DOI: https://doi.org/10.53350/pjmhs2115113148

ORIGINAL ARTICLE

A 5 Years Audit Report on Diabetic Ketoacidosis Patients from a Tertiary Care Hospital in Saudi Arabia

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ABSTRACT

Objective: To evaluate the causes of high admission rate of diabetic ketoacidosis (DKA) in adults with diabetes mellitus presenting to a tertiary care hospital in Saudi Arabia with specific emphasis on the clinical and biochemical phenotype and identify components of intervention and improve clinical outcomes in these patients.

Study Design: Observational study.

Place and Duration of the Study: Department of Diabetes & Endocrinology, Armed Forces Hospital Al-Hada, Taif, Kingdom of Saudi Arabia from 1st August 2015 to 31st January 2020.

Methodology: One hundred and fifteen patients with diabetes mellitus presenting with diabetic ketoacidosis during the last 5 years were enrolled. Approximately 50 different variables pertaining to the patients at the time of presentation were thoroughly scrutinized.

Results: There were 31 (28%) males and 81 (72 %) were females with type 1 DM 92%, type 2 DM 7% and 1% unclassified DM with a mean age of 20.90±7.4 years. 18% were diagnosed to have DM for the first time and others had a mean duration of DM of 8.0±3.6 years with an average daily insulin requirement being 64.0±20.2 units. Moreover 84% of patients were on basal bolus regimen and only 5% were on mixed insulin. 73% of the DKA episodes occurred in 15-25 years of age group. The commonest precipitating factors were non-compliance with insulin (44%) and respiratory tract infections (17%). Most common presenting symptoms were vomiting and abdominal pain present in 81% and 53% of patients. The mean blood sugar on presentation was 463±157.3 mg/dl whereas the mean HbA1c was 14±2.9. The mean pH and bicarbonate levels on presentation were 7.16±0.128 and 7±4.83 meq/L respectively. 80% of the patients were admitted to the general wards however 19% required ICU care. 69% of patients had a history of readmission with DKA and 29% were transferred from another periphery hospital. The mean duration of stay in the hospital was 2±3.8 days and the mortality was 0.9%.

Conclusion: A very low mortality rate is witness to excellent acute management of these very sick patients. However a very high non-compliance rate of 44%, combined with a readmission rate of 69% and a mean HbA1c of 14% are very alarming as far as long term prognosis is concerned.

Keywords: Diabetes mellitus, Ketoacidosis, Characteristics, DKA, Tertiary level care

INTRODUCTION

Diabetic ketoacidosis (DKA) is one of the most serious and sometimes fatal hyperglycemic emergencies in patients with type 1 diabetes mellitus. In the United States the frequency of DKA has increased during the last few years with more than 140,000 cases admitted every year.[1,2]

Diabetic coma was first described by August W. von Stosch in 1828.[3] Later on it was discovered that the urine from these patients contained significant amount of keto-acids.[4,5] Before the discovery of insulin the mortality in patients with DKA was almost 90% but since then it has reduced significantly and is presently less than 2%.[6] It occurs more commonly in individuals with higher level of HbA1C, longer duration of diabetes, in adolescents and females.[7,8] DKA is one of the most common causes of mortality among type 1 diabetes and it results in almost 50 % of deaths in patients with diabetes in individuals who are less than 24 years old.[1] However the inpatient mortality of DKA patients in US is less than 1%.[2]

In adults around 15-20% DKA is the initial presentation of type 1 diabetes but in children it is approximately 30-40%.[9-11] Globally infection is the most common cause of DKA but non-compliance with insulin treatment is the most common precipitating factor for DKA in young adults with type 1 diabetes mellitus.[12,13] In recurrent episodes of DKA psychological factors and eating disorders have been reported in 20% of patients.[12,14,15] Many medications that effect carbohydrate metabolism including anti-psychotic medications can precipitate DKA.[16,17] An unusual presentation that can delay diagnosis and treatment is called " euglycemic DKA" and has been reported specially with SGLT2 inhibitors.[18]

The main defect in the pathogenesis of DKA is absolute or relative deficiency of insulin. This is associated with the rise in the counter regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone).[19] Basically hyperglycemia develops by three mechanisms, gluconeogenesis, glycogenolysis and decreased peripheral utilization.[20] Furthermore insulin deficiency leads to activation of hormone sensitive lipase which causes breakdown of triglycerides and production of excess free fatty acids, which are further oxidized to ketoacids (beta hydroxybutarate and acetoacetate) in the liver a process mainly accelerated by glucagon.[21] Severe hyperglycemia and ketoacidosis also leads to an inflammatory state and a rise in proinflammatory markers leading to impaired insulin secretion and reduced insulin sensitivity.[22,23]

Mostly patients present with a short history of classic polyurea, polydipsia and weight loss. However gastrointestinal complaints occur frequently like abdominal pain has been reported in 46 % of patients and around two thirds of the patients give history of nausea and vomiting.[24] Due do acetones there may be fruity smell to the breath. Moreover physical examination will reveal signs of dehydration including loss of skin turgor, dry mucous membranes, tachycardia, and hypotension. Level of consciousness can vary from fully conscious to extreme lethargy. It has been reported that <20% of patients may present with unconsciousness.[1]

The classic syndrome of DKA comprises of hyperglycemia, ketonemia and metabolic acidosis. The most common diagnostic criteria for DKA are blood glucose >250 mg/dl, arterial pH <7.3, serum bicarbonate <15 mEq/l, with ketonemia and/or ketonuria. It is recommended that an anion gap of > 14 - 15 mEq/l is considered to be a high anion gap acidosis.[25,26] Severe DKA patients usually present with a bicarbonate level <10. mEq/l and/or a pH that <7.0, and have a serum total osmolality of >330 mOsm/kg and mostly have altered mentation.[27]

Ketonurea and ketonemia is assessed by the nitroprusside test. This may underestimate the severity of ketoacidosis, as it detects the acetoacetate rather than beta hydroxybutyrate which is the main ketoacid. Therefore it is recommended to measure the Beta hydroxybutyrate directly.[28] Some patients with DKA can present with mixed acid base disturbances. Only 46% of patients

present with high anion gap acidosis, 43% have mixed anion gap and hyperchloremic metabolic acidosis and 11% have hypercholoremic acidosis.[29] It is essential that DKA should be differentiated from a closely related condition hyperglycemic hyperosmolar syndrome (HHS).

The two main triggers for DKA are non-compliance and infections, if properly managed these can be mostly prevented. Therefore it was the objective of this study to thoroughly scrutinize all the variables and narrow down the gaps in the management of this very serious but preventable complication of diabetes mellitus.

MATERIALS AND METHODS

This is an observational study conducted at Armed Forces Hospital, Al-Hada Taif, Kingdom of Saudi Arabia. One hundred and fifteen patients admitted with DKA from 1st August 2015 to 31st January 2020 were enrolled. Any male or female patients with DM who was more than 14 years of age of DKA and required admission for the management were included. The demographic information and clinical data included the age, type and duration of DM, the regimen and the dose of insulin both basal and bolus were recorded. Moreover the symptoms at the time of presentation were documented including polyurea, polydipsia, fever, vomiting and abdominal pain. Vital signs e.g. both systolic and diastolic BP, heart rate, respiratory rate and oxygen saturation were looked into. Anthropometric data included height, weight and BMI. Biochemical parameters included BSR, pH, bicarbonate, anion gap, urea, creatinine, electrolytes and HbA1C. The disposition of the patients i.e. general ward or ICU was recorded. The type of management that was given to the patients standard protocol or ICU care. Mortality and any complications during the hospitalization were registered.

Data analysis was performed using SPSS-20. The normality test was done for numerical data to find out if it's either normally distributed or not. The differences between the means of normal distributed parameters were analyzed by T-test. The difference between the mean rank of non-normal distributed parameters were analyzed by Mann-Whitny test. P-value <0.05 was considered statistically significant.

RESULTS

There were 81 (72%) females and 31 (28%) were males. The mean age was 20.09 years and 68% of patients between 14–19 years of age. Most of the cases 92% were Type 1, 7% Type 2 and 1% remained unclassified with antibodies negative. Most of the patients 71% did not have any comorbid conditions but 30% had another associated illness mostly another autoimmune disorder. The average duration of diabetes at the time of presentation was 8.08 years, 18% of the patients were newly diagnosed, and most of the patients >40% had diabetes for between 5-10 years. 47% of the cases presented with vomiting and 32% with abdominal pain. Other symptoms were polyurea, polydipsia and fever 9%, 7% and 5% respectively. Basal bolus 84%, was the most common regimen of insulin and only 5% were on mixed insulin. The average daily dose of insulin the patients were consuming was 65.3 units. 49% patients were taking 50-70 units with 37% on 50-60 units and 18 % between 60-70 units. Patients on an average were taking more bolus than basal 40.31 units and 30.46 units respectively a ratio of 1.3:1. 89% of patients were not taking any other chronic medications but 4.5% of patients were on steroids, 1% on levothyroxine and 1% on growth hormone and HRT. Most of the patients around 90 % were fully conscious when admitted to the hospital (Fig. 1).

At the time of presentation 84% of patients had a systolic BP >100 mmHg and 16% <100 mmHg. 80% had a diastolic BP >60 mmHg and 20% <60 mmHg. The average HR was found to be 109/min with <100/ min 37%, 100–120 min/min 42% and >120/min 21%.

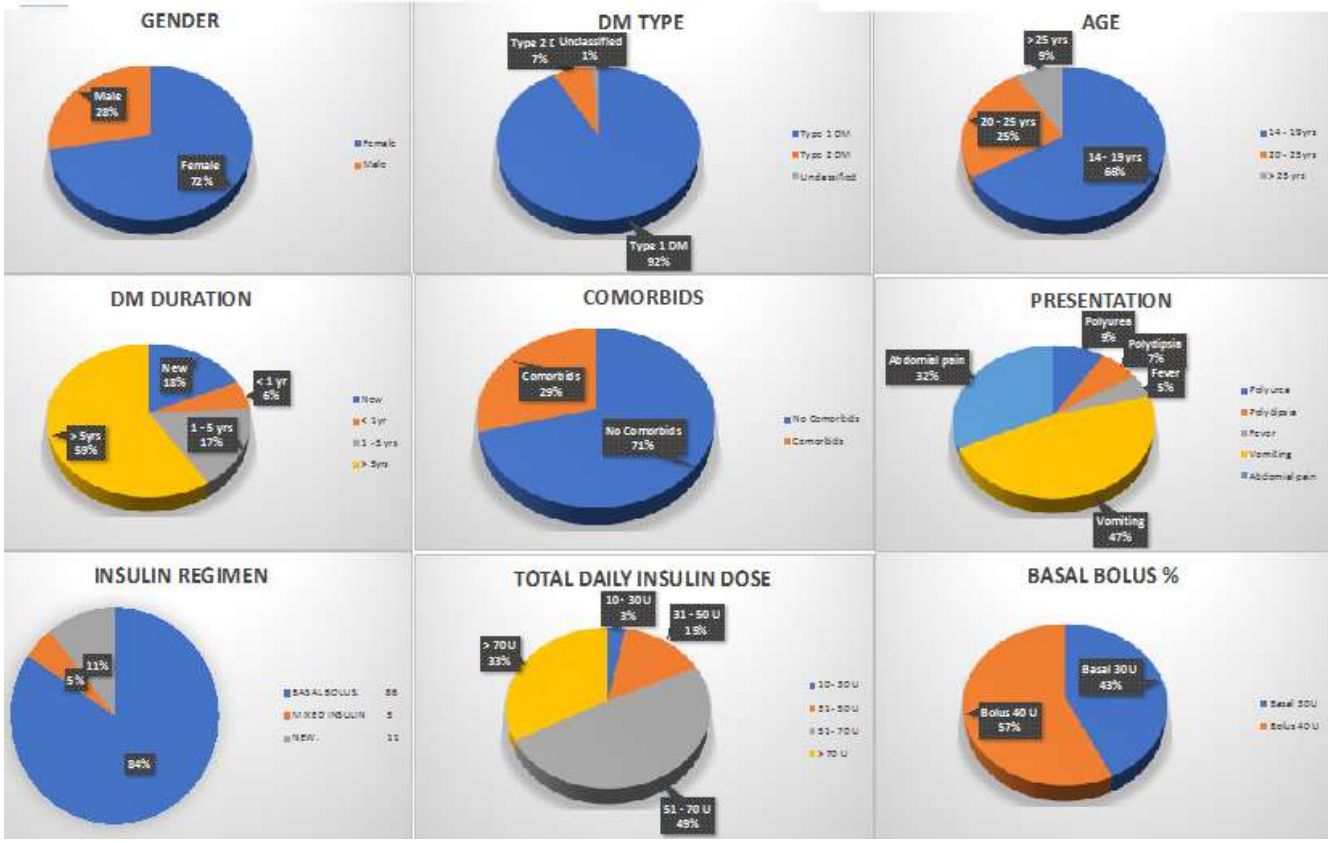
89% had normal temperature, 3% hypothermic and 3% were febrile. 93% of patients had a respiratory rate of 20–30 per min, 11% <20/min and 4% 30-40 per min. Most of the patients >95% had an oxygen saturation of >90% and <2% had a saturation of <90%. Anthropometric data including weight, height and BMI was not available in almost 70% of the subjects. However the measurements that were done showed an average BMI 20.95 kg/m^2 (Table 1). Non-compliance and infections were the most common precipitating factors, 44% and 17% respectively. 69% of patients gave history of multiple admissions due to DKA in the past. Non-compliance and infections were the most common causes of readmissions 38% and 35% respectively .The mean blood sugar was found to be 468 mg/dl and 35% had a blood sugar of >550 mg/dl. Average HbA1C was found to be 10.95% and 64% of patients had an HbA1C to be more than 10% (Table 2). Average pH was found to be 7.16 with <7, 7.1–7.24 and >7.25, 12%, 62% and 24% respectively. The mean bicarbonate was 7 mmol/L and 64% of patients had <10 mmol/L (Table 2). The mean anion gap was 23, while 63% of patients were found to have a AG of >20. 80% of patients were managed on the general wards while 20% of the patients required ICU admission. On an average patients were admitted for only 2 days and 72% of the patients were discharged within 2 days of admission. Only 1% of patients had any complications i.e. ARDS. Mortality was only 0.90% and 99.10% were discharged home.

Table 1: DKA patient's characteristics

Variable	Mean±SD
Age (years)	18±7.49
Duration (years)	8±3.6
Systolic BP (mmHg)	113±16.11
Diastolic BP(mmHg)	69±11.37
Heart rate	108±18.89
R/R	20±3.46
Temperature (C)	36.7±0.33
O2 Sat (%)	97±2.08
Height (cm)	160±11.80
Weight (kg)	49.65±13.73
BMI (Kg/m^2)	21.2±3.84
Urea (mmol/ L)	5±1.97
Creatinine (mmol/L)	95±95.49
Na (mmol/L)	133±4.55
K (mmol/L)	4.7±0.62
Chloride (mmol/L)	101±6.83
Osmolality (mOsm/kg)	278.5±11.54

Table 2: Biochemical characteristics of DKA patients

Variable		No.	%
BSR (mg/ dl)	150–350	25	28.0
	351–450	34	37.0
	551–750	30	33.0
	>750	2	2.0
PH	>7.25	14	24.0
	7.1-7.24	34	62.0
	< 7	7	12.0
HCo3 (mmol/L)	< 10	72	64.0
	10.1-15	26	23.0
	> 15	15	13.0
Anion Gap	<15	17	15.0
	15.1–20	24	22.0
	> 20	69	63.0
HbA1C	<7	7	7.0
	7.1 - 8	2	2.0
	8.1 - 10	29	27.0
	> 10	68	64.0



DISCUSSION

Higher prevalence of DKA has been reported in younger versus older, females versus males, depressed versus non depressed patients, individuals with fair/poor control versus excellent control and patients treated with multiple daily insulin injections versus patients on CSII pump.[9,30-32]

In the current study male to female ratio was found to be 1:2.6 (Fig. 1).This is consistent with findings reported from other studies from Saudi Arabia both in adult and pediatric populations.[33,34] Moreover even global data indicates that there is higher female prevalence as far as DKA hospital admissions are concerned.[35]

As far as age was concerned it was noticed that there was a decreasing trend in admission rate with increasing age. Around 61 % of the patients were between 14–20 years of age (Fig. 1). It has been reported that type 1 DM patients between 15-24 years of age are most likely to have an HbA1c >7.5.[35] This may be due to intensive self-care management which may be very stressful at times with other additional challenges in this age group.[36] Physiological factors such as insulin resistance, puberty, behavioral and social issues may play a significant role in the high prevalence of DKA seen in this age group of patients.[37,38]

More than 90% of patients were as expected type 1 diabetics but 7% of patients were found to be patients with type 2 diabetes who decompensated into DKA with another comorbid condition. One percent of patients remained unclassified presenting as DKA and on further investigations were found to be negative for antibodies for type 1 diabetes mellitus and being investigated for any other metabolic disorder with hyperglycemia (Fig. 1). The concept that DKA occurs only in type 1 diabetics is flawed and is increasingly seen in type 2 diabetes the number of cases of DKA seen in T2D represents approximately one third of cumulative cases.[39]

The average duration of diabetes at the time of presentation was 8.08 years. 18% of the patients were newly diagnosed, and most of the patients >40% had diabetes for 5–10 years (Fig. 1). It has been reported that the patients with longer duration of type 1 diabetes are at higher risk of DKA as seen in the present study.[8] It is important to note that 20% of patients who are admitted with DKA had no past history of diabetes.[40] Most of the patients 71% did not have any other comorbid conditions but 30% had another associated illness most commonly another autoimmune disorder i.e. adrenal insufficiency, hypothyroidism and autoimmune hepatitis etc. One patient who was admitted repeatedly and had antibodies including zinc transporter negative was suspected to have Mauriac Syndrome with primary amenorrhea, short stature and glycogen storage disorder (Fig. 1).

47% of the cases presented with vomiting and 32% with abdominal pain. Other symptoms were polyurea, polydipsia and fever 9%, 7% and 5% respectively (Fig. 1). Gastrointestinal complaints occur frequently like abdominal pain has been reported in 46% of patients and around two thirds of the patients give history of nausea and vomiting.[31]

Basal bolus 84%, was the most common insulin regimen and only 5% were on mixed insulin. The average daily dose of insulin the patients were consuming was 65.3 units. 49% patients were taking 50–70 units with 37% on 50–60 units and 18% between 60–70 units. Patients on an average were taking more bolus than basal 40.31 units and 30.46 units a ratio of 1.3:1 (Fig. 1). 89% of patients were not taking any other chronic medications but 4.5% of patients were on steroids, 1% on levothyroxine and 1% on growth hormone and HRT. Drugs including glucocorticoids, antipsychotics and growth hormone that alter carbohydrate metabolism are an important cause of precipitating DKA.[17-19]

DKA is a medical emergency and should be dealt accordingly with rapid assessment including history and physical examination. On this will depend further degree of urgency and

priority of management. One third of patients usually present with lethargy and stupor and less than 25% with loss of consciousness. Physical examination reveals signs of dehydration like dry mucus membranes tachycardia and hypotension.[1] Most of the patients around 90% were fully conscious when admitted to the hospital. At the time of presentation 16% of patients had a systolic BP <100 mmHg. The average HR was found to be 109/min with 100–120 min/min 42% and >120 /min 21%. 89% had normal temperature, 3% hypothermic and 3% were febrile. 93 % of patients had a respiratory rate of 20–30 per min, 11% <20/ min and 4% 30–40 per min. Most of the patients >95% had an oxygen saturation of >90% and <2% had a saturation of <90%. The most consistent feature was tachycardia about 63% had a heart rate of >100/min (Table 1).

Surprisingly anthropometric data was missing in 70/% of patients. This was a reflection of weakness in the long term management of these patients. Whatever data was available showed an average BMI of 20.9 Kg/ m^2. 44% of the patients had a BMI between 15-20 Kg/m2, 41% 20-25, 11% 25–30 and only 4% were above 30 Kg/m^2. It showed that obesity was not a big issue in this group of patients (Table 1). It has been reported particularly in females that one of the reasons of omitting insulin is fear of hypoglycemia, weight gain, along with psychological factors like eating disorders, rebellion and stress of chronic illness.[41,42]

Non-compliance and infections were the most common precipitating factors, 44% and 32% respectively. Among the infections it was URTI, gastroenteritis, dental, appendicitis and cholecystitis, 17%, 7%, 6%, 1% and 1% respectively. Infections have been reported as the most common precipitating factors with URTI and UTI predominant causes.[43] Non-compliance with treatment has also been reported as important precipitant of DKA.[10]

One of the alarming findings from this study is a very high readmission rate. 69% of patients gave history of multiple admissions due to DKA in the past. Non-compliance and infections were the most common causes of readmissions 38% and 35% respectively. 65% of patients gave history of a single readmission in the past while 35% gave history of multiple readmissions in the past and 6% of these patients were admitted to intensive care unit. Risk factors that are associated with higher frequency of admissions include younger age, higher HbA1C, infections, CSII, lower socioeconomic status, depression and psychiatric issues.[39,45-48]

The mean blood sugar was found to be 468 mg/dl, 28% of patients had a blood sugar of 150–350 mg/dl, 59% 351- 650 mg/ dl and 13% had > 650 mg/dl. It was estimated that 35% of patients had a blood sugar >500 mg/dl (Table 2). This is somewhat similar to the data presented in the literature.[48] However the blood sugar at the time of presentation can be very variable and 15% of patients have been reported to have blood sugar of even < 300 mg/dl. Average HbA1C was found to be 10.95% and 64% of patients had an HbA1C to be more than 10% (Table 2).

Average pH was found to be 7.16 with <7, 7.1– 7.24 and >7.25, 12%, 62% and 24% respectively. The mean bicarbonate was 7 and 64 % of patients had less than 10. The mean anion gap was 23, while 63% of patients were found to have a AG of >20 (Table 2). According to the American Diabetic Association DKA is classified as mild, moderate or severe mainly based on acidosis assessed by PH, anion gap and bicarbonate.[1] Severe DKA typically presents with a bicarbonate level <10 mEq/l and/or a pH<7.0, have total serum osmolality >330 mOsm/kg and usually present with mental obtundation[34], and they are likely to develop complications. According to the ADA criteria a significant number of patients would fulfill the criteria for severe DKA which seems to be a very worrying trend. There were almost 11% of patients who had impaired level of consciousness with severe DKA. 80% of patients were managed on the general wards while 20% of the patients required ICU admission. On an average patients were admitted for only 2 days and 72 % of the patients were discharged within 2 days of admission. It is recommended that all patients with hypotension, oliguria, serum osmolality >330 mOsm/kg and mental obtundation should be managed in the ICU and the rest of the patients can be transferred to general wards if the nursing staff are trained to manage the intravenous insulin infusion protocol.[49] It has been reported in the literature that if managed properly patients should be able come out of ketoacidosis in 10-18 hours[50,51], which was comparable in this study.

The mortality among the patients is comparable to what has been reported in the Western literatureand much lower than locally from Saudi Arabia.[1,41,52] Only 1% of patients had any complications i.e. ARDS. Mortality was only 0.90% and 99.10% were discharged home. This was mainly due to the fixed protocols for DKA management and intravenous insulin infusion. Moreover all the medical staff was very well trained to follow these guidelines. The effectiveness of these interventions have been reported previously.[53]

CONCLUSION

The acute management of these patients is quite satisfactory resulting in a very low mortality and morbidity, mainly due to three factors strict adherence to documented evidence based protocols, close monitoring of the patients and supervision of the medical staff in direct contact with the patients. However there are still some unmet targets. The readmission rate was noted to be unacceptably high and there were gaps noted in the documentation specially the anthropometric data which is a reflection of the weakness in the long term management of these patients. The most important leading causes of readmissions noted are non-compliance with insulin and infections, which is similar to as noted elsewhere. Multidisciplinary approach specially involving healthcare educators in close contact with patients is highly recommended. The most important parameters that are associated with high frequency of admissions are younger age, higher HbA1c, psychiatric issues, low socioeconomic status and females.

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