

Incidence and predictors of diabetic ketoacidosis among children with type 1 diabetes mellitus in Western Amhara Referral Hospitals, Northwestern Ethiopia, 2018: A Retrospective Follow-Up Study

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Abstract

Background Diabetic ketoacidosis remains a major cause of morbidity, hospitalizations and mortality in children with established type 1 diabetes mellitus. Therefore, this study aimed to determine the incidence and predictors of diabetic ketoacidosis among children with established type 1 diabetes mellitus at Western Amhara region.

Method Institution-based retrospective follow-up study was done on 393 children with established type 1 diabetes mellitus registered between September 2013 and September 2017 in Western Amhara referral hospitals. The collected data was entered into Epidata version 4.2 and further analysis were done using STATA version 14.1. Negative Binomial Poisson Regression analysis model was used.

Result The cumulative incidence and incidence density rate of diabetic ketoacidosis among children with established type 1 diabetes mellitus in western Amhara referral hospitals was 63.9% and 41.5 per 100 person-years respectively. The incidence of diabetic ketoacidosis increased with age at diagnosis [ARR:2.61, p-value<0.001], siblings only care givers [ARR:1.87, p-value <0.001], fathers only [ARR:1.51, p-value=0.004], omission of insulin (ARR:1.58, p-value <0.001), lower frequency of clinical visits [ARR:2.35, p-value=0.007] and baseline insulin dose >1.2 u/kg/day [ARR:1.39, p-value=0.015], diabetic education (no) [ARR:1.52, p-value=0.011]. But the risk was decreased with baseline insulin type (Lente and regular) (ARR; 0.73, p-value =0.006), base line insulin dose <0.6u/kg/day (ARR: 0.5, p-value=0.034) and community health insurance membership (no membership) [ARR: 0.49, p-value <0.001]. In general, this study revealed that a substantial number of patients had at least one episode of diabetic ketoacidosis and a higher rate of diabetic ketoacidosis.

Introduction

In children diabetic ketoacidosis is an acute life threatening and recurrent medical emergency that requires frequent hospitalizations, treatment and monitoring for multiple metabolic abnormalities and vigilance for complications. It is the leading cause of morbidity and mortality that continued to be a major public health concern [1]. It has considerable costs to the health care systems and adds burden of costs to the patients and families [2]. Despite the improvement in the treatment and care of type 1 diabetes mellitus and the development of guidelines, diabetic ketoacidosis is still a major cause of hospitalization and the leading cause of death in children with type 1 diabetes mellitus [1, 3–7]. According to international diabetic federation's estimation, the incidence of diabetes mellitus in Ethiopian children (0–14) was 30 per 1000 populations. The mean diabetes related expenditure per a child was 29 United States Dollars [8].

Evidences revealed that the common predictors of diabetic ketoacidosis among children with type 1 Diabetes Mellitus were age at diagnosis [9–20], sex [9–12, 14–16, 18–20], lack of healthcare insurance [16, 19, 20], residence [9, 14, 15, 19], primary care giver [14, 19], insulin dose [9–12, 14, 15, 19–22], missed insulin [9], co-morbidities like depression, epilepsy, bronchial asthma and down syndrome [13, 15, 21, 22], childhood infections [9, 15, 20, 23], lower frequency of clinical visits [11, 16, 18], omission of insulin [11, 18, 20], absence of diabetic education [11, 15, 19]. Moreover, protocols currently used for the management of DKA in sub-Saharan Africa were largely based on those used in developed world, which do not take into consideration co variables, associated with DKA unique to developing countries [24].

Diabetic ketoacidosis has an overall mortality between 15 and 31 per 10,000 patients, and cerebral edema (CE), which is a devastating complication, accounts for between 57% and 87% of DKA related deaths [12]. Even in developed countries, there is significantly excess mortality from ketoacidosis among children with type 1 diabetes

mellitus [25]. The incidence of DKA varies considerably between different countries and studies [26]. The majority of DKA cases occur in patients with previously diagnosed diabetes [24]. It occurs at a rate of 1–10/100 patient-years in children with established diabetes globally. The most recent rate of DKA was 4.81/100 patient-years in children with established type 1 diabetes mellitus in Germany [10]. Up to 90% of children with type 1 DM reported one or more episodes of DKA over the last 6 months in Sub Saharan Africa. Other studies show a variation from 25–90% [11, 27].

In developing countries like Ethiopia, the risk of dying from DKA is greater. Even though many patients with diabetes mellitus in Ethiopia keep dying from DKA, there is little documentation about DKA. This creates double burden of communicable and non-communicable diseases [28]. Therefore, this study aimed to determine the incidence and predictors of diabetic ketoacidosis among children with type 1 diabetes mellitus at Debremarkos and Felegehiwot referral hospitals, 2013–2017.

Methods

Study design, study setting, Study period and populations

Hospital based retrospective follow up study was done using routine hospital data at Western Amhara referral hospitals, from September 2013 to September 2017. The study was conducted at two referral hospitals in Amhara Regional State (Northwestern Amhara); Debre Markos Referral Hospital and Felegehiwot Referral Hospital. Debremarkos Referral Hospital is found in Debre Markos City administration located at 299 km Northwest of Addis Ababa. The Hospital provides service for more than 3.5 million people [29]. A database from Information Technology prepared excell sheet was seen and about 190 children with type 1 DM were registered during the follow-up period. Felegehiwot Referral Hospital is found in Bahirdar city Administration that was located 563km from Addis Ababa. The hospital served the population in the region and those from Benshangul Gumuz population totally more than 7 million people as a referral center [30]. In pediatric outpatient department, there were 246 diabetic children (from Information Technology prepared excel) registered during the follow-up period.

Sample size determination, technique and procedure

A total of 436 children with diabetes mellitus were registered at Debremarkos and Felegehiwot referral hospitals (purposively selected) between 2013 and 2017. The list of children with established type 1 DM was obtained from diabetic follow up logbooks (outpatient and inpatient departments) in each referral hospital. The study planned to include all children's records in those referral hospitals. But there were only 393 diabetic children's records available using the inclusion criteria.

Data collection instruments

Data was collected using English version structured checklist. The checklist addressed the socio-demographic factors and clinical characteristics. It was filled by trained data collectors.

Data collectors, procedure and quality control

Two BSc nurses were recruited to participate in data collection. Two health officers were recruited for supervision. Data collectors and supervisors were trained for one day about data collection procedure and the purpose of the research. A week before the actual data collection, checklist was pretested on 22(5%) of the diabetic children records from the same area. Amendments were done on the checklist after the pretest. On site supervision was carried out during the whole period of data collection on daily basis by the supervisor and principal investigator. At the end of each day, checklist was reviewed and crosschecked for completeness, accuracy and consistency by the supervisors and principal investigator and corrective measures was under taken. Exclusion criteria were considered.

Operational Definitions

- Established type 1 diabetes mellitus: at least with diabetic duration of one week.
- Missed insulin: any dose of daily insulin intentionally or unintentionally missed at least in the last one week of diabetes mellitus
- Diabetic duration:- after established DM, calculated from age at diagnosis and last follow up date
- Co-morbidities: diseases like burn, lipodystrophy, trauma, surgery, depression, bronchial asthma, epilepsy, down syndrome, cardiac, renal, hepatic diseases and etc. other than infection.
- Incomplete record:-if major socio-demographic characteristics like date of admission, final follow up date etc. were not recorded.
- Hyperglycemia: fasting blood sugar above 126 mg/dL, A1C \geq 6.5%, or random glucose concentration \geq 200 mg/dL in the presence of symptoms
- Fasting: no caloric intake for at least eight hours
- Diabetic ketoacidosis: criteria of Random Blood Sugar \geq 250 mg/dL and ketonuria in Ethiopia care set up and most developing countries. But, blood PH value $<$ 7.3 and hyperglycemia in most developed countries.
- Children: those who were less than 15 years old in Ethiopian care set up.

Data Analysis

Data were entered to the Epidata version 4.2 (Sweden) statistical software and further analysis were done using STATA version 14.1(College Station, Texas 77845 USA). Descriptive results were presented using frequency, percentage, mean, standard deviation, median, Interquartile range, cumulative incidence and incidence density were calculated and some of them were presented in graphs and tables. Incidence rate ratio was also calculated and reported. The analysis was started by testing the significance of the association between each predictor and the dependent variable using Bivariable Negative binomial Poisson regression analysis. Only the predictors with P-Value \leq 0.25 with the dependent variable as per Bivariable Negative binomial Poisson regression analysis result were entered to Multivariable Negative binomial Poisson regression analysis to determine different predictors of DKA episodes. The assumption of Standard Poisson regression model (mean equals variance) was checked and there was over dispersion depicted by comparison of mean and variance of the outcome variable and confirmed by the significance of dispersion parameter. So, Negative binomial Poisson regression analysis model was used. Model fitness was checked by Pearson chi square and deviance tests. And finally Multivariable Negative binomial Poisson regression analysis results were reported using adjusted incidence rate ratios at significance level \leq 0.05.

Results

Sociodemographic characteristics

A total of 393 (90.13%) registered patients' charts that fulfil the inclusion criteria were reviewed. Of these, almost half, 193 (49.1 %) were females. The median age of the patients was 10 (IQR:5–12) years. Slightly more than half, 224 (57%) of them were residing in rural area. Nearly half, 215 (54.71%) of them were given diabetic care by father and mother. The rest were given by father 54 (13.74%), mother 61(15.52%) and siblings only 63 (16.03%). Two hundred twenty two (56.5 %) of the study subjects had community health insurance. Regarding ethnicity almost all, 385 (98%) of patients were Amhara and the rest 8 (2%) were Gumuz (*table 1*).

Clinical characteristics

The mean insulin dose was 0.96 ± 0.32 (mean \pm SD) u/kg/day. The mean random blood sugar level was 390.5 ± 80.5 (mean \pm SD) mg/dl. The median frequency of visits at diabetic follow up clinic was every two months (IQR:1–3).

The majority, 363 (92.5%) of diabetic children were given diabetic education. About 211 (53.7%) of the patients were initiated on regular insulin and NPH but all the rest were on regular insulin and Lente. About 86 (22%) of patients missed insulin during the over all diabetic follow up. About 15 (17.7 %) of them who missed insulin did not get insulin from hospitals because of unavailability, 15 (17.7%) due to forgetfulness, 21 (24.7%) due to unavailability at home and the larger group 31(36.5%) from those who missed insulin did not have any documentation about the reason of discontinuation. Around 98 (25%) of the total patients had experienced infection during follow up.

Those who experienced infection had pneumonia 20 (20.6%), both pneumonia and urinary tract infection, 20 (20.6), both pneumonia and acute gastro enteritis, 18 (18.6%), AGE, 7(7.22%), urinary tract infection only 6 (6.2%), both urinary tract infection and acute gastro enteritis, 2 (2%) and others (Human immunodeficiency virus infection, 8 (2%), pulmonary tuberculosis, 4 (1%)) which were considered as precipitants of diabetic ketoacidosis.

Fifty six patients (14%) had chronic commorbidites; of which 17 (4.3%) had epilepsy, 10 (2.5%) malnutrition, 10 (2.5%) bronchial asthma, 7 (2%) lipodystrophy, 3 (1%) history of surgery and the rest 5 (2%) had anemia, congenital heart disease or peptic ulcer disease.

Three hundred ninety three patients who were followed for different periods in five years produced 605.05 person-years of observation. With in the follow up period, there were 251 DKA events producing an overall incidence rate of 41.5 per 100 person-years. The median number of DKA was 1 (IQR:0–2). A total of 251 (63.9%) of patients had at least one or more episodes of DKA (*table 2*).

Predictors of Diabetic ketoacidosis among children with established DM

Bivariable Negative Binomial Poisson Regression analysis of socio-demographic and clinical variables on incidence and predictors of diabetic ketoacidosis among children with established diabetes mellitus revealed that sex, age at diagnosis, community health insurance, primary caregiver, diabetic education, insulin type, insulin dosage, omission of insulin, clinical visits and ever infection were predictors of diabetic ketoacidosis. Whereas during the Multivariable Negative binomial Poisson regression analysis, age at diagnosis, primary caregiver, community health insurance, omission of insulin, frequency of clinical visits, baseline insulin dose, baseline insulin type and diabetic education remained significant predictors of diabetic ketoacidosis among children with

established type 1 diabetes mellitus. But, the significance of sex and ever infection was diluted in Multivariable Negative Binomial Poisson Regression analysis (*table 3*).

Diabetic children who were in the age group 10–15 years had 2.61 times higher (ARR: 2.61, p value < 0.001) probability of developing diabetic ketoacidosis than those who were in the age group 6–10 years. Children whose primary caregivers were siblings only had 87% increased (ARR: 1.87, p value < 0.001) rate of DKA as compared to patients whose primary care givers were father and mother living together. But, those who were given care by their father only had a 50% increased (ARR: 1.51, p value = 0.004) rate of DKA in comparison with those living with their father and mother together.

The rate of diabetic ketoacidosis was reduced by 27% (ARR; 0.73, p value = 0.006) when patients were initiated on Lente and Regular insulin as compared to patients with NPH and Regular insulin. Children at insulin dose >1.2 U/kg/day were expected to have a rate 1.39 (ARR: 1.39, p value = 0.015) times greater for DKA than those who were at 0.6–0.8 U/kg/day. The patients who were on less than 0.6 U/kg/day had a 50% decreased (ARR: 0.5, p value = 0.034) risk of DKA as compared to patients started on 0.6–0.8 U/kg/day.

There was a 58% increased (ARR: 1.58, p value < 0.001) rate of DKA when patients missed insulin compared to those with no omission of insulin. The rate of diabetic ketoacidosis increased by 2.35 times as patients had protracted clinical visits (>5 monthly) (ARR: 2.35, p value = 0.007) comparing with those having less than two monthly clinical visits. Children without community health insurance had a 51% lower (ARR; 0.49, p value < 0.001) risk of DKA than children who had community health insurance. Diabetic children who did not have any diabetic education were at about 52% more (ARR: 1.52, p value = 0.011) rate of diabetic ketoacidosis than those who were given (*table 3*).

Discussion

In children, type 1 diabetes mellitus is the most common form of diabetes [16] where diabetic ketoacidosis occurred most [4]. The current study attempted to determine the incidence and predictors of diabetic ketoacidosis among type 1 diabetic children. The current study found that the cumulative incidence and incidence density rate was 63.9% and 41.5 per 100 person-years respectively, which was consistent with many studies in sub-Saharan Africa [11, 27].

In other way, this finding was much higher than the findings in developed countries [10, 15, 31–36]. This might be due to difference in study period, sample size and other socio-demographic characteristics observed between the previous and our population. Moreover, currently, the diagnostics and screening ability becomes advanced than the previous that might play significant role detection rate.

Moreover, this study found that the cumulative incidence and incidence density rate among children with type 1 DM was lower than compared with findings in Tikur Anbessa Specialized hospital (74.4%) [37] and than that of Tanzania (89.9%) [11], Benin teaching hospital (77.1%) [24], Romania (67%), Taiwan (65%) [36]. The lower cumulative incidence might be explained by the improved diabetes education and prevention programs that have been implemented over the last decades. Similarly, the variation in the cut of point for DKA might contribute for the difference [7, 12, 38].

In other way, the cumulative incidence and incidence density rate was higher than the studies done in Saudi Arabia (33.1%) [15], Swedish cohort study (1.4 episodes per 100 patient years [32], Hvidoere study (4/100 patient years)

[33], United states (31.5%) [34], Germany (4.81/100 patient-years) [10], across five nations from England, Wales, the United State, Austria, and Germany (7.1%) [35], Systematic review in Sweden (14%), Canada (18.6%), Finland (22%) and Hungary (23%) [36]. This higher incidence density rate in the current study could be explained by the difference in economic development (well developed diabetic care setup) in those countries; the diagnostic modality was also different because DKA was diagnosed using PH value < 7.3; the variation of the cut off point for DKA, the difference in the age group which was considered 'children' could be much contributory for the lower incidence in those countries [10, 11, 14–16, 19, 26].

The current study also explored the potential predictors for the occurrence of DKA among diabetic children. In the present study, age at diagnosis of DM was identified as a significant predictor for DKA, age group 10–15 years was highly associated with DKA, which was consistent with many studies [10, 11, 14, 16, 17, 19, 20]. Greater personal responsibility, and less parental monitoring and endocrine changes leading to insulin resistance would be responsible for poor DKA control in this age group [10, 11, 19, 39].

In addition, in this study, patients who missed insulin had an increased rate of DKA as compared to those with no omission of insulin. Other studies [9, 11, 16, 23] also confirm that omission of insulin was an important predictor of DKA. Omission of insulin causes hyperglycemia, intracellular starvation leading to stimulation of counter regulatory hormones which accelerates lipolysis and ketoacidosis [14, 16, 19, 28, 39, 40].

DKA was significantly associated with primary caregiver other than father and mother together. Those children, who lived with their siblings only or fathers only, had increased risk of DKA. This was in line with other studies [14, 16, 19]. The reason may be parents (father and mother together) are probably more committed to their children with a chronic illness and ensure better compliance with medication. Children under care of their parents (both father and mother) also might enjoy a stable family structure that is supportive [10, 11, 14, 17, 19].

Higher insulin dose administration which is greater than 1.2 U/kg/day was also increased the rate of DKA. This finding was also in good agreement with previous studies [11, 14, 19]. This seemed to be as a result of suppression of endogenous insulin which in turn decreases basal insulin [12]. But, those children on insulin dose less than 0.6 U/kg/day was found to be protected from risk of DKA.

Consistent to the previous studies [14, 15, 19], the current study identified the lower frequency of clinical visits to be significantly associated with risk of DKA. This was obviously related to the lack of blood sugar monitoring and professional diabetic care [10, 11, 14–16, 19].

This study could establish the risk of insulin type on the rate of DKA. Patients who were on Lente and regular insulin combination had decreased rate of DKA as compared to patients on Neutral protamine hagedorn (NPH) and regular insulin combination. Longer duration of action and the driving down of glycated hemoglobin safely as a result of Lente insulin might account for the difference [16, 39].

Community health insurance was significantly associated with rate of DKA. This was consistent with other studies [14, 15, 19, 20]. Contrary to those studies, the present study showed that diabetic children with no community health insurance had decreased rate of DKA. This might be due to many children who did not have community health insurance most probably afforded to cover the expense. In addition, patients with community health insurance might not have close diabetic follow up. And the status of community based health insurance could not be revised the next year and not well documented.

In the current study, diabetic education was significantly associated with the rate of DKA which was consistent with many studies [10, 11, 14–16, 19]. Patients who did not have any diabetic education had increased rate of DKA.

Strength of the Study

As to the researcher's knowledge, it was the first study to establish the incidence and predictors of DKA among established type 1 DM in the study areas and even in the country. It was a cohort study that can strongly suggest cause and effect relationship between variables. The study areas were wider referral hospitals with large catchment area.

Limitation of the Study

Since the study was a retrospective study, it had its own limitation associated with poor documentation. Many other socio-demographic, clinical and economic factors for DKA couldn't be assessed. There was some difficulty comparing findings due to limited data in Ethiopia and inaccessibility to other country study report. The finding was based on patient data on the card according to the physician diagnosis. Sometimes, it might lead to misdiagnosis of DKA or other precipitants or predictors. The variation in the cut off point for the diagnosis of DKA and the difference in the age group which was considered 'children' were the other challenges of the study; it might distort the result. In conclusion, this study revealed that a substantial number of patients had at least one episode of diabetic ketoacidosis and a higher rate of diabetic ketoacidosis. Age at diagnosis, primary caregiver, frequency of clinical visits, omission of insulin, baseline insulin dose, baseline insulin type, diabetic education, and community health insurance membership were identified as significant predictors of diabetic ketoacidosis. The most suffered age group was from 10–15 years.

Conclusions

This study revealed that a substantial number of patients had at least one episode of diabetic ketoacidosis and a higher rate of diabetic ketoacidosis. Age at diagnosis, primary caregiver, frequency of clinical visits, omission of insulin, baseline insulin dose, baseline insulin type, diabetic education, and community health insurance membership were identified as significant predictors of diabetic ketoacidosis. Early identification of patients at risk for this higher incidence of diabetic ketoacidosis and intervention programs targeting these predictors should be implemented.

Abbreviations

CE: cerebral edema

DKA: Diabetic ketoacidosis

DM: Diabetes Mellitus

DMRH: Debre Markos Referral Hospital

FHRH: Felege Hiwot Referral Hospital

Declarations

Ethics approval and consent to participate

Ethical clearance letter was obtained from the Debre Markos University, College of Health Science. Furthermore, a permission letter was obtained from each study setting (Debre Markos Referral Hospital and Felege Hiwot Referral Hospital).

Consent for publication

Not applicable

Availability of data and material

Data will be available upon request of the corresponding author.

Conflict of interests

“The authors’ of this reviewer declares that there is no conflict of interests”

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Authors’ contribution

MS: Conception of research protocol, study design, literature review, data extraction, data analysis, interpretation and drafting the manuscript. GD, TG, CT and MY: data analysis, reviewing the manuscript, data extraction and quality assessment. All authors have read, edited for language, made for the necessary revision and approved the manuscript.

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Tables

Table 1: Socio-demographic characteristics of diabetic children with established diabetes mellitus at western Amhara referral hospitals, Northwestern Ethiopia, 2013-2017: (n=393)

Socio-demographic characteristics		Frequency	Percent (%)
Sex	Male	200	50.89
	Female	193	49.11
Age at Diagnosis of Diabetic mellitus (IQR:5-12) (in years)	<=5	105	26.72
	6-10	162	41.22
	10-15	126	32.06
Residence	Urban	169	43
	Rural	224	57
Primary caregiver	Father	54	13.74
	Mother	61	15.52
	Father and mother	215	54.71
	Siblings only	63	16.03
Community health insurance	Yes	222	56.49
	No	171	43.51
Ethnicity	Amhara	385	98
	Others	8	2

Table 2: Clinical characteristics of diabetic children with established diabetes mellitus, at Western Amhara referral hospitals, Northwestern Ethiopia, 2013-2017 :(n=393)

Patient characteristics		Descriptive statistics (n=393)	
		Frequency	Percent (%)
Random blood sugar level (mg/dl)	mean±SD	390.5±80.5	
	250-299	48	12.21%
	300-349	47	11.96%
	≥350	298	75.83%
Insulin type	Regular insulin and NPH	211	53.69%
	Lente and Regular insulin	182	46.31%
Insulin dosage (U/kg/day)	mean±SD	0.96±0.32	
	< 0.6	13	3.31%
	0.6-0.8	157	39.95%
	0.8-1.2	141	35.88 %
Diabetic education	>1.2	82	20.87%
	Yes	363	92.37%
Omission of insulin	No	30	7.63%
	0	306	78.12%
	1-3	78	19.85%
Clinical visits (monthly)	>3	9	2.29%
	<2	112	28.50%
	2-5	277	71.48%
Infection	>5	4	0.05%
	Yes	98	25%
Comorbidity	No	294	75%
	Yes	56	14.25%
	No	337	85.75 %

Table 3: Negative Binomial Poisson Regression analysis result for incidence and predictors of diabetic ketoacidosis among children with established diabetes mellitus at Western Amhara referral hospitals, Northwestern Ethiopia, 2013-2017

Patient characteristics		Total person-years	DKA rate per 100 person-years	Unadjusted rate ratio (95% CI)	Adjusted rate ratio (95% CI)	P.value
Sex		298.8	35.8	1	1	
	Male (107)					
	Female (145)	306.25	47.4	1.38 (1.12,1.71)	1.0 (0.81,1.23)	0.998
Age at diagnosis (years)		236.25	32.2	0.86 (0.67,1.11)	0.78 (0.61,1.0)	0.052
	<=5 (76)					
	6-10 (84)	261.4	32.14	1	1	
	10-15 (92)	107.41	85.65	5.06 (3.9, 6.51)	2.61 (1.95,3.5)	< 0.001
Primary caregivers						
	Father (43)	83.3	51.3	1.67 (1.26,2.23)	1.51 (1.14,1.99)	0.004
	mother (30)	103.6	29	0.89 (0.62,1.28)	0.91 (0.66 ,1.26)	0.566
	Father & mother (125)	314.8	39.71	1	1	
	Siblings only (54)	102.8	52.5	1.71 (1.31, 2.24)	1.87 (1.46,2.39)	< 0.001
Community health insurance						
	Yes (126)	222.22	56.7	1	1	
	No (126)	382.8	32.9	0.3 (0.24 ,0.37)	0.49 (0.37 ,0.64)	< 0.001
Insulin type						
	Regular and NPH (159)	331.4	48	1	1	
	Lente and Regular (93)	273.7	34	0.71(0.56 ,0.88)	0.73 (0.59 ,0.92)	0.006

dosage day)	< 0.6 (8)	30.1	26.6	0.5 (0.26,0.94)	0.5 (0.27,0.95)	0.034
	0.6-0.8 (82)	247.7	33.1	1	1	
	0.8-1.2 (90)	200.1	45	1.16 (0.89,1.5)	1.06 (0.81,1.37)	0.69
	>1.2 (72)	127.2	56.62	2.04 (1.57,2.65)	1.39 (1.06,1.81)	0.015
Omission of insulin	0 (172)	136.1	31.61	1	1	
	≥1 (80)	456.42	44.92	1.58 (1.26,1.97)	1.58 (1.26,1.97)	< 0.001
Clinical visits (monthly)	< 2 (43)	136.1	31.61	1	1	
	2-5 (205)	456.42	44.92	1.76 (1.31,2.36)	1.16 (0.86,1.56)	0.327
	>5 (4)	12.6	31.8	1.87 (0.93,3.78)	2.35 (1.26,4.4)	0.007
Ever infection	yes (86)	199.6	43.05	0.70 (0.57,0.880)	1.07 (0.87,1.32)	0.53
	no (165)	404.3	40.5	1	1	
Diabetic education	Yes (231)	570.4	40.5	1	1	
	No (21)	34.7	60.6	2.36 (1.63,3.41)	1.52 (1.10,2.09)	0.011

NB: In the patient characteristics (variables) column, the numbers in brackets were number of episodes (events) in each category.