Characteristics and burden of diabetic ketoacidosis in diabetic patients in the period of COVID-19 outbreak in Ethiopia

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Abstract

Background**:** Diabetic ketoacidosis (DKA) is an acute life-threatening complication of diabetes mellitus. This study aimed to evaluate the clinical characteristics and the burden of DKA cases during the period of the COVID-19 outbreak in Ethiopia.

Methods: An institutional-based retrospective chart review study was conducted. 178 randomly selected patients' medical charts were included. Data were collected from medical records in the period between October 2020 to July 2022. To investigate the association between the dependent and independent variable, binary and multivariable logistic regression were done with statistically significant at $P \leq 0.05$.

Results: A total of 178 medical records were reviewed. The mean (±SD) age of the patients was 41.3 (±13.2) years and 45% of patients had type 2 diabetes. Acute diabetic complications were documented in 25.8% of patients where DKA was the commonest (16.3%). Nearly half of the DKA patients (n=13, 44.8%) were presented with poly-symptoms at the time of diagnosis. Furthermore, missing drug (31%) was the most frequent precipitating factor followed by community-acquired pneumonia (21%), and multiple factors (17%). Besides, patients in the DKA group had a higher mean length of hospital stay (3 days versus 2.6 days).

Conclusion: The poly-symptoms were the common clinical features of DKA at the time of presentation. Pneumonia and a history of missing drugs were identified as leading precipitating factors of DKA. Even though the DKA complication is low in this research, diabetes health education at the community and institutional level, routine screening for diabetes at health centers, and treating the infections early are strongly recommended.

Introduction

Diabetic Ketoacidosis (DKA) represents a state of acute metabolic stress, that results when the body suffers due to an absolute or relative insulin deficiency for the metabolism of glucose(1). Diabetic Ketoacidosis (DKA) is the most common and serious complication of diabetes worldwide(2).

Worldwide about 537 million adults (20-79 years) are living with diabetes predicted to rise to 643 million by 2030 and 783 million by 2045. Even though the epidemiology is not understood fully ketosis-prone atypical diabetes is mostly increasing in sub-Saharan African communities (3, 4). In the African region, it is estimated there are around 1 in 22 adults (24 million) adults are living with diabetes and 1 in 2 (54%) people living with diabetes are undiagnosed(5). Ethiopia has a prevalence rate of Diabetes, reaching up to 6.5% mostly high was found in Dire Dawa city administration (14%) and the lowest (2%) in the Tigray region(6). Even though the prevalence of DKA decreased with age the overall worldwide prevalence was 0–128 per 1000 people and the incidence was 0–263 per 1000 people with Type 1 diabetes(7). In Ethiopia, the incidence of DKA in diabetes at diagnosis of DM is 35.8%(8).

Diabetic ketoacidosis (DKA) is an acute life-threatening complication of diabetes mellitus characterized by the triad of hyperglycemia, acidosis, and ketosis that occurs in the presence of very low levels of effective insulin action(9, 10). DKA is widely diagnosed using the diagnostic criteria: fasting plasma glucose greater than 250mg/dL, arterial pH 7.3, serum bicarbonate less than or equal to 18mEq/L, an anionic gap greater than 10, and urine dipstick ketone level ⩾+2(11).

Although the mortality rate of DKA has fallen significantly in the last two decades from 7.96% to 0.67%, in developing countries, it is still high which contributed to 12% in-hospital mortality(12). The two most common precipitating factors are non-adherence to insulin treatment and infection were the principal DKA precipitating factors as result in provoking the release of counterregulatory hormones and might result in DKA(12, 13).

As most DKA cases occur in patients with a known history of diabetes, DKA can be prevented by education for DM patients, screening for complications as per national guidelines, counseling support, and frequent random blood glucose follow-up. Many studies reported that improvement in the quality of care for diabetes was reflected by a decrease in diabetes-related hospitalizations(2, 14, 15).

A systematic review and meta-analysis study done during the COVID-19 pandemic reported that statistically significant increase in DKA occurrence among newly diagnosed T1DM patients (RR 1.41; 95% CI 1.19, 1.67; $p < 0.01$) (16). But another study has reported no fluctuations in the prevalence of DKA (17). Limited studies were done on DKA in Africa and no study in Ethiopia during the COVID-19 pandemic. One study done in South Africa reported DKA appears more commonly in COVID-19-infected patients with type 2 DM and at a young age (18). In Egypt, the increased prevalence of DKA is common in patients with newly diagnosed DM (19). Our study aimed to evaluate the clinical characteristics and the burden of DKA cases during the period of the COVID-19 outbreak in Ethiopia.

Methods

Setting and Design

The retrospective chart review study design was conducted from 1st November 2020 to 31st July 2022. Data were collected from a randomly selected medical charts of patients admitted with diabetes emergencies at public and private hospitals in Jemma Zone, Ethiopia.

Population

Our source population were all diabetic patients with age greater than 14 years admitted to public and private hospital at Jimma Zone, Ethiopia from 1st November 2020 to 31st July 2022.

Sample Size Determination and Sampling Technique

The minimum sample size was calculated using the Single Population Proportion formula $n = Z^2pq/d^2$, where, n is the required sample size, p is the expected prevalence of acute complications of DM, 73.9%

(20), i.e., q = 1–p, and d error (precision), i.e., 5%.

$n_1 = (Z\alpha_{/2})^2 * p(q)/d^2 = 1.96^{2*} 0.74(0.26)/0.05^2 = 296$

Since the sample was going to be taken from a relatively small population of < 10 000 (total admitted DM patient to the hospital were 356), then the sample size was adjusted as below.

Final sample (n_2) = n_1 = 296 = 162

$1 + n_1/N$ 1 + 296/356

As such, the sample size calculated was 162, and with 10% contingency (for incomplete card), the final sample size (n) was 178. Systematic random sampling was used to select patients using K random numbers of N/n every 2 of medical records.

K = N/n = 362 / 178 = 2

Data collection

An Excel data collection form was developed. The study was approved by the institutional research review committee, Jimma, Ethiopia. The form included the patients' age, nationality, gender, type of diabetes, length of hospital stays, associated comorbidities, precipitating factors, laboratory values, referral status, and outcome status. The major source of the patient's data was the patients' medical records both paper and electronic. Meticulous care was taken with the identification of data and data entry.

Statistical methods used in the analysis

The data were analyzed with Stata 14.2. The descriptive statistics were performed on all variables as total and across the three types of patients (New, type 1, and type 2). The descriptive statistics included frequencies and percentages for categorical variables. Similarly, mean, median, and standard deviation, with 95% confidence interval (CI) for the continuous variables were also used. The inferential correlational analysis was performed for the categorical variables to explore the significant differences among categories proportions using the Chi squares test. The one-way analysis of variance (ANOVA) is used to determine the difference of mean random blood sugar, age, ketone, and mean length of hospital stay between DKA and non DKA patient. Binary and multivariable logistic regression statistical analysis were done to show the relationship between precipitating factors including skipping drug, infection, and other independent risk factors like gender, religion, and age for DKA occurrence.

Data quality control

The questionnaires were pretested on 10% of the sample size. The data collectors and supervisors were trained before actual data collection, and the principal investigator supervised the data collectors closely. During data collection, both the principal investigator and data collectors checked the data for its

completeness and missing information at each point. Furthermore, the data were also checked during and after entry into the computer before analysis.

Ethical approval

and consent form

Ethical clearance was obtained from Firoomsis primary hospital institutional research review committee (FIRRC) with a formal letter of permission and support.

Operational definition

The following operational definition (diagnosis criteria) was considered for the current study purpose (21).

- **DM**: In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dl (11.1 mmol/l).
- **DKA**: ketonemia of 3 mmol /l and over or significant ketonuria (more than 2 + on standard urine sticks) PLUS blood glucose over 11 mmol /l or known diabetes mellitus venous bicarbonate (HCO3)) below 15 mmol /l and /or venous pH less than 7.3
- **HHS**: a plasma glucose level > 600 mg/dL and increased effective plasma osmolality > 320 mOsm/kg in the absence of ketoacidosis [1].

Results

Socio-demographic characteristics

Out of 178 reviewed medical charts, 80 (45%) patients were known type 2 and majority of them were from rural area 135 (75.8%). The mean (± SD) age of the patients was 41.3 ± 13.2 years. An acute diabetic complication was documented in 46 (25.8%) patients where DKA was the commonest in 29 (16.3%) of them. About 86(48.3%) of admitted patients were newly diagnosed DM (Table 1)

Table 1
Sociodemographic characteristics of the DM admissions.

Variables	Frequency (N)	Percentage (%)
Gender		
Female	32	18
Male	146	82
Address		
Rural	135	75.8
Urban	43	24.2
Age category		
14–30	49	27.5
31–45	61	34.3
46–60	54	30.3
>61	14	7.9
Duration of DM		
New	86	48.3
one to five years	86	48.3
More than ten years	6	3.4
Acute complication types		
No acute complication	132	74.2
DKA	29	16.3
HHS	17	9.6
Hypoglycemia	0	0
DM: Diabetes Mellitus; DKA: Diabetic Keto-acidosis; HHS: Hyperosmolar Hyperglycemic State		

Among the patients admitted to the hospital, 81 (45.5%) was taking oral hypoglycemic antidiabetic medication and most of the patients 62 (34.8%) were taking a combination of metformin and glibenclamide an antidiabetic medication. Only 44 (24.7%) patients skipped their medications before presentation to the hospital (Table 2).

Table 2
Type of drug regimen, drug missing history, and specific drugs

Variables	Frequency (N)	Percentage (%)
History of missing drugs		
Yes	44	24.7
No	134	75.3
Drug Regimens		
No Drug	87	48.9
Insulin	13	7.3
Oral Antidiabetic	78	43.8

Acute complication (DKA) and precipitating factors

Among 29 DKA patients, 24 (83%) of them have identified possible documented precipitating factors. Majority of DKA patients were male (n = 24, 82.8%) and less than 45 years of age category (n = 18, 62.1%). However, patients diagnosed with acute complications have a history of skipping drug 9 (19%) and about 6 (13%) of DKA patients were diagnosed with community-acquired (Table 3).

Table 3
Precipitating factors for Acute complication of DM admitted to FH, Jimma.

Precipitating factors	Frequency (N)	Percentage (%)
CAP	6	12.5
Dyspepsia	1	2.1
Malaria	1	2.1
UTI	1	2.1
Hypertension	1	2.1
Missing Drug	9	18.8
More than one factors	5	10.4
No factors identified	24	50
CAP: community acquired pneumonia; UTI: urinary tract infection		

Moreover, more DKA were developed in type 2 DM (n = 16, 55.2%) than type 1 DM (n = 13, 44.8%). Most of known DM patients developed DKA (n = 19, 65.5%) than newly diagnosed diabetes mellitus (n = 12, 44.5%) (Table 4).

Table 4
Association between DKA and age, gender, and type of DM.

Variables		DKA Complication		Odds ratio	P value
		No (N/%)	Yes (N/%)		
Gender	Female	27 (18.1)	5 (17.2)	1.06	0.91
	Male	122 (81.9)	24 (82.8)		
Type of DM	New	60 (40.3)	12 (41.4)		0.98
	Type 1	22 (14.8)	4 (13.8)		
	Type 2	67 (44.9)	13 (44.8)		
Residence	Rural	103 (69.1)	22 (75.8)	0.71	0.47
	Urban	46 (30.9)	7 (24.1)		
Age categories in years	14–30	41 (16.3%)	8 (83.7%)	0.98	0.93
	31–45	51(16.4%)	10 (83.6%)		
	46–60	45 (16.7%)	9 (83.3%)		
	> 61	12 (14.3%)	2 (85.7%)		
DM: Diabetes Mellitus; DKA: Diabetic Keto-acidosis					
DKA clinical presentations and investigations					

Majority of the DKA patients (n = 17, 58.6%) were presented with Polysymptoms (polydipsia, polyuria and polyphagia) (Table 5). Furthermore, the DKA patients were presented with a high mean of random blood glucose profile 480.4 (± 86.2) mg/dl (Table 6).

Table 5
Clinical symptoms of DKA at the time of presentation.

DKA	Symptoms						Total
	Polysymptoms only	Polysymptoms and weight loss	GI symptoms	AFI	Follow up	Others	
No	72	0	44	0	33	0	149
Yes	9	4	4	5	2	5	29
Total	81	4	48	5	35	5	178

Table 6
Mean comparisons of patients' RBS on DKA admission.

DKA complication	RBS on presentation		P value
	Mean (± SD)	N	
No	344.27(± 89.42)	149	0.000
Yes	480.41(± 86.15)	29	

Table 7
Mean comparisons of patients' serum creatinine at time of DKA admission.

DKA complication	Summary of serum creatinine		P value
	Mean (± SD)	N	
No	0.98 (± 0.29)	124	0.76
Yes	0.96(± 0.20)	24	

The mean serum electrolytes of the DKA group were 142 mmol/L (serum sodium), 4.98 mmol/L (serum potassium), 6.8 mg/dL (serum calcium) and 98.63 mmol/L (serum chloride) (Table 7). Furthermore, DKA patients recorded statistically significant higher mean urine ketone levels at the time of presentation when compared to the non-complicated group 2.34(± 1.00). But it was not statistically different in mean urine glucose (2.61) between DKA and the other group (Table 8)

Table 8
urine ketone and glucose profile of patients with DKA on admission.

DKA complication		**Urine Ketone**	**Urine Glucose**
No	N, Mean (± SD)	149, 0.00(± 0.00)	149, 2.57(± 1.10)
Yes	N, Mean (± SD)	29, 2.34(± 1.01)	29, 2.52(± 1.15)
P value		0.00	0.81

However, patients in the DKA group had statistically non-significant higher mean length of hospital stay (3 days versus 2.6 days). There was no recorded death in this study. All patients improved and discharged with appointment.

Discussion

Our study revealed the prevalence of diabetic ketoacidosis among admitted DM patients is low 29 (16.3%) which is similar to the studies in Saud Arabia (18–22%) (22), and in Nigeria (12.2%) (23). But the result is different from previous studies done in Ethiopia (40% at Hawassa university comprehensive

specialized hospital (24), 73.9% at Jimma Medical Center, Southwest Ethiopia(25), 48.3% at public hospitals in northwest Ethiopia(26)), 46.7% in 12 different Arab countries(27) and 48.7% at a district-level public hospital in Cape Town (28). The variation might be due to the outbreak of COVID-19 in that patients were at home and always follow their treatment.

In this study, DKA prevalence is more common in type 2 DM patients (45%) than in type 1 DM (13%). This finding is different from the previous studies done in Hawassa university comprehensive specialized hospital (24) the prevalence of DKA was 28.7% in type 1 DM and 11.28% in type 2 DM and also in Colorado American university, 25–30% in type 1 and 4–29% in type 2 DM (29).

Our study also revealed that the prevalence of DKA is higher in males 24 (83%). This result is in line with previous studies done in Bahrain there was a higher prevalence of DKA in males 131 (58.5%) than in females 93 (41.1%)(2) and Hawassa that DKA was more common in males. In this study, the prevalence of DKA in newly diagnosed DM and known DM was 41% and 59% respectively. This current finding is in line with studies conducted in Debre Tabor General Hospital Ethiopia, the prevalence of DKA in type one diabetes and type 2 was 43% and 57% respectively(30).

We have revealed in our study that complication of DKA has developed more in the age category 31 – 45 type 2 DM with DKA tend to be older at presentation between 46 to 60 years old, 7 (54%), than type 1 DM with age category 14 to 30 years old, 3 (75%). This result is contrary to previous studies from our country that complications of DKA are developed between the 15-34 years category(31).

Our study shows a history of missing drug 9 (31%) was the most frequent precipitating factor followed by community-acquired pneumonia 6 (21%), and more than one factor 5 (17%) which statistically significant difference between no precipitating factors, p-value 0.000 (95%CI 2.18; 6.91). An institutional-based retrospective follow-up study in other parts of Ethiopia similarly reported that drug discontinuation had high odds of developing DKA (AIRR = 2.91, 95% CI = 2.02–4.22)(32). The study conducted in a tertiary care hospital, in Mysuru, has demonstrated infections in 57 (52%) and poor compliance to antidiabetic treatment in 23 (21%) being the most common cause of DKA(33). A recent study conducted in Pakistan showed that infections (36.5%) and inadequate insulin doses (22.5%) were the predisposing factors frequently revealed(34). But a study conducted in 2020 identified different precipitating factors for DKA including socioeconomic disadvantage, adolescent age (13–25 years), female sex, high HbA1c, previous DKA, and psychiatric comorbidities(35).

We found the mean random blood sugar (480.9 ± 89.2) in DKA complication comparable in all the underlying types of DM, with a tendency to be higher in type 2 DM (492.7± 74.9). The result is consistent with the reports at a university hospital in Damascus in 2015, 478±166(36), and also comparable with the results from the study(11).

The study conducted as a prospective, observational design in a tertiary hospital from July-December 2018 revealed that DKA patients presented with severe vomiting (32.2%), abdominal pain (27.9%), and depressed mental state (DMS) (26.8%)(34). But our study on contrary reported the most common clinical

features in DKA were Polysymptoms (polydipsia, polyuria) with or without weight loss (44.8%), fever, headache, and cough (17.2%), GI symptoms (vomiting, diarrhea, abdominal pain) (13.8%), and few at follow up (6.9%). Similar to our study polyuria (96.9%), polydipsia (92.4%), weight loss (16.8%), vomiting (8.0%), and abdominal pain (8.9%) were the most common symptoms on presentation of the DKA patients at the Medical ward of Shashemene Referral Hospital, Ethiopia(12). This result is also not similar to the cross-sectional study conducted at Dilla referral hospital reported dry mouth (30.2%) followed by altered mentation (27.8%) as a common presentation of DKA(37).

Missing drugs (31%), and infection (45%) commonly community-acquired pneumonia (69.2%), urinary tract infection (23.1%), and malaria (7.7%) are the most identified precipitating factors for admitted DKA in our study. This finding agreed with studies conducted at North Wollo and Waghimra zone public hospitals, Amhara region, Northern Ethiopia(38), and a retrospective study conducted at Debre Tabor General Hospital from June 1 to June 30 of 2018(31). Another study done in Pakistan from August 2019 to February 2020 found that the most common precipitating factors as infections (69.0%) and non-compliance to treatment (53.5%) which supports our study(39).

All (100%) patients admitted with DKA diagnosis were improved and discharged with a mean length of hospital stay of greater than three days than others (two days). This result is lower than a study done in Debre Tabor General Hospital, Ethiopia around five days(31), sub-Himalayan region nine days(40), and in KwaZulu-Natal in which the estimated hospital stay was around nine days(41)

Limitations of the Study

The challenge was the missing information due to poor documentation of all necessary patient data. Since the study was based on secondary data, some important risk factors like education status and patient income were not available, and unable to analyze them.

Conclusion And Recommendations

DKA is a common and often life-threatening acute complication of diabetes mellitus mostly in patients with type 2 and newly diagnosed DM with precipitating factors including community-acquired pneumonia and a history of missing drugs. The overall clinical features at presentation commonly Polysymptoms and weight loss need to be addressed early at outpatient by the physician in the hospital and all patients with a history of drug discontinuation and accompanied infection always must be considered seriously. Community awareness of this serious complication is also needed, including routine screening for diabetes at health centers, and treating the infections early with possible antibiotics.

Efforts must be targeted at decreasing the frequency of missing drugs possibly by giving health education on continuous and regular drug taking, creating strategies to ensure continuous DM drug supply, and fully initiating the management of hyperglycemia and DM follow-up. Further studies can

explore the reason for drug discontinuation at a community level and discuss the solution with responsible bodies.

Abbreviations

AFI: Acute Febrile Illness; ANOVA: Analysis of Variance; CAP: Community-Acquired Pneumonia; CI: Confidence Interval; DKA: Diabetic ketoacidosis; DM: Diabetic Mellitus; GI: Gastrointestinal; HbA1c: Hemoglobin A1C; HHS: Hyperosmolar Hyperglycemic Syndrome; Mg/dl: Milligram per Deciliter; RBS: Random Blood Sugar; SD: Standard Deviation; UTI: Urinary Tract Infection

Declarations

Ethical consideration and consent

Ethical clearance was obtained from Firoomsis primary hospital institutional research review committee (FIRRC) with a formal letter of permission and support. The chief clinical director of Firoomsis primary hospital has been permitted to review patients' medical charts. Confidentiality of the information was maintained and privacy was maintained by extracting the data using medical record numbers. The Firoomsis primary hospital institutional research review committee waived informed consent owing to the nature of the retrospective study design. All methods were performed in accordance with the relevant guidelines and regulations.

Consent to publication

Non-applicable

Availability of data and materials

Data will be available upon request from the corresponding authors.

Conflict of interest

The authors declare that they have no competing interests.

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Authors contributions

DTD and DGA contributed to the conception and design of the study. MMK organized the database. DTD performed the statistical analysis. DGA and GD wrote the first draft of the manuscript. All authors contributed to the manuscript revision, and read, and approved the submitted version.

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