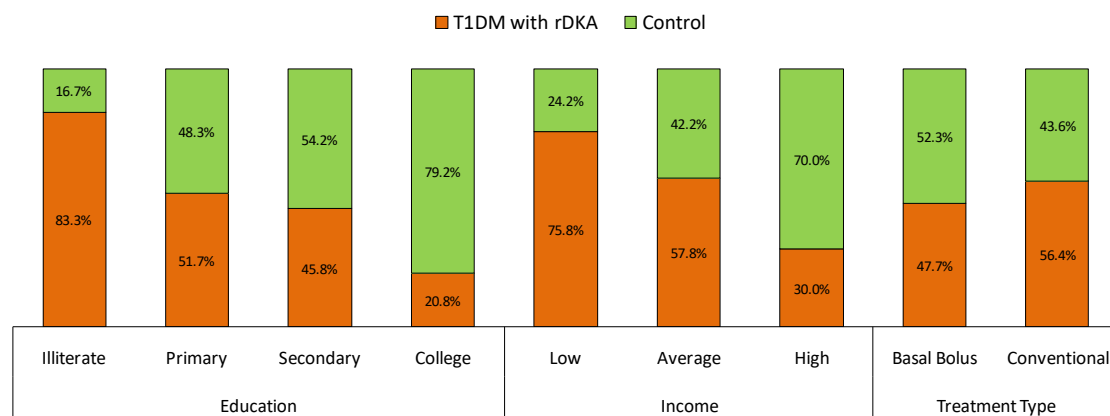


Figure 1: Parents' Socio-economic status as well as Treatment Type of the Patients

The percentage distribution of the parents/guardians of the study patients regarding socio-economic status (education and income) as well as type of treatment received by the patients

Abbreviations: rDKA (recurrent DKA); T1DM (Type 1 Diabetes Mellitus)

Existing Comorbidities and Diet Adherence of the Patients

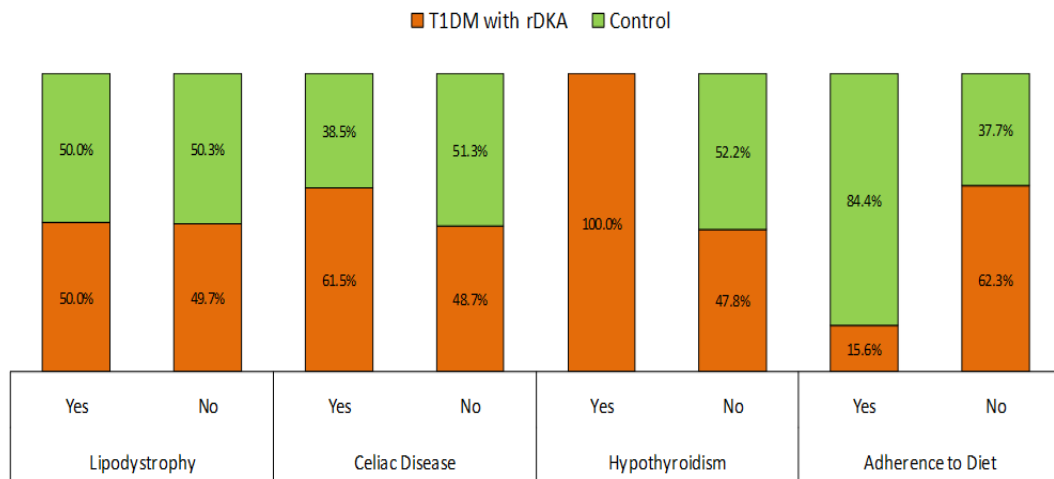
Assessment of the patients' hospital records revealed the presences of comorbidities. These comorbidities were lipodystrophy (at injection site of insulin in the body), Celiac disease and hypothyroidism. Also, the levels of adherence to dietary advices (pediatric dietitian) by the patients were also evaluated. Table 3.2 details the distribution of the patients for both groups with respect to comorbidities as well as their adherence to dietary advice.

Table 2: Frequency of the Patients with respect to Comorbidities
and Adherence to Die Abbreviations: N (number)

Variables	N	Case	Control	p-value
Lipodystrophy, <i>n</i> (%)				
Yes	12	6 (50.0)	6 (50.0)	0.33
No	155	77 (49.7)	78 (50.3)	
Celiac Disease, <i>n</i> (%)				
Yes	13	8 (61.5)	5 (38.5)	0.37
No	154	75 (48.7)	79 (51.3)	
Hypothyroidism, <i>n</i> (%)				
Yes	6	6 (100.0)	0 (0.0)	0.01
No	161	77 (47.8)	84 (52.2)	
Adherence to Diet, <i>n</i> (%)				
Yes	45	7 (15.6)	38 (84.4)	0.001
No	122	76 (62.3)	46 (37.7)	

The number of patients having lipodystrophy for those with recurrent DKA and control groups is 6, while those with Celiac disease for patients with recurrent DKA is 8 (representing 61.5%) and 5 (representing 38.5%) for patients in the control group.

All the 6 patients having hypothyroidism (100%), were patients with recurrent DKA with none of the patients in the control group having hypothyroidism. In contrast however, while only 7 patients (representing 15.6%) with recurrent DKA were adherent to dietary advice, the significant majority of the patients that adhered to dietary advice (i.e. 38 patients, representing 84.4%) were in the control group. Figure 3.2 graphically presents the frequency distribution of the comorbidities and diet adherence of the patients.



The percentage frequency distribution of the patients with respect to presence of comorbidities (Lipodystrophy, Celiac Disease and Hypothyroidism), as well as their adherence to dietary advice

Abbreviations: rDKA (recurrent DKA); T1DM (Type 1 Diabetes Mellitus)

Sex-based characteristics of the patients with T1DM and recurrent DKA

The distribution of the patients with T1DM and recurrent DKA (case group) regarding socio-economic status, treatment type, comorbidities as well as adherence to dietary advice, based on sex is summarized in Table 3.

Table 3 General characteristics of the patients with T1DM and recurrent DKA

Features	T1DM with rDKA			p-value
	All	Male	Female	
n (%)	83 (100.0)	37 (44.6)	46 (55.4)	
Education, n (%)				
Illiterate	20 (100.0)	7 (35.0)	13 (65.0)	0.12
Primary	31 (100.0)	19 (61.3)	12 (38.7)	
Secondary	27 (100.0)	9 (33.3)	18 (66.7)	
College	5 (100.0)	2 (40.0)	3 (60.0)	
Income, n (%)				
Low	25 (100.0)	11 (44.0)	14 (56.0)	0.94
Average	37 (100.0)	16 (43.2)	21 (56.8)	
High	21 (100.0)	10 (47.6)	11 (52.4)	
Type of Treatment, n (%)				
Basal Bolus	61 (100.0)	25 (41.0)	36 (59.0)	0.2
Conventional	22 (100.0)	12 (54.5)	10 (45.5)	
Lipodystrophy, n (%)				
Yes	6 (100.0)	3 (50.0)	3 (50.0)	0.78

No	77 (100.0)	34 (44.2)	43 (55.8)	
Celiac Disease, n (%)				
Yes	8 (100.0)	4 (50.0)	4 (50.0)	0.74
No	75 (100.0)	33 (44.0)	42 (56.0)	
Hypothyroidism, n (%)				
Yes	6 (100.0)	2 (33.3)	4 (66.7)	0.56
No	77 (100.0)	35 (45.5)	42 (54.5)	
Adherence to Diet, n (%)				
Yes	7 (100.0)	5 (71.4)	2 (28.6)	0.13
No	76 (100.0)	32 (42.1)	44 (57.9)	

Abbreviations: rDKA (recurrent DKA); T1DM (Type 1 Diabetes Mellitus)

Age and Clinical Characteristics of the Patients

The age and clinical presentation of the study patients are summarized in Table 3.4. The mean age of the patients with recurrent DKA was 10.88 ± 3.38 years, which is similar to that of the patients in the control group (10.67 ± 3.32 years). The average units of insulin administered to the patients with recurrent DKA were 40.92 ± 21.82 units/ day which was higher compared to 35.25 ± 19.0 units/ day as observed in the control group. The mean diabetes duration in patients with recurrent DKA was 3.92 ± 3.08 years which was relatively higher than that observed in the control group (i.e. 3.12 ± 2.33 years). These observed differences between the study groups were not statistically significant at $p < 0.05$.

Table 4: Mean Age and Clinical Characteristics of the Patients

	T1DM with rDKA (Mean±SD)	Control (Mean±SD)	p-value
Age (years)	10.88±3.38	10.67±3.32	0.68
Insulin (Units/ day)	40.92±21.82	35.25±19.0	0.07
Duration of DM (years)	3.92±3.08	3.12±2.33	0.06
Number of DKA Events	4.58±3.56	0.6±0.49	0.001
HbA1c (%)	11.55±2.37	10.29±2.26	0.001

Abbreviations: rDKA (recurrent DKA); DM (Diabetes Mellitus); T1DM (Type 1 Diabetes Mellitus)

Regarding number of DKA events as well as HbA1c, the patients with recurrent DKA had statistically significantly higher values ($p < 0.05$) compared to those in the control group (i.e. Number of DKA Events [4.58 ± 3.56 case vs. 0.6 ± 0.49 control]; HbA1c [11.55 ± 2.37 % case vs. 10.29 ± 2.26 % control]). These details are graphically presented in Figure 3.

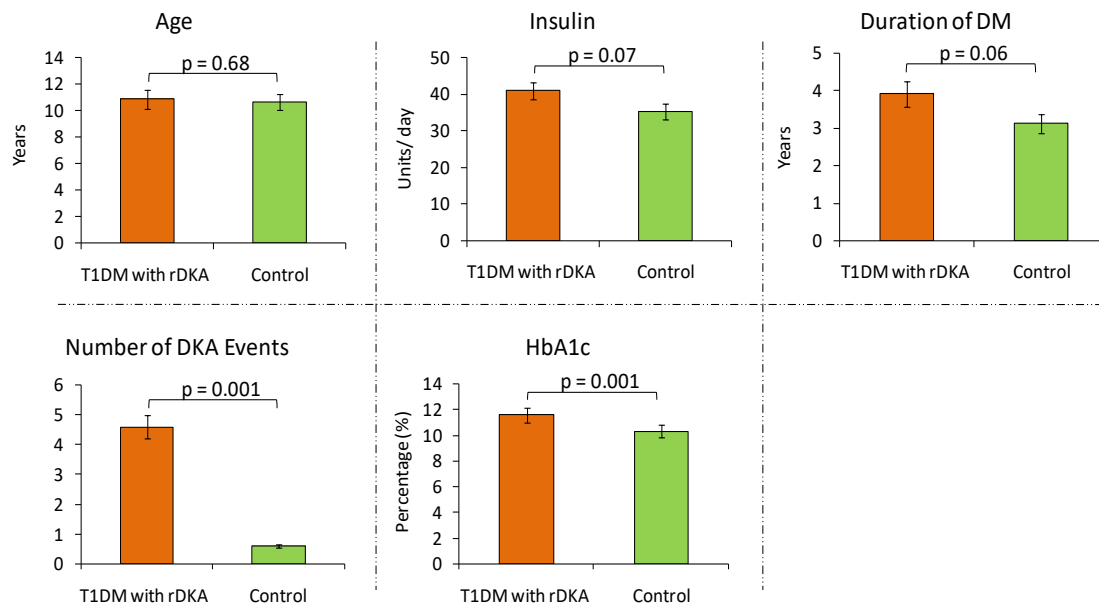


Figure 3 Clinical Characteristics of the Patients

Comparisons regarding age, insulin administration, and duration of diabetes between patients with recurrent DKA and the control group were not statistically significant at $p < 0.05$. However, significantly higher ($p < 0.05$) DKA events as well as HbA1c levels were observed in patients with recurrent DKA compared to the control group. Error bars indicate standard error of mean (SEM).

Abbreviations: rDKA (recurrent DKA); DM (Diabetes Mellitus); T1DM (Type 1 Diabetes Mellitus)

Association between the Clinical Features of the Study Patients

Pearson's correlation was used to evaluate the association between the different clinical features of all the study patients. The Pearson's correlation matrix (Table 3.5) indicates the correlation strength of each variable compared to another. Age had strong positive correlation with number of insulin units administered per day ($r = 0.63$), and moderate positive correlation with duration of diabetes ($r = 0.22$) as well as with HbA1c ($r = 0.24$); all of which were statistically significant and $p < 0.05$ (2 tailed).

Number of insulin units per day showed moderate positive correlation with duration of diabetes ($r = 0.34$) as well as with number of DKA events ($r = 0.25$) at $p < 0.05$ (2 tailed). Number of DKA events showed moderate positive correlation with duration of diabetes ($r = 0.24$) and a weak positive correlation with HbA1c ($r = 0.17$); these correlations were significant at 0.05 level (2 tailed).

Table 5 Pearson's Correlation Matrix Showing Associations between
the Clinical Features of the Study Patients

Variables	Insulin Units	Duration of DM	DKA Events	HbA1c
Age	0.63**	0.22**	0.1	0.24**
Insulin Units		0.34**	0.25**	0.1
Duration of DM			0.24**	0.11
DKA Events				0.17**

** Correlation is significant at the 0.05 level (2-tailed)

4. DISCUSSION

With DKA being the most common cause of death in children who have diabetes, it is significantly, the leading cause of morbidity and mortality in children. According to epidemiological data, nearly 30% of children with a new diagnosis of T1DM present with DKA and 10% of children with a new diagnosis of T2DM present with DKA [10]. Therefore, in children with known diagnosis of DM, early identification of the development of DKA holds the key to achieving timely treatment and lifesaving interventions. However, to aid early detection or diagnosis of DKA, comprehensive evaluation of risk factors associated with this disease is necessary. Risk factors for DKA on initial diagnosis are younger age (<2 years), delayed diagnosis, and lower socioeconomic status [11]. In children with known T1DM, the risk of DKA is 1% to 10% per patient year, and risk factors for DKA include insulin omission, previous episodes of DKA, inadequate dosing of insulin, and infection [2, 12]. More worrisome however is recurrent DKA, where studies have suggested that risk factors ranges poor clinical management of diabetic condition, to socio-economic factors, lifestyle and cultural peculiarities [13, 14]. The present study was conducted to identify the risk factors associated with recurrent DKA among Iraqi children with known T1DM diagnosis.

Socio-economic status (comprising of education and income level) of the parents of the study patients were evaluated. Parents' education was observed to significantly influence the risk of having children with recurrent DKA as majority of the patients under this category, had parents with low levels of education (illiterate and primary education). Previous studies have highlighted the role of low parents' education on the poor management of T1DM in children [14], diagnosis of DKA [15]. Similarly, the present study observed children having parents with low income levels are more likely to have recurrence of DKA events relative to those with medium or high income parents. Since the overall wellbeing of a family; including access to quality health care services and appropriate nutrition (which are crucial for diabetic children),

depends significantly on the income level of that family [16]. For this reason, children of low income parents are at high risk of having recurrent DKA- a finding that is consistent with reports of Al-Obaidi, A.H.Alidrisi, A.A.Mansour and Alaqeel, A.A studies [17, 18].

The present study also evaluated the possible effect that the existence of comorbidities known to affect patients with T1DM; these included lipodystrophy, Celiac disease and hypothyroidism. While Pasi, R, K.S.Ravi and Frohlich-Reiterer, E et al studies have reported high cases of lipodystrophy and Celiac disease in patients with T1DM and as well as in children with severe recurrent DKA [19, 20], the present study observed no significant differences between the groups with respect to the two comorbid conditions. However, regarding hypothyroidism, all 6 patients who presented hypothyroidism were having recurrent DKA, as none of the patients in the control group showed symptoms of hypothyroidism. Thyroid dysfunction have been reported in newly diagnosed T1DM children [21]. Fatourech et al reported that hypothyroidism was detected in 9.6% of children with T1DM and was associated with higher rates of DKA (OR = 3.15, 95%CI = 1.48–6.71) [22]. These reports are in agreement with the findings of this study; hence it is suggested that children with T1DM should be routinely checked for hypothyroidism as this could signal the risk of developing DKA. Moreover, being a mostly subclinical condition, hypothyroidism may progress to severe levels without being detected.

Another factor analyzed was patients' adherence to dietary advice. From the findings of this study, majority (76 patients (62.3%)) of children who do not adhere to the proper diet were those with recurrent DKA while on the other hand an overwhelming majority (84.4%) of those who adhere to dietary advice were in the control group. Diabetes is a diet-dependent condition and as such the role of diet in the disease progression, management and treatment of diabetes cannot be overemphasized. Gilbertson et al reported that dietary quality and food choice are strong determinants of T1DM progression as well as development of DKA [23]. Additionally, many studies have highlighted the role of poor adherence to low-glycemic index diet as predictors of DKA in children with T1DM [24-26].

The patients in both study groups (case and control) had similar clinical characteristics in terms of insulin units administered per day as well as duration of DM; this further strengthens the basis of comparison between the 2 groups as the differences observed in this study can be ascribed to the condition of recurrent DKA and hence, identified as possible risk factors for recurrent DKA in T1DM pediatric patients. Interestingly however, HbA1c was significantly higher in patients with recurrent DKA compared to the control. This outcome is expected considering the significance of HbA1c as a prognostic marker for glycemic control in DM [27].

The association between DKA at onset of T1DM and long-term HbA1c has been established in Lee, M.S., et al and Semenkovich, K., et al studies [28, 29]. It is therefore suggested that high levels of HbA1c in children with T1DM should be recognized and an indicator of development of DKA or as a predictor of DKA in T1DM patients who have not recorded incidence of DKA events.

Pearson's correlation conducted in this study for all the study subjects combined revealed association between number of DKA events and units of insulin, age, duration of DM and HbA1c. However, these associations need to be explored further in future studies to decipher the interrelationships between the identified risk factors and the development of recurrent DKA.

5. CONCLUSION

From the findings of the present study that the education and income level of parents or guardians with T1DM children influence the propensity of re-occurrence of DKA in the children i.e. low education and income increase the risk of developing recurrent DKA in children with T1DM. Moreover, Hypothyroidism considered a risk factor and predictor for recurrent DKA and should be routinely checked in children with T1DM. Also, Non-adherence to dietary advice significantly predisposes T1DM pediatric patients to increase risk for developing DKA. In addition, an elevated serum level of HbA1c is a hallmark and an indicator of DKA and recurrent DKA in children with T1DM.

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