Clinical characterstics, precipitating factors and glycemic control among diabetic ketoacidosis patients admitted to university hopsital in Northwest Ethiopia: A hospital based observational study.

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Abstract

Aims: The aim of the study was to determine the clinical characteristics, precipitating factors and the level of glycemic control of diabetic ketoacidosis patients admitted to Debretabor General Hospital, northwest Ethiopia.

Methods: A retrospective, cross-sectional study was conducted at Debretabor General Hospital and data was collected from June 1 to 30, 2018.Participants included in the study were all diabetic patients with diabetic ketoacidosis admitted to the General Hospital during the study period. The primary outcome was to determine precipitating factors for DKA and the level of glycemic control of diabetic ketoacidosis patients. All the statistical data was carried out using Statistical Package for Social Sciences (SPSS).

Result: A total of 387 patients' medical records contained pertinent complete information included in this study. The mean age of the patients was 33.30± 14.96 years. The majority of patients were females 244 (63.0%). The most common clinical presentation was polyuria and polydipsia in (n=379, 97.9%) of patients. The most common precipitating factor was newly diagnosed diabetics mellitus 150(38.8%). Binary logistic regression showed that for every increase in the duration of the disease(DM) by 1 year, the likelihood of controlling hyperglycemia would increases nearly 1.5 times AOR:1.497 [1.203-1.814].

Conclusions: In this study, newly onset type 1 diabetes mellitus was the major precipitating factor for DKA. Polyuria and polydipsia were the most common presenting clinical characteristic of diabetic ketoacidosis. Long standing DM was found to be associated with good glycemic control among DKA patients.

1. Introduction

Diabetic ketoacidosis (DKA) represent a constellation of hyperglycemia, ketone bodies and metabolic acidosis in diabetic patients. A systematic review of literatures reported that the epidemiology of DKA has not been clearly elucidated among diabetes Mellitus (DM) patients. Once, patients are diagnosed with DM, they usually are placed on medications including hypoglycemic agent and insulin based on the level of glycemic control(1). Physical activities have been regularly recognized to optimize the level of glucose and hyperlipidemia which coexists commonly in DM patients(2). Despite continuous efforts to get control of DM and its complications, however, the achievement of an ideal glucose level is not always possible(3). Some patients face difficulties of keeping the glucose level up to the recommended point. Hyperglycemic episodes are one of the manifestations of abnormal or inadequate control of glucose in the body. When DM patients fail to attain appropriate level of glucose in the body, they encounter a triad of hyperglycemia, metabolic acidosis and production of ketone bodies which leads to the diagnosis of DKA(4). Often times, hyperglycemia is accompanied by the production of ketone bodies since the glucose is not effectively utilized by the body in spite of surplus state in the serum. The ketone bodies results in the disturbance of body acid-base balance and osmolality of the body fluid gives rise to metabolic acidosis(5).

Different factors have been reported as the Precipitating factors (PFs) for DKA. Infection has been found to be one of the leading precipitants of DKA in most studies(6, 7). An observational study conducted at a tertiary care center in Andhra indicated that infection was found to be the first leading cause of DKA, accounting for 43% cases. Among the infections, urinary tract infections were most common, followed by septicemia and pneumonia(8). In another hospital based descriptive study done in tertiary care hospital of Eastern Nepal, infection was the most common precipitating factor (56.25%) (9). A three year retrospective study done in Jimma in 2013 indicated that the most common precipitants of DKA were infections 59 %, and non-compliance to antidiabetic medications 32.3 %(10). On the contrary a prospective cross-sectional study done in Kenyatta National Hospital, Nairobi amongst the precipitating factors, missed doses had the major precipitating factor of KDA(11). Further, ,retrospective observational cohort study done in Saudi Arabia showed that missing /non-compliance of insulin dose caused 54.2% of DKA (12), cross-sectional study Benghazi-Libya (2007)(13). other studies done in New Zealand (14), Brazil (15), and Israel reported the same precipitating for DKA(16). First presentation of DM has also been identified as a significant PF among type 1 DM patients (17). A retrospective study done in Jimma University Specialized Hospital in 2013 showed that a newly diagnosed diabetes contributed 23.6 % of DKA(10).

The constellation of PFs make the glucose level rise and get the way for DKA to develop subsequently which on the other hand increase the prevalence of DKA in Ethiopia exponentially. However, emphasis has not been given to determine the most pertinent PFs since the down of time. Estimation of PFS in the context of developing country would help to direct interventions or strategies to reduce these factors and the occurrence of DKA. In light of this, the present studyaimed to determine the precipitating factors for diabetic ketoacidosis among diabetic patients admitted to Debretabor General Hospital (DGH) in northwest Ethiopia.

2. Methods

2.1 Study setting, design and period

A retrospective cross-sectional study was conducted at Debretabor General Hospital from June 1 to 30, 2018. Debre Tabor General Hospital is a government hospital found in Debre Tabor Town, South Gondar Zone of Amhara Regional state which is 667 kilometers far from Addis Ababa, the capital city of Ethiopia in Northwest direction and 102 kilometers far from Bahir Dar town. The hospital diabetic clinic gives a twice weekly outpatient service for DM patients. Based on patient fasting blood glucose level antidiabetic medication(s) dose adjustment and regimen change is made routinely.

2.2 Population

All DM patients with DKA who were admitted to inpatient ward of DGH from August 1, 2010 to May 31, 2018 were our study population. Participants included in the study were all diabetic patients whose

medical records contained complete pertinent data.

2.3 Sample Size determination and sampling technique

Single population proportion formula was used to calculate the minimum sample size based on the following assumptions: 5% level of significance (α), 5% marginal error (d), and 0.5 prevalence of good glycemic control among DKA patients.

n = Z2α2 p 1-pd2 n = (1.96)20.50.5(0.05)2 = 384.16

Since the total number of diabetic patients attending who developed DKA from August 2010 to May 2018(N)was less than 10,000 (682), the final corrected sample size was 246.

Corrected sample size = N*n N+n,(682*384)/(682+384) = 246,

But, due to easily accessibility of data we included all eligible subjects to attain the final sample size of 387 subjects.

2.4 Eligibility criteria

All DKA patients who were admitted to the inpatient ward of DGH and fulfilled the inclusion criteria August 2010 to May 31 2018 were included.

2.5 Study variables

PFs and level of glycemic control were our study variables. Independent variables include: age, gender, residence, type of DM, severity of DKA, admission blood glucose readings, blood pressure, respiratory rate, pulse rate, co morbidities, precipitating factors, frequency of serum glucose rebound, frequency of ketone rebound.

2.6 Data collection methods

Medical record of patients with DKA admitted to the hospital was traced from patient logbook and drawn from card room. Selection of medical records for sampling was based on the physician's confirmed diagnosis on patient logbooks. Participants included in the study were all diabetic patients with DKA admitted to DGH with age ≥15 years old whose medical records contained complete pertinent data. The data was collected by trained data collector using structured and pretested data extraction tool. Data was collected on patient demographics, presenting symptoms, precipitating causes of DKA, vital signs, biochemical profiles (admission blood glucose, admission urine ketone, urine glucose) at presentation to the inpatient department and time from presentation to resolution of urine ketones.

2.7 Data Analysis

All the statistical data was carried out using Statistical Package for Social Sciences (SPSS), version 22 (SPSS Inc., Cary, NC, USA). Descriptive statistics (mean, %, SD,) was calculated for categorical variables. Binary logistic regression was done to determine the factors that affect the level of glycemic control.

2.8 Ethics

The study was conducted after ethical clearance letter received from research and ethics review committee of school of pharmacy, University of Gondar College of medicine and health science, hospital clinical director and head of the medical ward of DGH. Data was collected anonymously.

2.9 Operational definitions

DKA is defined as admission blood glucose >250 mg/ dL and presence of ketonemia and/or ketoneuria (7).

Hyperglycemia is defined as random plasma glucose >200 mg/dL(18) and Hypoglycemia is defined as a blood glucose level ≤70 mg/dL(19).

Euglycemia is defined as serum glucose of between 100 and 200mg/dl once the patient is hospitalized with DKA (7, 20)

Clinical characteristics of DKA include a history of polyuria, polydipsia, weight loss, vomiting, dehydration, weakness, and mental status change.

Glycemic control: defined as poor and good glycemic control according to the incidence of rebound hyperglycemia or hypoglycemic state after admission of the patient due to DKA.

3. Results

3.1 Sociodemographic characteristics of DKA patients

Out of 387 patients, 305 (78.8%) and 82(21.2%) patients had type 1 DM and Type 2 DM, respectively. Among them, 244(63.0%) were females and 143(37.0%) were males. The female: male ratio was 1.7:1. The mean age of the patients was 33.30± 14.96 (range 15–64 years). More than half of the patients 264 (68.2%) were urban residents and the remaining 123(31.8%) were rural residents. Family history of diabetes was reported in only 50 (12.9%) of the patients.

The mean duration of DM was 26.21 (±39.62) months ranging from newly diagnosed ones to a maximum duration of 192 months. The mean frequency of DKA episodes was 1.5 times, maximum

frequency of DKA episodes was 8 times and the minimum was once (table 1).

Table 1: Sociodemographic characteristics of DKA patients admitted at DGH from August 2010 to May 31, 2018.

Characteristics	Frequency (%)
Age (mean ±SD)	33.29 (±14.96)
Sex	
Male	143(37.00)
Female	244(63.00)
Residence	
Urban	264(68.20)
Rural	123(31.80)
Family history	
Yes	50(12.90)
No	53(13.70)
Unknown	284(73.40)
Type of DM	
Newly diagnosed type 1 dm	146(37.70)
Newly diagnosed type 2 dm	21(5.40)
Known type 1 dm	159(41.10)
Known type 2 dm	61(15.80)
Duration of DM (mean±SD)	26.22(±39.67)
Mean frequency of DKA episode	1.50(±1.00)
1 time	272(70.30)
2 times	74(19.10)
3 times	20(5.20)
≥4 times	21(5.50)

3.2 Clinical characteristics of DKA patients

Polyuria and polydipsia (97.9%) were the most frequent clinical manifestations among patients with DKA followed by easy fatigability (82.9%) and abdominal pain (47.0%). The mean pulse rate, systolic blood pressure (SBP), diastolic blood pressure (DBP) , respiratory rate(RR) and body temperature at admission were 94.17(±14.54) ,104.30(±15.51), 67.84(±10.42), 24.85(±4.30) and 36.47(±0.94), respectively.

About 276 (71.3%) of patients had normal pulse rate and 108(27.9%) were tachycardic. About 227(58.7%), were normotensive and the remaining 73(18.9%) were stage 1 hypertension. Majority of the patients 224(57.88%) had (+3) ketoneuria and the remaining 163 (42.11%) had (≥+3) ketoneuria at the time of admission in the hospital. On the other hand, 161(41.60%) patients had urine glucose (+2) and 130(33.60%) patients were glucose +3 (Table 2).

Table 2: Admission clinical characteristics of DKA patients admitted at DGH from August 2010 to May 31, 2018.

Clinical characteristics	Frequency (%)
polyuria +polydipsia	379 (97.90)
Fatigability	321(82.90)
Abdominal pain	182(47)
Vomiting	70(18.10)
Others	36(9.3)
Pulse rate (means)	94.17(±14.54)
Normal	276(71.30%)
Tachycardia	108(27.90%)
Bradycardia	3(0.8%)
Temperature (^{0}C)	36.47(±0.94)(range 32.50-39.40)
Respiratory rate (mean± SD)	24.85(±4.300) (range 14-44)
Respiratory status	Frequency (%)
normal	261(67.40)
tachypnea	126(32.60)
SBP (mean± SD)	104.30(±15.510)(range 70-180)
DBP(mean± SD)	67.84(±10.422) (range 40-110)
BP status	
hypotension	46(11.9)
normal	227(58.7)
elevated	14(3.6)
stage 1	73(18.9)
stage 2	27(7.0)
Urine Ketone	
+3	224(57.88)
≥+3	163(42.11)
Urine glucose	
Urine glucose free	2(0.50)
+1	22(5.70)

+2	161(41.60)
+3	130(33.60)
+4	33(8.50)
Not measured	39(10.10)
Comorbidity	
No	355(91.70)
Yes	32(8.30)

3.3 Precipitating factors of DKA

About 258(66.67%) of DKA patients had known precipitating factor for DKA. The predominant precipitating factor of DKA was new onset type 1 DM 150(38.8%) followed by poor compliance to antidiabetic treatment (14.7%) and infections (13.2%). About 129 (33.33%) patients had no known precipitating factor (fig 1). Urinary tract infection was the most common infection 24 (47.05%) that precipitated DKA and respiratory tract infection 21(41.17%) was the second most infection that precipitate DKA.

3.4 Severity of DKA and Ketone bodies

About three-fourth (75.5%) of the patients was presented with mild DKA, approximately nineteen percent 74(19.1%) were presented with moderate DKA and the remaining 21 (5.4%) were severe DKA. Sixty-eight (17.6%) patients experienced rebound ketoneuria one times and six (1.6%) patients had rebound ketone two times in their hospital stay. The mean first ketone-free time was 9.23 (±10.954) hours and last ketone free time was 9.49(±11.05) hours (range 1-138) (Table 3).

Table 3: Severity of DKA and ketone bodies in DKA patients.

Severity of DKA and urine ketone bodies	Frequency (%)
Mild DKA	292(75.5%)
Moderate DKA	74(19.1%)
Severe DKA	21(5.4%)
Frequency of ketone rebound	
no rebound ketone	310(80.1%)
0ne times	68(17.6%)
two times	6(1.6%)
three times	1(0.3%)
four times	1(0.3%)
five times	1(0.3%)
Ketone free time (mean hours)	Frequency (%)
The first ketone free time after admission (mean hours)	9.23(±10.954)
The last ketone free time after admission (mean hours)	9.49(±11.051)

3.5 The level of glycemic control of DKA patients

The mean plasma glucose at admission and discharge was 443.63 (±103.33) and 172.94 (±80.60) mg/dl, respectively. The mean frequency of serum glycemic rebound was 6.78 (±4.43) times ranging from 0 to 32 times. The mean time at which first euglycemic state attended was 1.89(±1.36) (range 1-11) days and last euglycemic state attended was 4.37(±2.68) (range 1-11) days. Larger glucose rebound value (mean) was 263.86(±123.20) and smaller rebound value (mean) was 39.67 (±57.31). Nearly three-fourth (72.1%) of patients attended euglycemic state within fifth day. About 60% of the patients discharged with the serum glucose within the normal range and 127(32.8%) patients were discharged with serum glucose above the normal level (hyperglycemia). No hypoglycemic episode was observed during treatment in 317(81.90%) patients and one episode of hypoglycemia was observed in 47(12.1%) patients (Table 4).

Table 4: Plasma glucose at admission, discharge and hypoglycemic episode in DKA patients at DGH from June 1 to 30, 2018.

Glucose level at admission, during Hospital stay and discharge	Frequency (%)
Mean RBS at admission	443.63(±103.33)
Mean serum glucose at discharge	172.94(±80.60)
Mean number of times serum glycemic rebound	6.78(±4.43)
Mean day at which first euglycemic state attended(day)	1.89(±1.36)
Mean day at which last euglycemic state attended	4.37(±2.68)
Large glucose value after rebound (mean)	263.86(±123.20)
Smaller glucose level after rebound (mean)	39.67(±57.31)
Mean time for plasma glucose less than 250mg/dl	11.08(±15.121)
No of patients having plasma glucose 250 mg/dl within 6 hrs	186(48.06%)
No of patients having plasma glucose >250 mg/dl within 6 hrs	201(51.93%)
Glycemic level at discharge	
Hyperglycemia	127(32.80)
Euglycemic	239(61.80)
Hypoglycemia	21(5.40)
Episodes of hypoglycemia during treatment	
0	317(81.90)
1	47(12.10)
2	11(2.80)
3	10(2.60)
5	1(0.30)
8	1(0.30)

3.6 Determinants of glycemic control among DKA patients

Good glycemic control was observed in 239(61.76%) of patients. Different factors have been considered that affect the level of glycemic control. These factors include; age, gender, residence, type of DM, history of DM, duration of DM and systolic and diastolic blood pressure, severity of DKA, serum glucose level at discharge. On bivariate analysis, only two variables namely; the level of serum glucose at discharge and the duration of the disease were found to have significant association with glycemic control. A binary

logistic regression analysis revealed that only long-standing DM was found to be associated with good glycemic control among DKA patients. It was found that for every increase in the duration of the diseases by 1 month the likelihood of controlling hyperglycemia increases nearly 1.5 times AOR:1.497[1.203-1.814] (table 5).

Table 5: Factors associated with glycemic control among DM patients attending DGH,2018

Factors	Glycemic control		COR 95%CI	AOR95%CI
	Good 239(61.75)	Poor 148(38.25)		
Serum glucose at discharge (mg/dl)	130.95	240.74	0.954(0.949-0.970) *	0.974(0.969-1.041)
Duration of DM (months)	28.51	22.51	1.496[1.303-1.612]	1.497[1.203-1.814] *

AOR: adjusted odds ratio, COR: crude odds ratio, CI: confidence interval, * significant at 0.05 level

Kaplan Meir analysis indicated that the glycemic control decreases sooner among type 1 cases when patients are followed for a duration of hospital stay, [Log rank=3.15, p-value=0.03] (figure 2).

4. Discussion

Our study showed that the most common clinical presentation was polyuria and polydipsia in 97.9% of patients. This result was in line with the result of cross-sectional study done in Benghazi-Libya (13) (21). The same result was found in a research done in Nigeria (22).On the contrary abdominal pain appeared to be the most common presenting symptoms in a cross-sectional study conducted in Egypt (17) and vomiting was the major clinical presentation in a research done at Saudi Arabia (12). Nausea was the most common presentation in a study done in India (2015) (23)and Bangladesh (24). The frequent occurrence of the aforementioned symptoms in DKA patients could be due to the fact that the presence of insulin deficiency results in hyperglycemia which in turn causes an osmotic diuresis. Consequently, the diuresis results in polyuria and polydipsia(25).

The most common precipitating factors were new onset type 1 DM 150(38.8%) followed by poor compliance to antidiabetic treatment in 57(14.7%), and infections were seen in 51(13.2%) cases this is in line with research done in sub-Saharan Africa in which the main causes or precipitants of DKA were new onset diabetes, missed insulin doses and infections (26).On the other hand missed insulin dose was the most common PF in a cross-sectional study done in Zambia (27), cohort study done in Saudi Arabia (2015)(12), cross-sectional study Benghazi-Libya (2007)(13). other studies done in Nairobi(11), New Zealand (14), Brazil (15), and Israel reported the same finding(16).

Infection was also found to be the frequent reason for the incidence of DKA in different studies. For instance, a research done in Jimma (10), Egypt (17) India (2015) (23), India (2009)(28), Pakistan (29), South Africa (30)and Bangladesh (31) revealed that infection was the major precipitant of DKA. Our finding also showed that urinary tract infection 24(47.05%) was the most common infection that precipitated DKA and our result was supported with a research evidence obtained in Jimma (10), Zambia (27), India 2011 (8), India (2009)(28), Pakistan (29), Egypt (17). On the other hand respiratory tract infections was the predominant infection that precipitated DKA in a cross-sectional study done in Libya (2007) (13),and Kenya (11). As of the reason for the occurrence of frequent urinary tract infections, it can be explained that female patients took the large proportion of our sample population in whom urinary tract infection remain the most common infection(32). Overall, infectious diseases are more frequent and serious in patients with DM. Since the greater frequency of infections in diabetic patients is caused by the hyperglycemic environment that favors immune dysfunction and decrease in the antibacterial activity of urine (33).Residing in developing country where hygiene is a significant issue, attention should be sought on DM patients to keep their personal hygiene and to ultimately prevent infection.

The current study revealed that new onset type 1 DM was the major precipitating factor of DKA. this could be due to the fact that our sample population constituted large number of type 1 DM patients in which majority of them presented with first incidence of the disease with cardinal DKA symptoms due to absolute insulin deficiency unlike type 2 DM patients(34). Although our study showed that newly diagnosed DM was the major precipitating factor for DKA, both drug non adherence and infection contributed much. The reason for non-adherence may be due to scarcity of the antidiabetic medications or lack of awareness on how to use the drugs(35). Therefore, it should be highlighted that medications with the lowest possible price should be availed. Again, awareness should also be created on diabetic self-management and the importance of adherence in preventing the occurrence of diabetic complications.

This study further illustrated glycemic control of patients with DKA who were admitted to the inpatient ward of DGH. It was found that mean time at which plasma glucose lowers below 250mg/dl was nearly 11 hours. The reason for this long duration of time requirement for the attainment of euglycemic state was a frequent serum glucose rebound. In our study patients had a mean serum glucose rebound of around 7 times in which the patients' serum glucose increased by a maximum 263 mg/dl and a minimum of 40mg/dl from the baseline. Correcting this fluctuation of serum glucose takes time to obtain euglycemic state sooner because successful treatment of DKA requires a prompt correction of hyperglycemia (7, 36, 37) and the mainstay of treatment of hyperglycemia involves the administration of regular insulin via continuous intravenous infusion or by frequent subcutaneous or intramuscular injections. This ultimately helps to lower the blood glucose below 250 mg/dl within 6 hours of initiation of treatment (7, 38, 39). The current study was the first in its kind that assessed PFs and glycemic control of DKA patients admitted in DGH. In general, the present study provided an imperative finding regarding PFS and glycemic control among DKA patients. However, this study also had few limitations. Firstly, it was a retrospective review of records performed at one hospital that is difficult to generalize. The

retrospective nature of the study did not show causality between factors and the dependent variable. A prospective evaluation of DKA management and the PFs is required in the future perspective.

5. Conclusions

In this study, new onset type 1 DM was the major precipitating factor for DKA. Polyuria and polydipsia were the most common presenting clinical characteristic of DKA. Glycemic control among DKA patients was found to be unsatisfactory. Long standing DM was found to be associated with good glycemic control among DKA patients. Since, in our study most patients had poly symptoms at presentation, this could lead to dehydration and electrolyte imbalance. Therefore, strong measure should be devised in order to correct dehydration. Early detection of DKA should be sought while patients come up with poly symptoms as the symptoms are strongly related with the diagnosis of DKA. Inconsistent serum glucose level demonstrates the urgent administration of appropriate dose of regular insulin as soon as patients are diagnosed for DKA.

Abbreviations

DGH: Debre-tabor General Hospital

DKA: Diabetic Keto-Acidosis

DM: diabetes Mellitus

SD: Standard Deviation

SPSS: Statistical Manual for Social Sciences

USA: United States of America

Declarations

Ethical approval

This study was approved by University of Gondar, college of medicine and health sciences ethical approval committee with reference number 113/UoG/2018. Permission was obtained from Debre Tabor General Hospital. Informed written consent was received from participants.

Consent for publication

Not applicable

Availability of data

All data were included in the manuscript

Conflict of interest

The authors declared no conflict of interest

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Authors' contribution

Both authors contributed equally for the research

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Figures

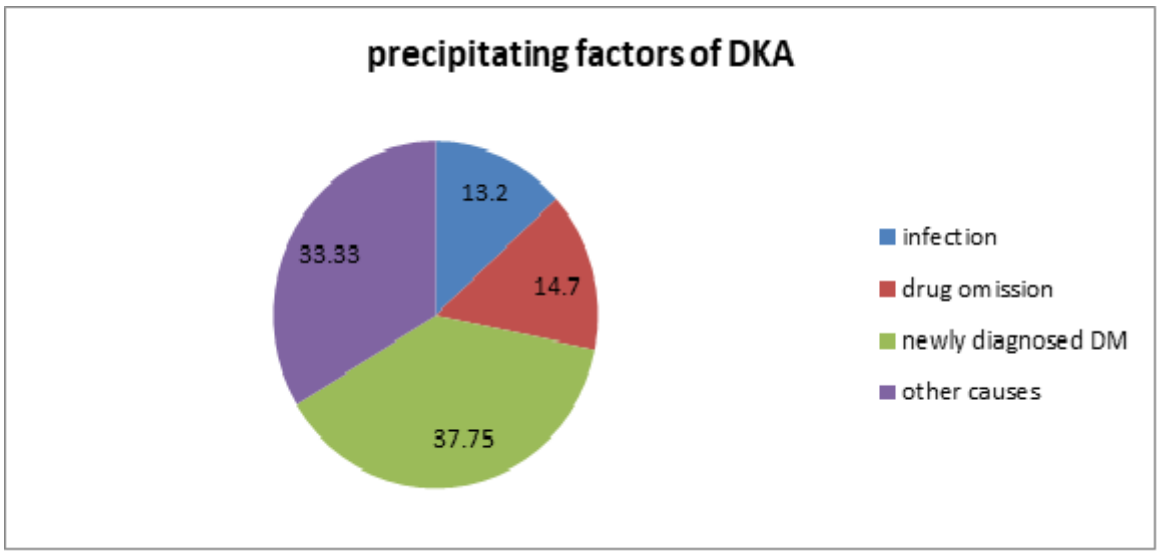

Figure 1

Precipitating factors for DKA among DM patients attending DGH, 2018.

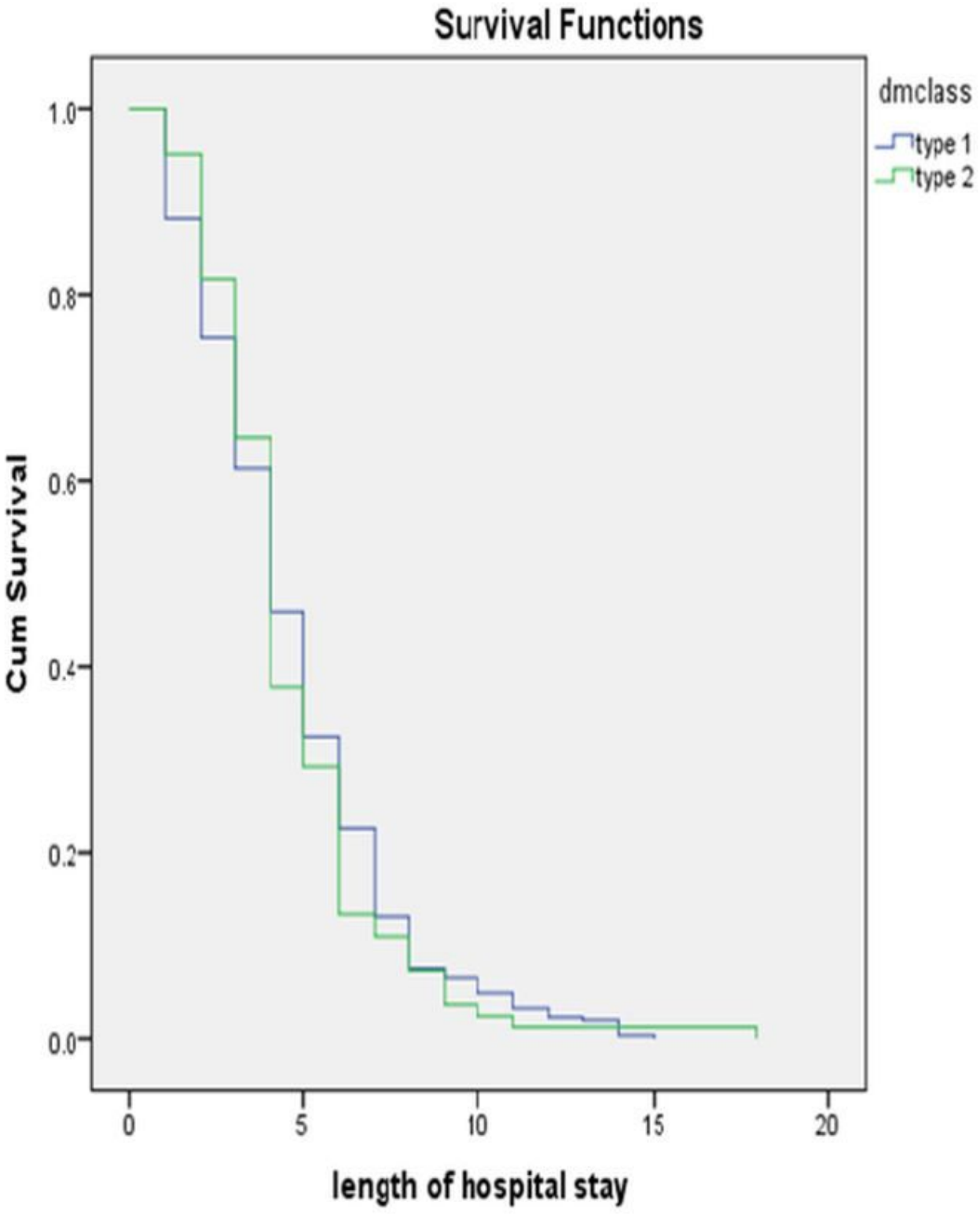

Figure 2

Precipitating factors for DKA among DM patients attending DGH, 2018.