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Original Article

Predictive factors of ketoacidosis in type 1 diabetes mellitus

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Abstract

Background Diabetic ketoacidosis (DKA) is an acute complication in type 1 diabetes mellitus (DM) and a significant cause of morbidity and mortality in developing countries. Diabetic ketoacidosis can be prevented by good management of the disease. Risk factors from previous studies that increase the DKA incidence were p eripubertal age, female gender, low socio-economic status, low parental education status, DKA at the first diagnosis of type 1 DM, infection, psychological problems, poor metabolic control, and non-compliance with insulin treatment.

Objective To determine whether sex, age, socio-economic status, parental education level, DKA at the initial diagnosis of type 1 DM, infection, psychological problems, poor metabolic control, and failing to take insulin as needed were predictive of DKA in type 1 DM patients.

Methods We conducted a retrospective cohort study using medical records from type 1 DM patients aged 0-20 years, at the Department of Child Health, Dr. Sardjito Hospital, Yogyakarta, from January 2011 to May 2017. We assessed for the occurrence and predictors of DKA. Logistic regression analysis was done to determine which factors increased DKA incidence.

Results A total of 57 type 1 DM patients were recruited, with DKA incidence of 37 (65%). Five (8.8%) DKA patients died. Multivariate analysis revealed that infection (OR 5.23; 95%CI 1.47 to 19.68; P=0.014) and DKA at the first diagnosis of type 1 DM (OR 5.37; 95%CI 1.40 to 19.52; P=0.011) were significant risk factors for DKA.

Conclusion Infection and DKA at the first diagnosis of type 1 DM are significant predictors of increased DKA incidence. **[Paediatr Indones. 2019;59:169-74; doi: http://dx.doi.org/10.14238/pi59.4.2019.169-74]**.

Keywords: *ketoacidosis; type-1 diabetes mellitus; predictor factor*

Diabetic ketoacidosis (DKA) is an acute complication of type 1 diabetes mellitus. This condition causes significant mortality and morbidity in type 1 DM patients. Mortality due to DKA in developed and developing countries is around 0.15-0.31% and 3.4-13.4%, respectively.[1,2] The social and economic burden inflicted by DKA is large, especially with regards to hospitalization. In the US, over 62% of hospital care in type 1 DM patients is associated with DKA incidence. The cost of type 1 DM treatment in hospitals doubles if complicated by DKA.[3]

Incidence rates of DKA vary and are influenced by geographic, socio-economic and health care facility conditions in each area. The prevalence of DKA varies considerably in many countries, ranging from 13-80%, with higher prevalence in developing countries than in developed countries. The incidence of DKA in children diagnosed with type 1 DM is 1-10% per patient per year.[1,4] In Indonesia, no exact data for incidence rate

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of DKA is available, but a Jakarta study in 2007 reported a prevalence of DKA in type 1 DM of 76.9%.[5] Based on medical record data in Dr. Sardjito General Hospital, Yogyakarta, the prevalence of DKA during 2014-2016 was 62.5%. Previous studies reported that the risk of DKA increases in children with poor metabolic control, history of DKA at first diagnosis, non-compliance with insulin treatment, infection, peripubertal age, and emotional/psychological problems, including eating disorders.[6,7,8]

Proper treatment of ketoacidosis generally results in good outcomes. The success of DKA management depends on initial identification of its signs and symptoms, especially in correcting dehydration, acidosis, electrolyte imbalance disorder, and hyperglycemia.[9] Diabetic ketoacidosis can be prevented by controlling the risk factors that trigger DKA. Predictors of DKA in a particular region should be identified to determine modifiable factors, in order to prevent DKA and lower its morbidity and mortality. This study aimed to identify characteristics of patients with DKA and predictive factors that affect the occurrence of DKA.

Methods

This study was a retrospective cohort study by examining medical record data at Dr. Sardjito General Hospital, Yogyakarta, from January 2011 - May 2017. The inclusion criteria were patients who had been diagnosed with type 1 DM, aged 0 days to ≤ 20 years, and treated at Dr. Sardjito General Hospital in the study period. Exclusion criteria were incomplete medical record data (i.e., missing two or more variables), overweight or obesity, using drugs that affect blood sugar levels (glucocorticoids, thyroid hormones, diazoxides, thiazides, or dilantin), or normal or high C-peptide level. The dependent variable was the occurrence of DKA. The independent variables were DKA upon diagnosis of type 1 DM, age, compliance to insulin treatment, infection, metabolic control, psychological problems, biological sex, parental education level, and socio-economic level. Compliance with insulin treatment was defined as a patient compliance to use appropriate insulin with recommended dose, not-compliance with insulin treatment was defined as a patient which use insulin not appropriate more than one day from recommended dose. Infection was defined as urinary, digestive, or respiratory tract infection that occurred before DKA, diagnosed from anamnesis, physical and laboratory examination in first 24 hours at hospital. Preschool was defined as 0-8 years of patient age, and peripubertal was 8-20 years of patient age. Parental education level was defined as a last formal educational state of the parental patient that from elementary until junior high school we categorized as low parental educational level, senior high school we categorized as middle parental educational level and diploma, university, magister and doctor we we categorized as high parental educational level. We assest metabolic control based on HbA1c level three month before until three month after DKA. Socio-economic level was graded based on family income; we categorized low socio-economic level if the family income below Rp 1.250.000, middle socio-economic level if the family income Rp 1.250.000 – Rp 5.000.000 , and high socio-economic level if the family income more than Rp 5.000.000.

Data were collected from medical records by filling out questionnaires by the researcher. The relationship between independent variables and the dependent variable was analyzed by bivariate statistical analysis (Chi-square test). From the bivariate analysis, variables with P values <0.25 were further analyzed by multivariative backward logistic regression method. This study was approved by the Medical Ethics Committee at Universitas Gadjah Mada.

Results

There were 57 cases (eligible subjek) of type 1 DM in Dr. Sardjito General Hospital during January 2011-May 2017. The basic characteristics of subjects are shown in **Table 1**.

The occurence of DKA was 65% (37/57). The signs and symptoms included shock (54.1%), nausea and vomiting (89.2%), abdominal pain (73%), Kussmaul breathing (86.5%), and decreased consciousness (59.5%). Mean (SD) laboratory results in the event of DKA were as follows: pH 7.10 (SD 0.12); HCO3 6.71 (SD 5.21) mEq/L; base excess (BE) -21.58 (SD 6.33); corrected sodium 141.51 (SD 8.07) mmol/L; potassium 4.32 (SD 1.07) mmol/L; blood glucose 509.3 (SD 151.6) g/dL, and positive ketonuria 3.4 (SD 0.6) mmol/L. A total of 10 (27%)

Table 1. Basic characteristics of subjects

Characteristics	Total (n=57)
Sex, n (%)	
Female	40 (70.2)
Male	17 (29.8)
Age, n (%)	
Infant to pre-school (0-8 year)	8 (14)
Peripubertal (8-20 year)	49 (86)
Parental education level, n (%)	
Low	24 (42.1)
Middle	17 (29.8)
High	16 (28.1)
Socio-economic level, n (%)	
Low	16 (28.1)
Middle	18 (31.6)
High	23 (40.4)
DKA at the initial diagnosis of type 1 DM, n (%)	
Yes	34 (59.6)
No	23 (40.4)
Mean duration of type 1 DM (SD), years	3.93 (3.00)
Nutritional status, n (%)	
Normal	37 (64.9)
Moderate & severe malnutrition	20 (35.1)
Infection, n (%)	
Yes	31 (54.4)
No	26 (45.6)
Kind of infection, n (%)	
Urinary tract infection	12 (38.7)
Respiratory infection	12 (38.7)
Gastrointestinal infection	4 (12.9)
Sepsis	3 (9.7)
Metabolic control, n (%)	
Poor	51 (89.5)
Moderate	4 (7)
Good	2 (3.4)
Mean HbA1C level (SD), %	11.12 (2.71)
Insulin therapy non-compliance, n (%)	
Yes	13 (22.8)
No	44 (77.2)
Psychological problems, n (%)	
Yes	18 (31.6)
No	32 (51.6)
No data	7 (12.3)
Mortality, n (%)	
Died	5 (8.8)

subjects with DKA required intensive care in the PICU. Mean (SD) length of treatment per episode of DKA was 8.17 (SD 6.21) days. The mortality rate from DKA was 5/37. The outcomes of DKA patients are summarized in **Table 2**.

Bivariate analysis revealed that infected subjects (OR 7.09; 95%CI 2.07 to 24.34; P=0.001) and DKA at the first diagnosis of type 1 DM (OR 7.26; 95%CI 2.15 to 24.49; P=0.01) had significantly different proportions for DKA occurence compared to those who had no infection or had no DKA at the first diagnosis of type 1 DM. The bivariate analysis results are presented in **Table 3**.

Table 2. Subjects' laboratory and clinical profiles as well as DKA outcomes

Clinical and laboratory profiles	Total subjects (n=37)
Clinical symptoms, n	
Shock	20
Nausea-vomiting	33
Abdominal pain	27
Kussmaul breathing	32
Decreased consciousness	22
Laboratory profiles	
Mean pH (SD)	7.10 (0.12)
Mean HCO3 (SD), mEq/L	6.71 (5.21)
Mean base excess (SD)	-21.58 (6.33)
Mean blood glucose level (SD), g/dL	509.3 (151.6)
Mean ketonuria (+) (SD), mmol/L	3.4 (0.6)
Mean corrected sodium (SD), mmol/L	141.51 (8.07)
Mean potassium (SD), mmol/L	4.32 (1.07)
Mean chloride (SD), mmol/L	102.44 (8,63)
Mean hemoglobin (SD), g/dL	13.63 (1.72)
Mean leukocyte count (SD), $x10^3/mm^3$	22.80 (11.92)
Hospitalization in PICU, n	10 (27)
Mean duration of hospitatization per DKA episode, days (SD)	8.17 (6.21)
Severity of DKA, n	
Mild	7
Moderate	10
Severe	20

To analyze the relationships between independent variables (predictors) and DKA, we performed a multivariate analysis. All variables with P value <0.25 from the bivariate analysis were included in the multivariate backward logistic regression analysis. The first step result of analysis is presented in **Table 4**.

Initial stage multivariate analysis revealed that psychological problems, poor metabolic control, insulin non-compliance, and female sex to have P values >0.05, hence, they were eliminated from the next stage of analysis. The previously uneliminated variables were analyzed using logistic regression. Any variable with P >0.05 could be eliminated. Variables that had significant associations with the incidence of DKA were infection (OR 5.23; 95%CI 1.40 to 19.52; P=0.014) and DKA at the initial diagnosis of type 1 DM (OR 5.137; 95%CI 1.47 to 19.68; P=0.011).

Table 3. Bivariate analysis of potential predictors of DKA

Predictors	DKA (n=37)	No DKA (n=20)	OR	95% CI	P value
Sex, n					
Female	28	12	2.07	0.65 to 6.67	0.22
Male	9	8			
DKA at diagnosis of type 1 DM, n					
Yes	28	6	7.26	2.15 to 24.49	0.01
No	9	14			
Peripubertal age, n					
Yes	4	4	2.06	0.46 to 9.33	0.43
No	33	16			
Infection, n					
Yes	26	5	7.09	2.07 to 24.34	0.001
No	11	15			
Metabolic control, n					
Poor	35	16	2.83	0.57 to 14.18	0.23
Moderate + well	2	4			
Psychological problem, n					
Present	14	4	2.17	0.60 to 7.85	0.09
Absent	16	15			
Insulin therapy non-compliance, n					
Yes	11	2	3.81	0.75 to 19.28	0.09
No	26	18			
Socio-economic level, n					
Low	12	4	1.92	0.53 to 7.00	0.31
Moderate + high	25	16			
Parental education status, n					
Low	17	7	1.51	0.51 to 4.86	0.42
Moderate + high	20	13			

Table 4. Multivariate logistic regression analysis

DKA predictors	OR	95% CI	P value
Infection	6.27	1.46 to 26.66	0.01
Psychological problem	1.72	0.31 to 9.43	0.53
Poor metabolic control	2.83	0.42 to 19.06	0.29
Insulin therapy non-compliance	3.98	0.47 to 33.49	0.20
DKA at diagnosis of type 1 DM	4.77	1.19 to 19.14	0.03
Female gender	0.51	0.11 to 2.26	0.37
DKA at the initial diagnosis of type 1 DM*	5.37	1.47 to 19.68	0.011
Infection*	5.23	1.40 to 19.52	0.014

*final result

Discussion

Ketoacidosis is an acute complication of DM, especially type 1 DM, indicating a severe insulin deficiency. In our study, 37 patients (65%) with type 1 DM had DKA, similar to previous studies in other countries.[1] The incidence of DKA in type 1 DM ranges from 13 to 80%, depending on the country and geographic conditions, although this environmental effect is still unclear. The incidence rate of DKA in developing countries is higher than in developed countries.[4] Himawan *et al.*[5] in Jakarta reported that the incidence of DKA in type 1 DM patients was 76.9%, of which 56.7% had only 1 episode of DKA,

13.3% had 2 episodes of DKA, and 30% had 3 or more episodes of DKA. However, Gillani *et al.*[7] *i*n Malaysia reported a DKA incidence of 44.5%,10 while Rewers et al. in Colorado, USA, reported a DKA incidence of 18.6% in type 1 DM patients. The occurence rate in our study was high because Indonesia is a developing country, with lower level of education, socio-economic conditions, and health care facilities than in developed countries.

The symptoms of DKA in our subjects were nausea and vomiting (89.2%), abdominal pain (73%), Kussmaul breathing (86.5%), shock (53.3%), and decreased consciousness (59.5%), similar to previous studies.[11,12] It is important to identify symptoms of DKA to recognize it as early as possible, so patients can be given appropriate treatment immediately to prevent worsening of the condition.[12]

In this study, a DKA diagnosis was established based on blood glucose > 200mg/dL, pH < 7.3, and/or HCO_3 <15 mEq/L and ketonuria.[9] We found that 54.1% of patients had severe DKA, a higher percentage than Hadi *et al.*[13] in Iraq, where 38.23% of patients had severe DKA. The high percentage of severe DKA in Dr. Sardjito General Hospital was probably because it is a central referral hospital, so referral patients tend to have severe cases.

In our study, 5 patients died (8.8%). This mortality rate was higher than in developed countries (0.15%-0.31%), but was relatively similar to that of developing countries (3.4%-13.4%).[1,2] Naveed *et al.*[6] reported that DM mortality caused by DKA in Pakistan was 7.5%. The economic and social burden caused by DKA in our study was considerable. The average length of hospitalization per episode of DKA was 8.17 (SD 6.21) days. Around 27% of DKA patients underwent PICU treatment. Children with severe DKA and children at risk of cerebral edema should be admitted to the intensive care unit.[1]

We found two significant predictive factors for the occurence of DKA in type 1 DM patients, infection and experiencing DKA at the time of initial diagnosis of type 1 DM. The incidence of infection before the occurrence of DKA was 54.4% in our subjects, which was slightly higher than in previous studies in Pakistan (26.19%) and in Iraq (45.58%).[6,13] At the time of infection, the body secretes growth hormone, glucagon, cortisol, and epinephrine, which are counter-regulatory hormones with an anti-insulin effect. Counter-regulatory hormone secretion causes an increase in the production of glucose and ketones, such as acetone and beta-hydroxybutyrate, through gluconeogenesis and glycogenolysis. The accumulation of these ketones triggers DKA.[4] In addition, chronic hyperglycemia leads to decreased immune function, increasing a person's susceptibility to infection.[14] This process occurs continuously in DM patients. If the blood sugar is continuously high, the patient is more susceptible to infection, and the infection will consequently trigger hyperglycemia and ketoacidosis.[14]

In our study, the most common infections were urinary tract infection (UTI) (38.7%) and respiratory infection (38.7%), similar to previous reports. Urinary tract infection is the most frequent infection in DM patients. About 25% of women with DM have asymptomatic UTIs and test positive for bacteria. The most common pathogen is *E. coli.* The increased incidence of UTI is thought to be due to autonomic neuropathy, resulting in decreased detrusor activity, decreased bladder sensation resulting in bladder distention, and increased residual urine and vesicoureteral reflux, leading to recurrent UTIs.[14]

For clinical purposes, portable blood ketone measurements are recommended for outpatients with a high risk of DKA. These high-risk patients can be taught to measure blood ketones following self-measurements of blood glucose. It is recommended to measure blood ketones after self-measurement of blood in the following conditions: blood glucose > 250 mg/dL, presence of DKA-initiating conditions such as infection, and presence of early DKA symptoms such as nausea, vomiting, and abdominal pain.[15]

The limitations of this study were the retrospective design and use of secondary data from medical records, especially where data were incomplete or there was possible information bias. Also, only a few psychological disorders in the medical records were actually confirmed by psychological or psychiatric examinations. Therefore, determination of psychological disorders in the data may have been biased. Some medical records also did not include data regarding the patient's psychological condition. Data on eating disorders also could not be obtained from the medical records. Eating disorders are closely related to psychological disorders and affect blood sugar levels. In addition, data on infection were obtained

from medical record data through history, physical examination, or supporting laboratory tests, but not using gold standard examinations such as culture or polymerase chain reaction (PCR). Furthermore, compliance on insulin use was also merely judged by history or medical records.

In conclusion, 65% of patients with type 1 DM had DKA and the mortality rate was 8.8%. Infection and DKA at the initial diagnosis of type 1 DM are significant predictors of DKA incidence in type 1 DM patients. According to our study, to limit likelihood of DKA, patients with active infection and early DKA symptoms, such as nausea, vomiting, and abdominal pain, measure blood or urine ketones if random blood glucose level exceeds 220 mg/dL.[14]

Conflict of Interest

None declared.

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