ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF PUBLIC HEALTH
DEPARTMENT OF PREVENTIVE MEDICINE

MAGNITUDE AND ASSOCIATED RISK FACTORS OF DIABETIC KETOACIDOSIS IN NEWLYDIAGNOSED DIABETTIS MELITTUS CHILDREN IN ADDIS ABABA, ETHIOPIA

BY: HELEN ATKILT

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Magnitude and Associated Risk Factors of Diabetic Ketoacidosis in Newly Diagnosed Diabetes Mellitus Children in Addis Ababa, Ethiopia.

BY: Helen Atkilt

Advisors: Muluken Gizaw (MPH)
Dr. Ayele Belachew (MD, MPH)

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By: - Helen Atkilt (BSc.)

Approved by examining board

Dr Wakgari Deressa, PhD _____

Chairman, Department of Graduate committee

Advisors

Muluken Gizaw(MPH) _____

Dr. Ayele Belachew (MD, MPH) _____

Examiners

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2. _____

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Acronyms

AA----÷-----Addis Ababa

AAU-------÷Addis Ababa University

AARHB----÷Addis Ababa Regional Health Bureau

DM----÷----Diabetes Mellitus

DKA--------÷Diabetic Ketoacidosis

HHS--------÷Hyperosmolar Hyperglycemic State

FMoH ----÷Federal Ministry of Health

Abstract

Background: Diabetic Ketoacidosis (DKA) is one of the most serious acute complications of Diabetes Mellitus (DM) and the leading cause of morbidity and

mortality in children with type 1 diabetes. The mortality rate for DKA ranges from 2 to 5 % in developed countries and 6 to 24% in developing countries.

Objectives: To assess the magnitude and associated factors of DKA in newly diagnosed Diabetic Mellitus children in Addis Ababa.

Method: A facility based cross sectional study was conducted in selected hospitals in Addis Ababa. Data was double entered from the paper-based abstraction sheet into Epi info version 7 and exported to SPSS version 21 for analysis. A descriptive analysis was performed. Bivariate and multivariate logistic analysis was used to identify factors associated with the magnitude of newly diagnosed Diabetic Ketoacidosis. Categorical variables were compared if necessary using odds ratio with levels of significance set at 5%.

Result: The magnitude of DKA in newly diagnosed children found to be 35.8%. The significant predictors of DKA among newly diagnosed children were age of the child, parents' knowledge of the sign and symptoms of DKA 0.51(0.273, 0.95) sign and symptoms of DKA before the onset of DKA 0.348(0.206, 0.59) and infection prior to DKA onset 3.45(1.97, 6.04).

Conclusion: The overall magnitude of DKA in children with newly diagnosed type 1 diabetes in Addis Ababa is low. In particular, children between 9-12 years of age and children whose parents don't know the sign and symptoms of DKA have a high risk of DKA at primary diagnosis of DM. The Diabetic Association should give different workshop for health professional and work on awareness creation for the society using different communication media.

1. Introduction

1.1Background

Diabetic Ketoacidosis(DKA) is one of the most serious acute complications of Diabetes Mellitus (1). The international society for Pediatric and Adolescent Diabetes define DKA as a blood glucose level >11mmol/l(≈200 mg/dl),Venous PH <7.3 or bicarbonate < 15mmol/L, ketonemia and ketonuria (1).

Diabetic ketoacidosis (DKA) results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counter regulatory hormones: catecholamines, glucagon, cortisol and growth hormone (1-3). DKA is a medical emergency that requires treatment and monitoring for multiple metabolic abnormalities and vigilance for complications. DKA is the leading cause of death and permanent disability in children and adolescents with new onset diabetes (1-3).

Diabetic Ketoacidosis is manifested as dehydration, rapid, deep, sighing (Kussmaul respiration) nausea, vomiting, and abdominal pain mimicking an acute abdomen progressive obtundation and loss of consciousness, increased leukocyte count with left shift, non-specific elevation of serum amylase, fever only when infection is present(1).

The younger the child, the more difficult it is to obtain the classical history of polyuria, polydepsia, and weight loss. Infants and toddlers in DKA may be misdiagnosed as having pneumonia, reactive airways disease (asthma), or bronchiolitis and therefore treated with glucocorticoids and/or sympathomimetic agents that only compound and exacerbate the metabolic derangements. Because the diagnosis of diabetes is not suspected as it evolves, the duration of symptoms may be longer, leading to more severe dehydration and acidosis and ultimately to obtundation and coma(1-3).

Every year worldwide, approximately 79,100 children under 15 years of age develop type 1 diabetes. Up to 80% of these young people already have DKA when they are diagnosed with diabetes. There is a wide geographic variation in the frequency of DKA at onset of diabetes. Frequency of DKA in newly diagnosed DM children ranges from 15-70% in Europe and North America (2-4).

DKA is the leading cause of morbidity and mortality in children with type 1 diabetes (3). The mortality rate for DKA ranges from 2 to 5 % in developed countries and 6 to 24% in developing countries (4). The mortality rate of DKA in developing countries is

higher due to the higher rates of infection, protein energy malnutrition, less developed medical services and delay in health seeking behavior (5, 6).

DKA remains a major source of mortality and morbidity due primarily to the development of cerebral edema, which is the gravest complication of DKA (4). Despite advances in many areas of the management of DKA, the mortality from Cerebral edema has remained constant for decades. This rare disorder, complicating about 1% of cases of DKA in children, is lethal in 20% to 50% of victims (4-6).

Other serious complications of DKA may include renal failure, which although extremely rare, may necessitate dialysis. Incidences of increased thromboembolic events are known to occur in children with DKA following dehydration, central venous catheter placement in ICU or idiopathic elevation of von Wille-brand factor. Although rare in children compared with adults, acute pancreatitis may present in children with severe DKA and unresolving abdominal pain despite treatment (7).

DKA at onset of diabetes is more common in under five children and in children whose families don't have access to medical care due to social and/or economical reasons. Geographical factors like climate may influence the number of people affected with DKA. Countries nearer the equator have high prevalence of DKA due to hot climates which lead to more rapid dehydration and onset of hyperglycemia particularly in young children (8).

Among the developed countries the frequency of DKA is lower in countries where the background incidence of type 1 DM is higher (8). Having first degree relatives with diabetes is associated with an up to six fold lower risk of DKA at diagnosis (1). In places like ours, where medical services are less developed, the risk of dying from DKA is greater and children may die before they receive treatment.The true incidence of DKA in Sub Saharan Africa is unknown but unlike the western country DKA is uniquely frequent among type 2 diabettes (9). Some observational studies in Africa suggested high prevalence of DKA at diagnosis, which is 80% to 88% (10).

1.2 Statement of the problem

For large areas of the World, particularly in Africa and South East Asia, there are few data or none at all, on the frequency of DKA in children. The magnitude of DKA in children in Africa from few pocket studies is much higher than the developing countries. In Ethiopia like other African countries the magnitude and risk factors of DKA in newly diagnosed DM children is not well studied. Without the knowledge of the magnitude and associated risk factors of DKA in children the preventable associated risk factors will not be handled and this leads to increase magnitude of DKA in children.

1.3 Significance of the study

The proposed study on magnitude and associated risk factors on newly diagnosed DM children is important to contribute to the effort toward reducing morbidity and mortality related to DKA. These findings will also help for policy makers for planning since there is paucity of published data on magnitude and risk factors of DKA in newly diagnosed DM children in Ethiopia. Understanding factors associated with DKA has the potential of improving our knowledge of the disease, enhancing the development of patient, professional and population based interventions to reduce the proportion of children whose first presentation is DKA. This study will also give clue for further prospective studies.

2. Literature review

2.1 Magnitude of DKA

DKA (diabetic ketoacidosis) is one of most severe acute complications of DM. Diabetic ketoacidosis (DKA) has been recognized as the main complication and potentially fatal emergency in children and adolescents with type 1 diabetes mellitus (T1DM) (11). In younger children less than four years who do not have first degree relatives with DM and who are from low socioeconomic family, DKA occur at onset of DM (3).

Diabetic ketoacidosis (DKA) results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counter regulatory hormones: catecholamines, glucagon, cortisol and growth hormone (1, 5). The combination of low serum insulin and high counter regulatory hormone concentrations results in an accelerated catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis), impaired peripheral glucose utilization resulting in hyperglycemia and hyperosmolality, and increased lipolysis and ketogenesis, causing ketonemia and metabolic acidosis(1-4).

The Current criteria for diagnosis of DKA published by the International Society for Paediatric and Adolescent Diabetes is blood glucose >11mmol/L,venous pH<7.3or bicarbonate<15mmol/L, and ketonaemia and ketonuria(1) but there are different cut off point for diagnosis from study to study(1,5).

Many children in sub-Saharan Africa are diagnosed with diabetes only when they present with DKA which quite often is misdiagnosed. In many sub-Saharan African countries, diabetic patients just die because healthcare facilities are overstretched by even more urgent healthcare needs, HIV/AIDS, malaria and other tropical diseases. (9-11)There are no proper registries or data-bases for diabetic patients attending outpatient clinics. Poor healthcare infrastructures and lack of medical care facilities in hospitals and clinics have led to erratic insulin supply, poor storage and shortage of syringes and blood glucose monitoring facilities. Poorly trained health professionals and lack of proper public health education have led to diminished public awareness, jointly contributing to a high incidence of undiagnosed DKA in sub-Saharan Africa. Patient nutritional status affects the DKA complications rate, and because child malnutrition is a common phenomenon in sub-Saharan Africa. Infections are the second most common cause of death in diabetic patients after DKA in sub-Saharan Africa unlike in the developed world where cardiovascular and renal complications are the major cause of

death. Diabetic patients with DKA therefore are at even greater risk of death secondary to infections (9, 11).

Recent epidemiological studies indicate that the incidence of type 1 diabetes is increasing worldwide, with the greatest increase in children aged 5 years old. Perhaps most alarming is that the diagnosis of type 1 diabetes in children aged 5 years is frequently associated with concurrent diabetic ketoacidosis (DKA) (8).There is a significant variation in the frequency of DKA between (and in some cases within) different countries around the world (2).

A systematic review done from 65 studies and 5 different continent in age group between 0-20 years stated the highest frequency of DKA being in UAE(80%), Romania(67%), Taiwan(65%) and Saudi Arabia(59%) and the lowest frequency were seen in Sweden(14%), Canada(18.6%), Finland(22%) and Hungary(23%) (8).Another population based study conducted in under 15 children in Austria for around 20 years (1989-2009) reported that the frequency of DKA to be 37.2%. The same study DKA was defined as, mild DKA PH<7.3 and/or >7.1 and severe DKA as PH<7.1 or clinical sign of severe acidosis such as hyperventilation or unconsciousness (12).

A hospital based cross sectional study in under 19 years of age in Iran, (1995-2005), showed that the frequency of DKA to be 24%.This study considered DKA as blood glucose level >250mg/dl, arterial PH<7.3, blood bicarbonate <15mmol/L and ketonuria greater than 2+ in dipstick urine test with recent positive symptoms of polyuria, polydepsia, nocturia and weight loss (13).

A follow up study from 1982 to 2001 in Finland revealed that the frequency of DKA in newly diagnosed DM children less than 15 years to be 18.1% PH<7.3 and 22.4% bicarbonate <15mmol/L and children with severe DKA were 3.2% (PH<7.1) (14).

A cohort study done in Italy in <17 years old children revealed that the frequency of DKA at new onset of diabetes to be 34.7% (PH<7.3) and 7.2% at PH<7.1 (which is the severe DKA) (15). A cross sectional study conducted in America to assess the trends of DKA at different time found the frequency of DKA to be 30.2% in 2002-2003, 29.1% in 2004-2005 and 31.5% in 2008-2010(16).

A retrospective study conducted in Benin teaching Hospital by Alphonsus N Onyiruka and Emeka Lfebi from 1996 to 2011 in children and adolescent reported the frequency of DKA to be 77.1%.Of whom 40.5% were males and 50.9% were females. The mean age at presentation was 12.7± 2.6 years. In the same study 52.3% of the families of the patients were from middle social class, 69.4% had symptoms for 2.3 weeks before presentation. In the same study DKA was diagnosed as hyperglycemia blood glucose level >11mmol/L, acidosis (serum bicarbonate <15mmol/L) and ketonuria > +1) (9).

A retrospective study conducted at Tikur Anbesa specialized referral Hospital from September 1997 to September 2007, the frequency of DKA in children less than 12 years of age, was found to be 80%. The mean age at presentation was 6 years and the lowest age was nine and half months. The study defined DKA as patient presenting with vomiting, dehydration, kussmaul breathing, lethargy or coma and biochemically random blood sugar (RBS) > 250 mg/dl, glucosuria and ketonuria (3).

2.2 Associated risk factors for DKA

A systematic review on 40 studies in 31 countries on the associated factors of DKA on newly diagnosed children found out different risk factors. In this systematic review the effect of age was reported in 32 studies. These studies showed that children<2 years old had three times the risk of presenting in diabetic ketoacidosis compared to children aged ≥ 2 years significantly. Twenty one studies reported the effect of sex on the frequency of diabetic ketoacidosis, of which only one study showed the significant effect of sex on DKA. In this systematic review the effect of family history on DKA was reported by six studies. Although having a first degree relative with type1 diabetes decreased the frequency of diabetic ketoacidosis in three studies it did not predict a diagnosis of new onset diabetes before (17).

The others associated risk factors reported by this systematic review were parental consanguinity, parental education, family structure, ethnicity, health insurance status, residence, family income, parental employment, delayed diagnosis(>24hours), diagnostic error, number of medical consultation before diagnosis, preceding illness/febrile illness(17).

The systematic review done in 65 countries revealed that latitude and background incidence of type 1 DM was significantly associated with frequency of DKA. The frequency of DKA decreases with the higher background incidence of DM. There were no significant associations with study size, period of study design or method of case identification (8).

In a study conducted in Austria girls were significantly at higher risk of developing DKA than boys and the frequency of DKA found to be negatively associated with age at onset of DKA and in children less than 2 years of age the frequency was 60%.In the same population based survey from 3331 children under 15 years one female patient with age of 14.3 years died due to cerebral edema (12) and another cross sectional study in Iran girls were presented more frequently (60%) with DKA than did boys but the difference was not statistically significant (p=0.58).No death were recorded among the study populations(13).

A study in Finland stated as there is no significant difference between boys and girls in developing DKA. Under five children tended to develop DKA than older children but it is not statistically significant. When we see the frequency of DKA in under four years of age in this study it is significantly higher than older children and the frequency of severe DKA is significantly higher in under two children. The frequency of DKA is higher in under five children (23.7%), followed by age group between 10-14 (23.1%) and DKA is least observed among children between 5-9.99(11.3%) years of age (p=0.001) (14).

The frequency of DKA was significantly higher in under 2 children than the other group in a study done in Italy. Of whom 9.4% of the patients had first degree relatives with diabetes. DKA occur in less frequency in children who have first degree relatives with type 1 than children who do not have first degree relatives with type 1 diabetes. First degree relatives and age at onset of DKA found to have a significant association with DKA (15).

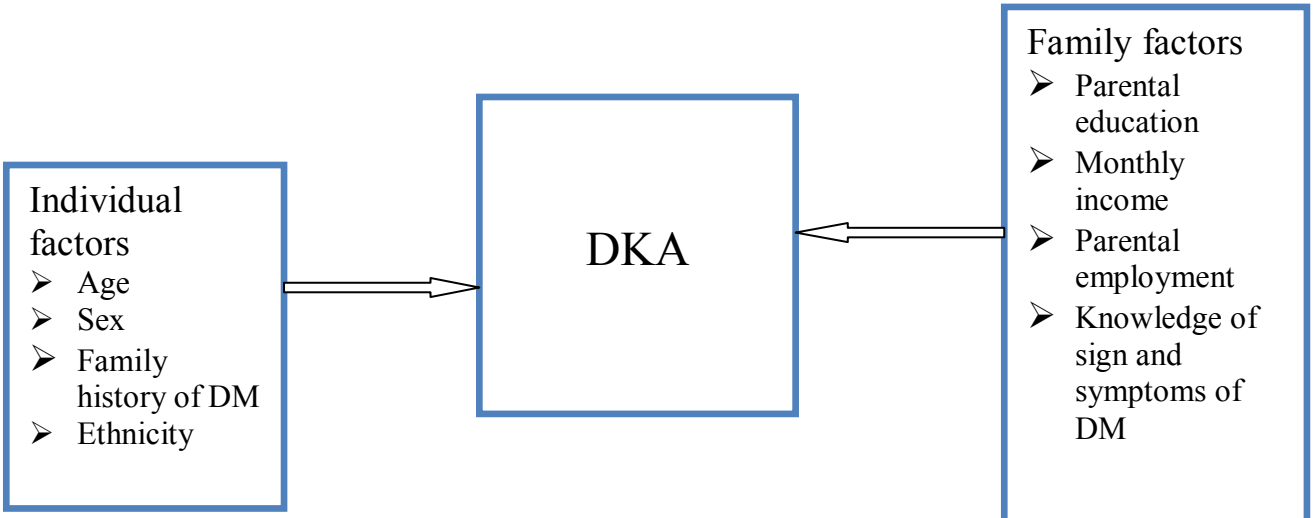
In a study in America the overall frequency was higher in the 0 to 4 years of age group (39%) and lowest in 15 to 19 year age group (23%). The same study household income showed a significant association with DKA, the odds of children with low household

income had a higher risk of developing DKA than children with high hose hold income. Gender and parental education did not show significant association in developing DKA (16).

A study in Bennin indicated as socioeconomic status and first degree relatives with DM got a significant relation on developing DKA (10).

In a study conducted at Tikur Anbesa one fourth of the cases had family history of DM, 81.2% were from Addis Ababa and nearby town. Significant number of children (53.5%) had families who joined secondary and higher education. In this study average monthly income and level of education did not show significant association with DKA. In 44.6% of patients the precipitating factor for DKA was infection. Over all the study revealed around 7 deaths with 6% case fatality rate. Of these deaths one of the patients died because of cerebral edema (3).

CONCEPTUAL FRAME WORK



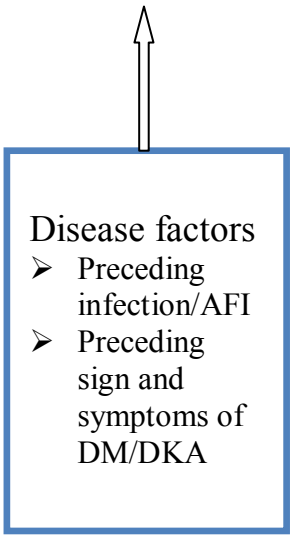


Figure 1 Conceptual frame work

The above conceptual frame work was adopted from different literatures. In the above conceptual frame work there are factors that are not included in this study like diagnostic error, delayed diagnosis because it is difficult to measure those factors in our situation. Health insurance is not included in this study because it was not applicable in our country. Other than the above factors individual factors, disease factors and family factors were included in this research.

3. Objectives

3.1 General Objective

✓ To assess the magnitude and risk factors of DKA in newly diagnosed DM children between January 2009 and December 2014.

3.2 Specific Objectives

- ✓ To assess the magnitude of DKA in newly diagnosed DM children
- ✓ To determine the associated risk factors for DKA in newly diagnosed DM children

4. METHODS

4.1Study Area

This study was conducted in Addis Ababa from January 1 to March 30 2015.Addis Ababa is the capital and largest city of Ethiopia. Based on the 2007 Census conducted by the Central Statistical Agency of Ethiopia (CSA), Addis Ababa has a total population

of 2,739,551, of whom 1,305,387 are men and 1,434,164 women; all of the population is urban inhabitants (18)

According to Addis Ababa Regional Health Bureau (AARHB) 2006 report, under its administration there are six hospitals, one Public health laboratory and two health science colleges. There are also 52 hospitals in the metropolis, of which 6 are owned by AARHB, 5 by federal government, 3 by NGO's, 3 by Defense force and police and 35 by the private owners. There are 80 health centers owned by the city administration, and 3 by NGO's. There are also more than 760 private clinics at different levels. (19)

4.2 Study design

An institution based cross sectional study was conducted using routine hospital data and interview.

4.3 Population

4.3.1 Source population

All less than 12 years of age children with DM who were admitted in pediatric ward to one of the selected hospitals between January 2009 and December 2014.

4.3.2 Study Subjects

All Children less than 12 years with DKA who were admitted to the wards of the pediatric ward in the selected hospitals between January 2009 and December 2014.

Exclusion criteria

- ✓ All Children less than 12 years with DKA who were admitted to the wards of the pediatric in the selected hospitals between January 2009 and December 2014 who referred from health facilities outside Addis Ababa were excluded.

4.3.3 Sample size determination

Sample size was calculated using epi info 7 stat calc using single population proportion with the assumption; for the first specific objective

- 95% confidence interval
- 4% margin of error(d)
- 80% expected prevalence (study from black lion)
- 10% non response rate

$$n = \frac{(z1-\alpha/2)^2 \times p\,(1-p)}{}$$

d^2

By considering all this, the total sample size was 421

4.3.4 Sampling procedures

The sample hospitals for this research were all governmental hospitals which have pediatric department in Addis Ababa. We chose governmental hospitals because governmental hospitals have high pediatric patient flow, most people in Addis Ababa use governmental hospitals and governmental hospitals are cooperative in supporting research programs than nongovernmental hospitals. Governmental hospitals that have pediatric department and have pediatric patient flow, Tikur Anbesa, Zewditu Memorial and Yekatit 12 hospital were included in the study (fig 2). The clinical records of all children less than 12 years who were admitted in the pediatric wards by developing DKA were reviewed and children who were referred from health facilities outside Addis Ababa were excluded. The number of children who developed DKA in Black lion, Yekatit and Zewditu hospitals from Jan 2009 to Dec 2014 were 300,210 and 205 respectively and sample size was distributed proportionally to each hospitals. Data was collected using systematic random sampling with k value of 2. K value was calculated by dividing the number of DKA patient in each hospital divided by the number of sample size which allocated to each hospital. The first chart was selected randomly.

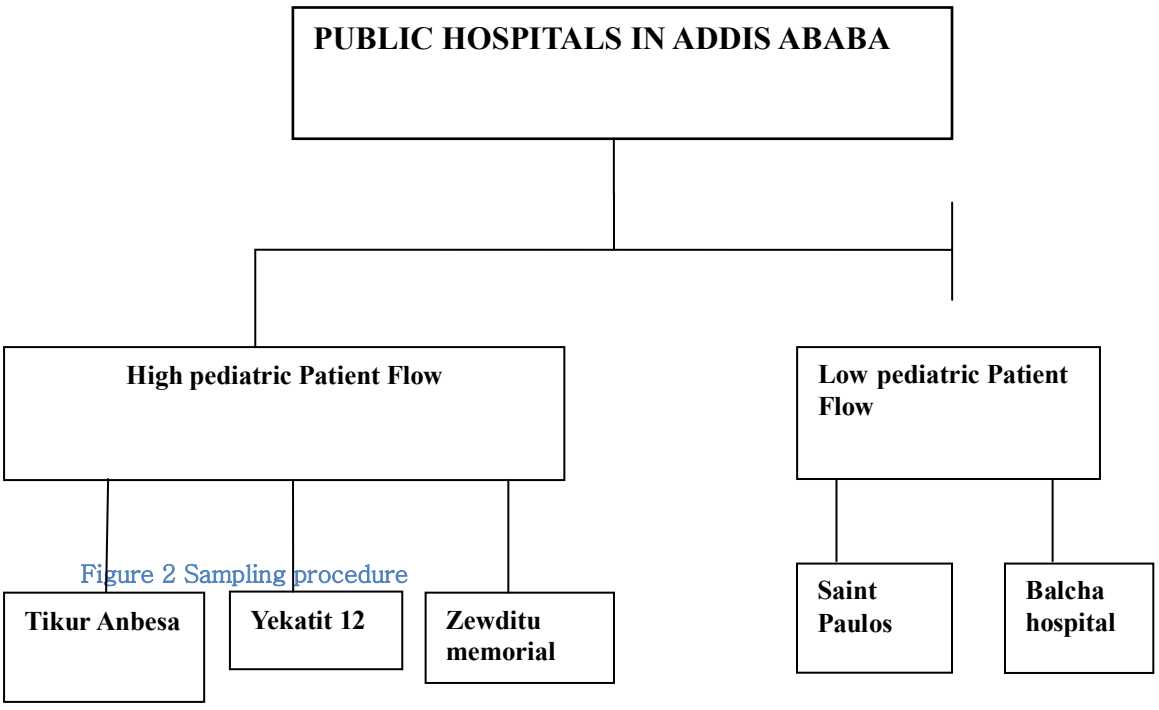


Figure 2 Sampling procedure

4.4 Data collection procedures

A checklist that measures the socio-demographic characteristics, clinical information of DKA was used to collect the data. Data abstraction sheet/guiding questionnaire has been prepared due to inaccessibility of guiding questionnaire in this research topic. The guiding questionnaire was filled by trained data collectors .Data which are not included in the patient card were asked to the parents/guardians when they come with the child in the sample hospital for follow up. DM patients have follow up in different hospitals and they go to the hospitals every 1-3 months.

Data was collected by 8 health professionals who were trained for one day about data collection procedure and the purpose of the research. Training was given by the principal investigator. Data quality was assessed every day after data collection, if there is incomplete information in the chart the data collectors were go to the next interval till the sample size reaches and misfield check list was filled.

4.5 Data Analysis procedures

Data was entered to Epi info version7 statistical software and exported to SPSS (statistical package for the social sciences) version 21. The data was looked for outliers and checked accordingly. Outliers were corrected by transforming in to categorical variable. Continuous variables like age, monthly income was recoded in to their respective category. Descriptive analysis was performed using frequency distribution, mean, median, tables and graphs.

Bivarite analysis was carried out using crude odds ratio to assess the relationship between dependent and independent variables. The significance of the relationship between dependent and independent variables was checked using p value and $p< 0.05$ was determined as a significance relationship. Moreover, multivariate analysis was used to identify the associated risk factors by controlling possible confounding factors using logistic regression. All variables whether they are significant in the bivariate analysis or not were included in the multivariate analysis and variables were entered hierarchically to fit the logistic regression model.

4.6 Study Variable

Dependent variable

- Diabetic ketoacidosis in newly diagnosed children

Independent Variables

- Age
- Sex
- Family income
- First degree relatives with DM
- Preceding infection/AFI
- Preceding sign and symptoms of DKA/DM
- Parental employment
- Parental educational status
- Knowledge of sign and symptoms of DM

4.7Operational Definition

- **Diabetic Ketoacidosis in newly diagnosed children:-** children between 0-12 years who have blood glucose level ≥ 250mg/dl, Ketonuria and ketonemia and diagnosed being Diabetes Mellitus patient for the first time.
- **Age:-** the child's age at the time of diagnosis.
- **First degree relatives with DM:-** child's mother, father or sibling with DM.
- **Preceding infection:-** any infection 1-2weeks before the onset of DKA.
- **Preceding sign and symptoms of DM/DKA:-** a child who had polyuria, polydepsia and weight loss 1-2week prior to DKA.
- **Knowledge of the sign and symptoms of DM/DKA**:-parents who know the three poly symptoms (polyuria, polydepsia and polyphagia) and weight loss were considered knwowledgable.

4.8 Ethical consideration

The proposal was submitted to the Review and Ethics Committee (REC) of the School of Public Health, College of Health Sciences of Addis Ababa University for approval.

Following the approval by REC, an official letter of co-operation was written to the concerned bodies by the School of Public Health AAU. As the study was conducted through review of medical records and interview, the study participant informed about the purpose of the study and the importance of their participation in the study. And also they informed as they could not participate; stop at any time in between data collection or jump (decline) to answer some of the questions if they feel uncomfortable without losing the benefit that would got in the institution. Their participation was purely on voluntary. The recorded data wasn't not be accessed by a third person and were kept confidentially.

4.9Dissemination of results

Result will be submitted to Addis Ababa University School of Public Health. Result shall be disseminated for stakeholders specially Addis Ababa Health Bureau and shall be presented to different workshops

5. RESULT

Socio demographic characteristics

A total of 421 charts from under 12 year children who diagnosed to have DKA between January 2009 and December 2014 were revised. Of 421 charts, we found 395 under 12 children who came for refill (follow up) and answer the socioeconomic and clinical risk factors that are not included in the chart, making the response rate of 93.8%. Among a total of 395 patients with DKA who were hospitalized during the 5-year period under review, 142(35.8%), 95% CI (31.6, 40.8) were newly diagnosed. Of 142 newly diagnosed DM children at the primary diagnosis of DKA, 65(45.77%) were females and 77(54.22%) were males giving a male to female ratio of 1:1.2. The mean age at presentation in relation to gender was for boys7.4 ± 3.74 years and for girls 6.66 ± 3.85 years. When both sexes were combined, the mean age at presentation was 7.08±3.8 years. Of 395 children the marital status of the mother/father/guardian who the child live 330(83.1%) were married, 14(3.5%) were single, 36(9.1%) were single and the rest were divorced. The age category below was taken from different literatures.

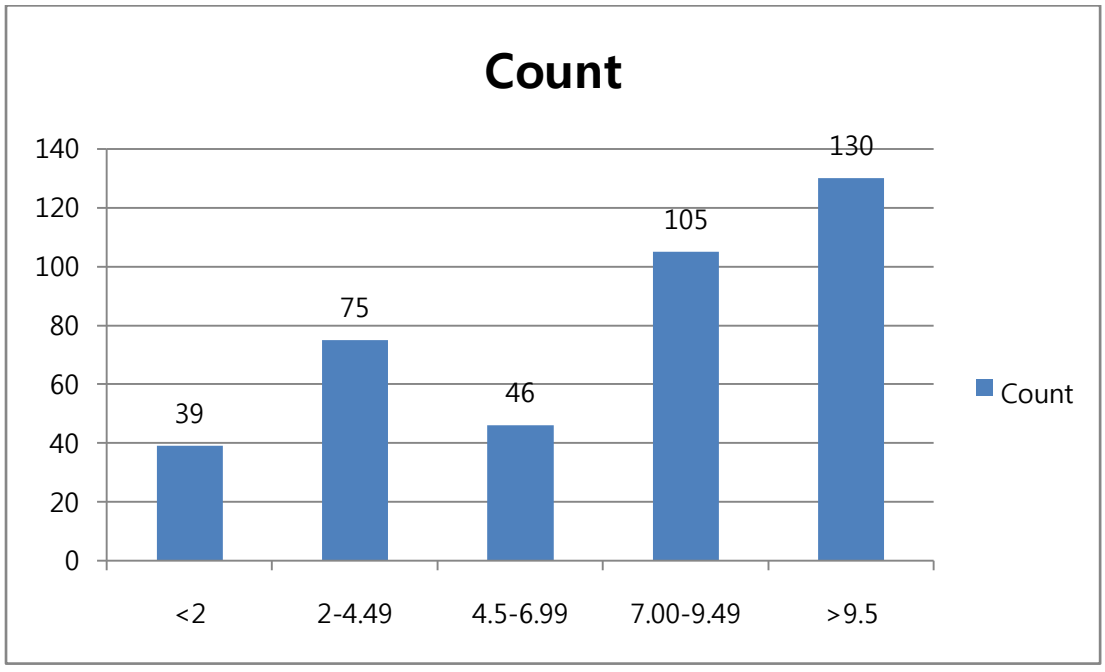


Figure 3 age category of children under 12 years of age who developed DKA from Jan 2009–Dec 2014 in three different hospitals in Addis Ababa, Ethiopia.

Among 395 children who developed DKA, the mean and standard deviation of family income was 2569±1216 with median income of 2500. Of 395 under 12 children 182(45.8%) was

orthodox Christian, 113 (2.5%) Muslims and 60(15.1%) were protestants. When we see the educational levels of the mother of the child 100(25.2%) were above grade 12, 93(23.4%) were 9-12 grade and 8.8% of the mothers do not read and write at all. Of 395 children father 114(28.2%) were civil servant, 111(27.5%) daily laborer and 98 (24.3 %) were merchant. When we see the occupation of the children mother 28(6.9%) were unemployed, 92(22.8%) civil servant and 58(14.4%) were merchant.

Table 1 socio demographic characteristics of children under 12 who developed DKA from January 2009 to December 2014 G.C in 3 different hospitals Addis Ababa, Ethiopia.

Variables		Frequency N=395	Percent
Sex	Male	221	55.7
	Female	174	43.8
Religion	Orthodox	182	45.8
	Islam	113	28.5
	Protestant	60	15.1
	Catholic	20	5.0
	Others	20	5.0
Ethnicity	Amhara	125	31.5
	Tigre	62	15.6
	Oromo	126	31.7
	Gurage	50	12.6
	Others	32	8.1
Mother education	Unable to read & write	35	8.8
	Read and Write	74	18.6
	Grade 1-8	93	23.4
	Grade 9-12	93	23.4
	Above 12	100	25.2
Marital status	Single	14	3.5
	Married	330	83.1
	Separated	36	9.1
	Widowed	15	3.8

Mother occupation	**Unemployed**	**28**	**6.9**
	Civil servant	**92**	**22.8**
	Student	**11**	**2.7**
	House wife	**137**	**33.9**
	Daily labor	**57**	**14.1**
	Merchant	**58**	**14.4**
	Others	**12**	**3**
Father occupation	**Civil servant**	**114**	**28.2**
	Daily labor	**111**	**27.5**
	Merchants	**98**	**24.3**
	Others	**43**	**10.6**
Family income	**<=1000 birr**	**163**	**40.3**
	10001-2200	**118**	**29.2**
	2201-3400	**80**	**19.8**
	3401-3600	**21**	**5.2**
	>3600	**20**	**5.0**

Clinical characteristics

Among the 395 under 12 children who developed DKA from January 2009 to December 2014, 253(63.7%) were known DM children with DKA and the rest 142(35.8%) were found to have DKA and type 1 DM at the same time (they are newly diagnosed). From these children 131(33.0%) of them have first degree relatives with DM and 66.5% of the children do not have first degree relatives with DM. Forty two eight percent of the parents of the children knows about the sign and symptoms of DM/DKA. Of 395 children who developed DKA 80(19.8%) present with abdominal pain, 129 (31.9%) vomiting and 66(16.3%) of children present with dry mouth which is the sign of dehydration. (Table 2)

Table 2, Clinical characteristics of under 12 children who developed DKA from January 2009 and December 2014 in three different hospitals in Addis Ababa, Ethiopia.

Variable		Frequency N=395	Percent
Child first degree relatives with DM	**Yes**	**131**	**33.5**
	No	**264**	**66.5**
Parent's knowledge about the sign and symptoms of DM/DKA	**Yes**	**170**	**42.8**
	No	**225**	**56.7**
Sign and symptoms of DKA before the onset of DKA	**Yes**	**253**	**63.7**
	No	**142**	**35.8**

Which sign and symptoms of DKA	**Polyuria**	**12**	**3.0**
	Polydepsia	**38**	**9.6**
	Weight loss	**36**	**9.1**
	Polyuria & Polydepsia	**117**	**29.5**
	Polyuria & Weight loss	**38**	**9.6**
	Polydepsia & weight loss	**12**	**3.0**
Infection before the onset of DKA	**Yes**	**108**	**27.2**
	No	**287**	**72.3**

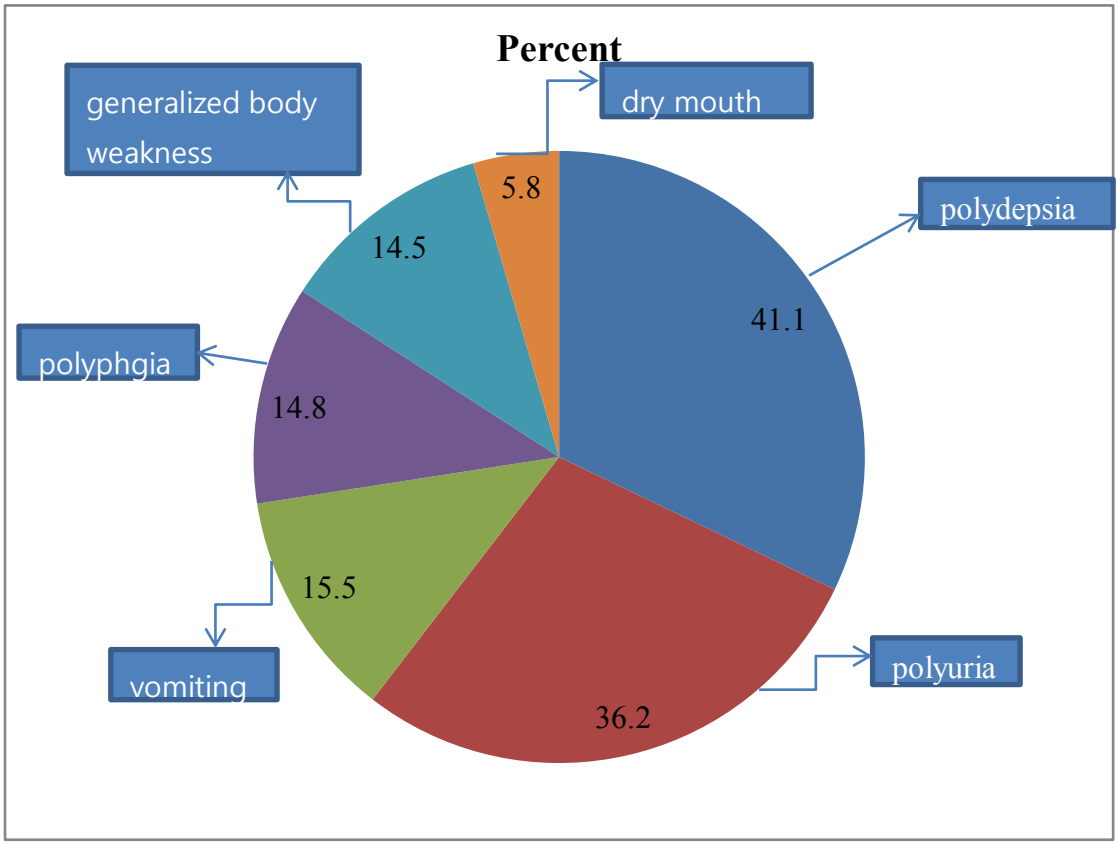


Figure 4 Parents knowledge about the sign and symptoms of DM/DKA in 3 hospitals Addis Ababa, Ethiopia.

Out of 395 children, 108(27.2%) children had infection prior to infection. Of these 108 children who had sign and symptoms of infection, 8.2% of children had dysuria, fever 7.7% and 1.4% of children had skin lesion prior to DKA.) Insulin discontinuation was the cause of DKA in 34.8% of children who are known type DM patients.

In this study the frequently reported presenting symptoms of DKA were vomiting (31.9%) abdominal pain (19.8%) dry mucous membrane (16.3%) and polydepsia (11.9%).

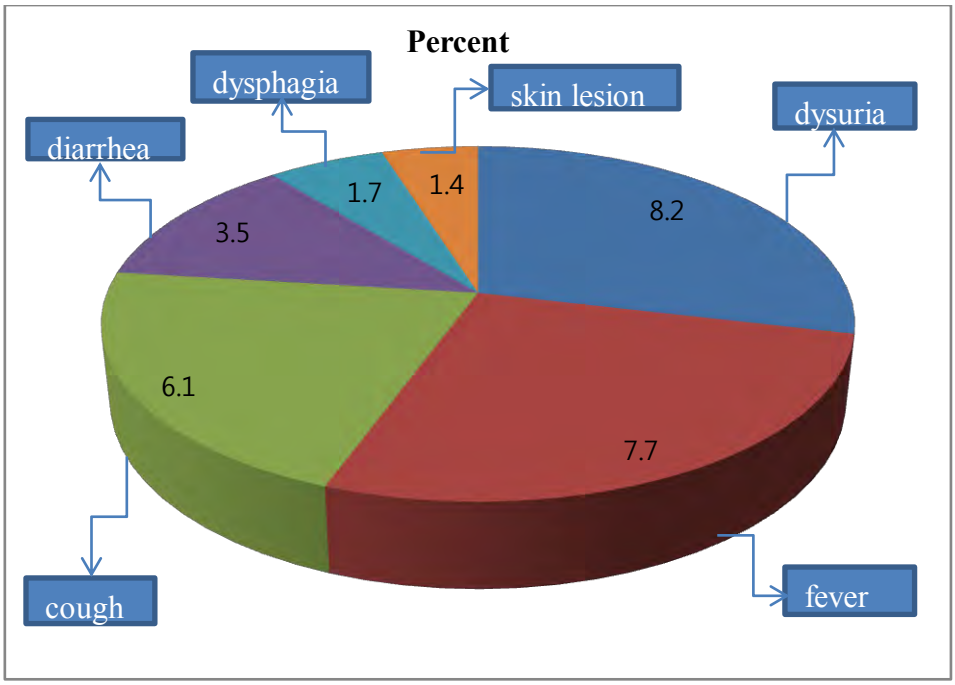


Figure 5 sign and symptoms of infection in children under 12 years of age who develop DKA at primary onset of DM in 3 hospitals Addis Ababa, Ethiopia.

Bivariate Analysis

Bivariate analysis for categorical variables was done using odds ratio to see the strength and direction of association between DKA and the associated risk factors. In this analysis age of the child, family history DM, preceding sign and symptoms DKA/DM, knowledge of sign and symptoms of DM/DKA and preceding infection found to have significant association with DKA at primary diagnosis of DM.

Although males presented more frequently (55.7%) with DKA than did females (40%), the difference was not significant (p=0.61). In this bivariate analysis the role of religion in developing DKA was not significant.

Though the frequency of Orthodox Christian and Islam religion were the highest, the difference in developing DKA was not significant.

In this study Oromo and Amhara were the frequently presented ethnicity but they do not have significant association with developing DKA than the other ethnicity. Children who have mothers above grade 12 are four times more likely to develop DKA at primary diagnosis of DM than mothers who are unable to read and write.

The odds of a child who is from married parents, developing DKA at primary diagnosis of DM is 2% less than from a child who is from single parents but it was not significant.
Children who are from household with > 3600 income are 15% more likely to develop DKA at primary diagnosis of DM than children whose household income is ≤ 1000 but not significant.

Children who have first degree relatives with DM have 37% less likely to develop DKA at primary diagnosis of DM than children who do not have first degree relatives with DM significantly.

Children who have parents who know the sign and symptoms of DM have 51% less likely to develop DKA at primary diagnosis of DM than children who their parents do not know the sign and symptoms of DM, OR 0.49 (0.32,0.76).

Though the type of sign and symptoms of DM/DKA which the child has prior to DKA dignossis have no significant association with developing DKA at the primary diagnosis of DM, children who have the sign and symptoms of DKA/DM 1-2 weeks prior to developing DKA are 41% more likely develop DKA than children who do not have sign and symptoms of DM/DKA.

Children who have the sign and symptoms of infection 1-2 weeks before developing DKA are 2 times more develop DKA than children who do not have the sign and symptoms of infection OR 2.14(1.36, 3.37).

Multivariate analysis

In multivariate analysis the independent variables that were not significant in the bivariate analysis like sex, marital status, family income etc. were not significant in the multivariate analysis too.

In Multivariate analysis, after controlling the effect of sex, marital status, family income, mother education, family history of DM, knowledge of the sign and symptoms of DM, preceding sign and symptoms of DKA/DM and preceding sign and symptoms of infection age found to the significant factors for developing DKA at the primary onset of DM. Age group between 2-4.49 years have significant association with developing DKA in newly

diagnosed children, AOR of 3.133(1.217, 8.063) with p value of 0.018, age group 5-9.4, AOR= 2.611 with 95% CI and (1.398, 8.498) and p-value 0.007 and age group above 9 years is also have significant association AOR =4.022(1.685, 9.603) and p value of 0.002, as age group less 2 take as a reference.

Children who their parents know the sign and symptoms of DM/DKA have 49% times less likely to develop DKA at primary diagnosis of DM than children who their parents do not have knowledge about the sign and symptoms of DM with p value of 0.034 controlling for the rest of the independent variables.

Children who have first degree relatives with DM had significant association with new onset DM/DKA in bivariate analysis but it is not significantly associated in multivariate analysis adjusting for the other independent variables.

The odds of developing new onset DM with DKA are 3.455 times higher in Children who had infection before 1-2 week of DKA than who do not have the sign and symptoms of infection adjusting for the rest of independent variables

Table 3,Bivariate and multivariate analysis of DKA in newly diagnosed DM children in 3 hospitals, Addis Ababa, Ethiopia from January 2009 December 2014

VARIABLE		DKA new		COR (CI=95%)	AOR (CI=95%)
		Yes	No		
Age Group	<=2 year	22	17	Ref.	Ref.
	2-4.49	24	51	2.75(1.27,6.1)	3.13(1.21,8.06)*
	4.5-6.99	20	26	1.68(0.71,3.98)	2.61(0.93,7.29)
	7-9.49	41	64	2.02(0.25,0.96)	3.44(1.39,8.49)*
	>9.5	35	95	3.51(1.67,7.38)	4.02(1.68,9.60)*
Mother education	Unable to read & write	20	15	Ref.	Ref.
	Read and Write	30	44	1.96(0.86,4.42)	1.71(0.62,4.7)
	Grade 1-8	35	58	2.21(1.0,4.87)	1.61(0.53,4.9)
	Grade 9-12	32	61	2.54(1.2,5.6)	1.80(0.58,5.5)
	Above 12	25	75	4.0(1.78,8.97)	3.03(0.92,10.0)

Family income	**<=1000 birr**	**6**	**13**	**Ref.**	**Ref.**
	10001-2200	**67**	**90**	**0.62(0.22,1.72)**	**0.36(0.1,1.3)**
	2201-3400	**33**	**85**	**1.19(0.42,3.34)**	**0.69(0.182,2.6)**
	3401-3600	**30**	**50**	**0.77(0.264,2.24)**	**0.31(0.07,1.23)**
	>3600	**60**	**15**	**1.15(0.29,4.46)**	**0.4(0.07,2.2)**
Child first degree relatives with DM	**Yes**	**38**	**93**	**0.63(0.4,0.0.9)**	**0.77(0.389,1.520)**
	No	**104**	**160**	**Ref.**	**Ref.**
Parent's knowledge about the sg. & Sx. of DM/DKA	**Yes**	**46**	**124**	**0.49(0.32,0.76)**	**0.51(0.27,0.95)***
	No	**96**	**129**	**Ref**	**Ref.**
Symptoms and sign of DKA before the onset of DKA	**Yes**	**181**	**72**	**Ref.**	**Ref.**
	No	**72**	**70**	**0.41(0.27,0.63)**	**0.35(0.21,0.59)***
Infection before the onset of DKA	**Yes**	**53**	**55**	**2.14(1.36,3.37)**	**3.455(1.97,6.04)***
	No	**89**	**198**	**Ref.**	**Ref.**

N.B. Ref. is designated for reference

*:-indicates statistically significant results at p value <0.05.

6. DISCUSSION

Slightly one third of children in the present study manifested with DKA at first diagnosis of diabetes. This is not surprising as a similar low magnitude has been reported in a previous study in Italy (15). The same is true of reports from Iran (24%) (13), Sweden (14%), Canada (18.6%), Finland(22%) and Hungary (23%) (8). However, some studies have reported higher magnitude, UAE(80%),Romania(67%),Taiwan(65%),all reflecting the well known wide geographic variation in frequency of DKA at onset of pediatric diabetes mellitus (8). The differing in magnitude might be explained by differences in study population, the back-ground prevalence of diabetes in the given population, presence or absence of family history of T1DM, socioeconomic status, delayed diagnosis and treatment as well as the definition of DKA used in the particular study (9).

A study conducted in black lion hospital found the magnitude of DKA to be 80%,when we compare with our study, it is high which might be due to the smaller sample size(143), the study was conducted only in black lion hospital and because severe cases are referred to black lion hospital the magnitude might be exaggerated (3). Another retrospective cross-sectional study conducted in Benin teaching hospital found the frequency of DKA in newly diagnosed children to be 77.1% (9), and this frequency is higher relatives to our study because this study included children under 15 years of age and because the study period was 15 years.

In systematic review on 40 studies in 31 countries on the associated factors of DKA on newly diagnosed children, age was the most common factor described: 32 studies reported the effect of age on presentation (1) and this is consistent with our research.

In the systematic review that included 40 studies, three studies reported on the influence of parental education and of these studies the study in German did not find significant association on developing DKA (16), similar to this study our research did not find significant association.

Three studies examined the effect of family income and two European studies found that family income had no significant effect on risk of presenting in diabetic ketoacidosis and this result is consistent with our results (17). This might be due to the reason that even though parents who get higher income and having higher level of education they may not be aware of DM/DKA and seek medical advice earlier.

Marital status of the child mother has no significant association in developing DKA in newly diagnosed DM children both in bivariate and multivariate analysis. Marital status of the child parent's is indirect predictor of DKA. In single, divorced and widowed mother the family income is supposed to be lesser than in married but family income has no significant association with DKA so do the child parent's marital status.

In agreement with our study a German study which adjusted for age, sex, having a single parent, and social status also failed to show a significant association with a family history of either type1or type2 diabetes in siblings, parents, or grandparent.(17) Although having a first degree relative withtype1Diabetes decreased the frequency of diabetic ketoacidosis in three studies,(17) it did not predict a diagnosis of new onset diabetes before progression to diabetic ketoacidosis, this might be because in young children it is very difficult to find the classical symptoms of DKA which are polyuria, polydepsia and weight loss so the parents of the child might not consider the other sign and symptoms of DKA as the sign of DKA.

In this cross sectional study the odds of developing DKA in newly diagnosed DM children is 0.510 times lower in children whose parents' know the sign and symptoms of DM/DKA than parents' who don't know the sign and symptoms of DM with 95% CI (0.273, 0.952) and P value of 0.034.This is because parents' who know the sign and symptoms of DM might seek health care before their children develop DKA.

Three studies in the systematic review by Usher smith JA et.al included data on the effect of a preceding infection or febrile illness. In two, a history of infection or febrile illness was associated with an increased risk of diabetic ketoacidosis (17) and similar to this our study found the odds of children who had infection 1-2 weeks prior to DKA at primary onset of DM is 3.455 times higher than children who didn't have infection prior to DKA at primary onset of DM at 95% CI (1.97,6.04) and p value of 0.0001.Infection is known to cause inflammation, pro-inflammatory Cytokine release, and a counter regulatory response that Collectively lead to insulin resistance and metabolic decompensation (17).

Strength and limitation

Strength

• This study include both the clinical and socioeconomic factors using both secondary data and primary data

• Gives an insight for researchers especially for prospective study

Limitation

• Using secondary data have incomplete data

• Selection bias is possibly introduced during secondary data collection because patients with incomplete records and who did not come for follow up during data collection period were excluded

- Recall bias

7. Conclusion

The overall magnitude of DKA in children with newly diagnosed type 1 diabetes is high. In particular, children between 9-12 years of age have a high risk of DKA at onset. Children's age, the knowledge of sign and symptoms of DKA, sign and symptoms of

DKA prior to onset of DKA and infection prior to DKA are found to be the significant explanatory variable of DKA in primary onset of DM.

8. **Recommendation**

- ✓ We recommend the Diabetic Association to give different workshop for health professional and to work on awareness creation for the society using different communication media
- ✓ We recommend all the health facilities to give health education about the sign and symptoms of DM and the acute complications of DM
- ✓ We recommend the health professionals to give attention on treating children with infection that don't have known sign and symptoms of DKA.
- ✓ We recommend further prospective study to Health science Researchers on protective factors and on complications of DKA.

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10.ANNEXES

Annex 1 -Questionnaires

ADDIS ABABA UNIVERSITY COLLGE OF HEALTH SCHOOL OF PUBLIC HEALTH

Questionnaire on assess prevalence and associated risk factors of DKA in new onset DM children

Introduction:

My name is _____. I am a student of Addis Ababa University and I am conducting a research on magnitude and risk factors of DKA on newly diagnosed DM children in ADDIS ABABA

001. Interviewer: code ____/___/___ Name _____

002. Date of Interview ____/___/____ Time _____

003. Checked by Supervisor: Signature _____day _____month _____ year____

1.Socio-Demographic Variables (circle)			
No	Questions	Coding Categories	Skip
101	What is the age of the child (Enter in the space)	_____ year	
102	The child sex?	1. Male 2. Female	
103	What is the child religion?	1. Orthodox 2. Islam 3. Protestant 4. Catholic 5. Others (Specify)	
104	The child Ethnicity?	1. Amhara 2. Tigre 3. Oromo 4. Guarage 5. Others (Specify)	
105.A	What is the child mother educational level?	1. Unable to read & write 2. Read and Write 3. Grade 1-8 4. Grade 9-12 5. Above 12	
105. B	What is the child father educational level?	1. Unable to read & write 2. Read and Write 3. Grade 1-8 4. Grade 9-12 5. Above 12	
106	What is the child parents/guardian marital status	1. Single 2. Married 3. Separated 4. Widowed/partner died	
107.A	Occupation of the child mother/guardian	1. Unemployed2. Civil servant 3. Student4. House wife 5. Daily laborer 6. Pensioned 7.Merchant 8.others/specify	
108.B	Occupation of the child father/guardian	1. Unemployed2. Civil servant 3. Student4. House wife 5. Daily laborer 6. Pensioned	

		7.Merchant 8.others/specify	
109	What is the average family income per months?	_____ Birr	

2. ASSOCIATED RISK FACTORS OF DKA			
201	Is the child known type 1 DM?	1.Yes 2.No	
202	Did the child have any sign and symptoms of DKA 1-2weeks before the onset of DKA	1.Yes 2.No	If 2,Skip to number 204
203	If yes, which sign and symptoms?	1. Polydepsia 2.polyuria 3.Weight loss 4.1 & 2 5.1&3 6.2&3 7.others	
204	With which DKA symptoms did the child present?	----------	
205	Does the child have first degree relatives with DKA?	1. Yes 2. No	If 2,Skip to number 207
206	If yes, whom?	----------	
207	Do the child parents know the sign and symptoms of DKA/DM?	1.Yes 2.No	If 2 Skip to number 209
208	If yes, which sign/symptoms?	----------	
209	If the child is known DM patient, did he/she omit insulin before onset of DM?	1.Yes 2.No	
210	Did the child have any infection 1-2week before the onset of DKA?	1.Yes 2.No	If 2 Skip to number 211
211	If yes, which symptoms?	----------	