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Surabaya, 7 Agustus 2023



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9 November 2021

Dear Editor-in-Chief

Indian Journal of Forensic Medicine & Toxicology

We would like to submit our original research article entitled "***Risk Factors for Diabetic Ketoacidosis in Children with Type 1 Diabetes Mellitus: a Single-center, Cross-sectional Study in Indonesia***" for publication in Indian Journal of Forensic Medicine & Toxicology.

Diabetic ketoacidosis (DKA), the leading cause of mortality in childhood with diabetes mellitus (DM), is the first presentation in some patients. The factors associated with DKA in children can be categorised into individual factors (age, sex, ethnicity, family history of diabetes, body mass index and parental consanguinity), family factors (parental education, family structure, health insurance status, rural versus urban residence, family income, parental employment and social status), physician-related factors (delayed diagnosis, diagnostic error, number of medical consultations before diagnosis, delayed treatment and presence of a structured diabetes care team) and disease-related factors (duration of symptoms, pattern and frequency of symptoms and preceding infection or febrile illness). The aims of this study is to determine risk factors for DKA in children with T1DM.

We hope that this article could be considered for publication in Indian Journal of Forensic Medicine & Toxicology.

Sincerely yours,



Nur Rochmah

Department of Child Health

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1 **Risk Factors for Diabetic Ketoacidosis in Children with Type 1 Diabetes**
2 **Mellitus: a Single-center, Cross-sectional Study in Indonesia**

3
4 **Nur Rochmah^{1,2*}, Muhammad Faizi^{1,2}, Umamah², Anang Endaryanto¹, Soetjipto³**

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17 **Abstract**

18 **Background:** Diabetic ketoacidosis (DKA), the leading cause of mortality in
19 childhood with diabetes mellitus (DM). Identification of risk factors for DKA in children
20 with type 1 DM (T1DM), can aid in reducing the incidence of DKA. **Objective:** To
21 determine risk factors for DKA in children with T1DM. **Methods:** This was a single-
22 centre, cross-sectional study of patients aged 0–16 years diagnosed with T1DM who
23 were hospitalised in or visited Dr. Soetomo General Hospital in Surabaya between
24 January 2016 and June 2021. Data on sex, age, parental educational background,
25 parental occupation, parental age, family history of DM and DKA frequency were
26 collected, and statistical analyses using the SPSS software. **Results:** The risk of
27 DKA was higher in children with working mothers (OR 9.3, 95%; CI 2.168–40.182, p
28 = 0.003). Significant correlation between maternal age younger than 40 years and
29 DKA frequency (OR 1.73, 95%; CI 8.684–3.478, p = 0.000). The highest frequency
30 of DKA was observed in children with low parental educational level, whereas there
31 was no correlation between age at diagnosis and parental educational level with
32 DKA. **Conclusion:** Young maternal age and working mothers might be associated
33 with increased frequency of DKA in children with T1DM.

34

35 **Keywords:** diabetic ketoacidosis; type 1 diabetes mellitus; risk factor; parental age;
36 occupation

37 **Introduction**

38 Approximately 26 per 100,000 children are diagnosed with type 1 diabetes
39 mellitus (T1DM) every year, with the rate continually increasing approximately 4%
40 per year. Despite the increased life expectancy associated with the improvements in
41 diabetes care, the mortality rate remains higher in children with T1DM than in the
42 general population and the leading cause of death is diabetic ketoacidosis (DKA).
43 Globally, the incidence of DKA at presentation varies, ranging from 13% to 80%.¹
44 Children presenting with DKA are at higher risk for life-threatening complications
45 including cerebral oedema, cerebral ischaemia and hypoxic brain injury. These
46 patients are also more likely to require admission to an intensive care unit, which
47 contributes to greater healthcare spending.^{2,3}

48 It is unclear why only some children present with DKA. Furthermore, whether the
49 development of DKA is a consequence of delayed diagnosis and treatment or a
50 reflection of a particularly aggressive form of diabetes remains unknown. Therefore,
51 identification of factors associated with DKA at diagnosis and understanding the
52 relative importance of delayed diagnosis and treatment are important for the
53 advancement of our understanding of DKA and for the development of patient-,
54 professional- and population-based interventions to reduce the rate of children
55 presenting with DKA.⁴

56 The factors associated with DKA in children can be categorised into individual
57 factors (age, sex, ethnicity, family history of diabetes, body mass index and parental
58 consanguinity), family factors (parental education, family structure, health insurance
59 status, rural versus urban residence, family income, parental employment and social
60 status), physician-related factors (delayed diagnosis, diagnostic error, number of
61 medical consultations before diagnosis, delayed treatment and presence of a
62 structured diabetes care team) and disease-related factors (duration of symptoms,
63 pattern and frequency of symptoms and preceding infection or febrile illness).⁵ In a
64 study examining the association of parental educational level with DKA prevalence,
65 Sadauskaite-Kuehne et al. found that the DKA prevalence was higher in Lithuanian
66 children than in Swedish children (21.3% vs. 7.3%, $P < 00001$) and that younger age
67 at the time of diagnosis and low maternal educational level influenced DKA in
68 Lithuanian children.⁶

69 **Materials and methods**

70 This was a cross-sectional study including children diagnosed with T1DM
71 based on the International Society for Pediatric and Adolescent Diabetes guidelines.
72 Patients with T1DM aged 0–16 years who were hospitalised in or visited the
73 Pediatric Endocrinology Outpatient Clinic at Dr. Soetomo General Hospital in
74 Surabaya between January 1, 2016 and June 30, 2021 were included, and patients
75 with incomplete medical records during recruitment were excluded. A total 50
76 patients signed informed consent and joined the study. Data for the study were
77 obtained from the medical records of the Pediatric Endocrinology Outpatient Clinic
78 and from interviews with the parents of inpatients.

79 *Data Analysis*

80 All statistical analyses were performed using SPSS version 21. Univariate
81 analyses were performed to determine frequency of variables, and chi-squared test
82 (Fisher's exact test) was performed to analyse the association between independent
83 and dependent variables. Multivariate logistic regression analysis was performed to
84 analyse risk factors that affect in DKA in children. The results were reported as odd
85 ratios (ORs) with 95% confidence intervals (CIs). A p value of <0.05 was considered
86 to indicate statistical significance.

87 **Results and Discussion**

88 The baseline characteristics of 50 patients with T1DM included in the study
 89 are summarised in Table 1. Briefly, the male/female ratio was 1:1.5, 32 patients
 90 experienced at least one DKA episode, and 6 patients experienced DKA more than
 91 once.

92

93 **Table 1. Baseline characteristics of the patients with T1DM included in the**
 94 **study**

Variable	N = 50	95
Sex		96
Female	30	97
Male	20	98
Family history of DM		99
Yes	4	100
No	46	101
DKA		102
Yes	32	103
Never	18	104
Sex of patients experiencing DKA		105
Female	14	106
Male	18	107
Socioeconomic status		108
Low	10	109
Moderate	40	110
Maternal occupation		111
Working	25	112
Nonworking	25	113
DKA frequency		114
Once	26	115
More than once	6	116
Parent age (years)		117
- Father		118
20–40	22	119
40–60	27	120
>60	1	121
- Mother		122
20–40	33	123
40–60	17	124
>60	0	125
Parental educational level		126
- Father		127
Elementary school	9	128
Junior high school	6	129
Senior high school	26	130
Academic	9	131
- Mother		132
Elementary	10	133
Junior high school	10	134
Senior high school	22	135
Academic	8	136

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Bivariate analysis revealed that there was an association between working mothers and DKA (OR 9.33, 95% CI 2.168– to 40.182, $p = 0.003$), indicating an increased DKA risk among children with working mothers.

Multivariate analysis revealed significant correlation between maternal age below 40 years and DKA frequency (OR 1.73, 95% CI 8.684–3.478, $p = 0.000$). The highest DKA frequency was among the patients with low parental educational level. However, there was no statistically significant correlation between parental educational level and DKA.

The present study, which aimed to provide updated information on potential factors associated with the development of DKA, revealed a number of key findings: parental occupation, sex, family history of DM, DKA frequency, socioeconomic status and parental educational level.

First, we found that parental occupation was association with the risk of DKA in children with T1DM. Specifically, children with working mothers were at higher risk of DKA. The signs and symptoms suggesting DKA might have been recognised earlier in the children with nonworking mothers included in the study. Two studies examined the effect of parental employment on the frequency of DKA. A study in Sweden found that the risk of DKA was higher in children with nonworking mothers (OR 4.8, 95% CI 1.8–13.1), whereas another study in Lithuania reported that the paternal employment status did not have an effect on the rate of DKA (OR 1.17, 95% CI 0.53–2.57).⁴

In the present study, the educational level was senior high school in majority of the fathers and mothers of the children who experienced DKA (52% and 44%, respectively). Several studies reported that higher parental educational level was a protective factor in DKA.^{6,7,8} As suggested in other studies, better parental educational level may aid in the improvement of metabolic regulation in children with T1DM.^{9,10}

The current study cohort was predominantly composed of female children with T1DM, whereas DKA developed predominantly in male children, with a male/female ratio of 1.3:1. A systematic review of 21 studies revealed that sex did not have an effect on the frequency of DKA in 20 studies and that only one study including 2121 subjects reported a small, albeit statistically significant, increase in the frequency of DKA in female patients (OR 1.30, 95% CI 1.07–1.58, $p = 0.0079$).⁴

In the current study, only four patients had a family history of type 2 DM and none of the patients had a family history of T1DM. Azab et al. stated that a positive family history of T1DM was associated with increased T1DM risk among relatives.¹¹ These results are in contrast with the study by Roche et al. who described the abrupt onset of T1DM and the absence of family history.¹²

Numerous studies demonstrated that younger age was associated with increased DKA risk at onset. In some studies, most of the patients with newly diagnosed T1DM and DKA were younger than two years of age,¹³ which may be due to the lower efficacy to control metabolic deterioration and/or low speech ability in expressing issues in younger children.⁷ In contrast, only 6 (12%) patients with T1DM who were 5 years of age or younger experienced DKA.

One major study limitation of the present study is the small sample size because of the lower rates of T1DM in Asian populations compared with Caucasian populations; therefore, the current study findings might not be representative of other populations.

187 **Conclusion**

188 The present single-center, cross-sectional study in Indonesia has identified
189 several factors associated with DKA in children with T1DM, which might be
190 considered as important targets to reduce the incidence of DKA at diagnosis in
191 Indonesia, especially East Java. The risk of DKA was influenced by local culture.
192 Young and poor children were disproportionately affected, although DKA occurred
193 even in children from affluent and well-educated families.

194 Increased public awareness and greater medical alertness concerning the
195 symptoms and signs of DKA are warranted. Additionally, improved access to care
196 may additionally reduce the severity and cost of initial T1DM treatment in children.
197

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200 endocrine teams of Dr. Soetomo General Hospital in Surabaya, Indonesia, for their
201 support of the study.

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Round 1

Round 2

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Notifications

[IJFMT] Editor Decision	2021-11-23 02:15 AM
[IJFMT] Editor Decision	2021-12-15 04:23 AM

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Round 1

Round 2

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Submission accepted.

Notifications

[IJFMT] Editor Decision	2021-11-23 02:15 AM
[IJFMT] Editor Decision	2021-12-15 04:23 AM

Nur Rochmah, Muhammad Faizi, Umamah, Anang Endaryanto, Soetjipto:

We have reached a decision regarding your submission to Indian Journal of Forensic Medicine & Toxicology, "Risk Factors for Diabetic Ketoacidosis in Children with Type 1 Diabetes Mellitus: a Single-center, Cross-sectional Study in Indonesia ".

Our decision is to: Accept Submission

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Risk Factors for Diabetic Ketoacidosis in Children with Type 1 Diabetes Mellitus: a Single-center, Cross-sectional Study in Indonesia

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Abstract

Background: Diabetic ketoacidosis (DKA), the leading cause of mortality in childhood with diabetes mellitus (DM). Identification of risk factors for DKA in children with type 1 DM (T1DM), can aid in reducing the incidence of DKA. **Objective:** To determine risk factors for DKA in children with T1DM. **Methods:** This was a single-centre, cross-sectional study of patients aged 0–16 years diagnosed with T1DM who were hospitalised in or visited Dr. Soetomo General Hospital in Surabaya between January 2016 and June 2021. Data on sex, age, parental educational background, parental occupation, parental age, family history of DM and DKA frequency were collected, and statistical analyses using the SPSS software. **Results:** The risk of DKA was higher in children with working mothers (OR 9.3, 95%; CI 2.168–40.182, $p = 0.003$). Significant correlation between maternal age younger than 40 years and DKA frequency (OR 1.73, 95%; CI 8.684–3.478, $p = 0.000$). The highest frequency of DKA was observed in children with low parental educational level, whereas there was no correlation between age at diagnosis and parental educational level with DKA. **Conclusion:** Young maternal age and working mothers might be associated with increased frequency of DKA in children with T1DM.

Keywords: diabetic ketoacidosis; type 1 diabetes mellitus; risk factor; parental age; occupation

Introduction

Approximately 26 per 100,000 children are diagnosed with type 1 diabetes mellitus (T1DM) every year, with the rate continually increasing approximately 4% per year. Despite the increased life expectancy associated with the improvements in diabetes care, the mortality rate remains higher in children with T1DM than in the general population and the leading cause of death is diabetic ketoacidosis (DKA). Globally, the incidence of DKA at presentation varies, ranging from 13% to 80%.¹ Children presenting with DKA are at higher risk for life-threatening complications including cerebral oedema, cerebral ischaemia and hypoxic brain injury. These patients are also more likely to require admission to an intensive care unit, which contributes to greater healthcare spending.^{2,3}

It is unclear why only some children present with DKA. Furthermore, whether the development of DKA is a consequence of delayed diagnosis and treatment or a reflection of a particularly aggressive form of diabetes remains unknown. Therefore, identification of factors associated with DKA at diagnosis and understanding the relative importance of delayed diagnosis and treatment are important for the advancement of our understanding of DKA and for the development of patient-, professional- and population-based interventions to reduce the rate of children presenting with DKA.⁴

The factors associated with DKA in children can be categorised into individual factors (age, sex, ethnicity, family history of diabetes, body mass index and parental consanguinity), family factors (parental education, family structure, health insurance status, rural versus urban residence, family income, parental employment and social status), physician-related factors (delayed diagnosis, diagnostic error, number of medical consultations before diagnosis, delayed treatment and presence of a structured diabetes care team) and disease-related factors (duration of symptoms, pattern and frequency of symptoms and preceding infection or febrile illness).⁵ In a study examining the association of parental educational level with DKA prevalence, Sadauskaite-Kuehne et al. found that the DKA prevalence was higher in Lithuanian children than in Swedish children (21.3% vs. 7.3%, $P < 00001$) and that younger age at the time of diagnosis and low maternal educational level influenced DKA in Lithuanian children.⁶

Materials and methods

This was a cross-sectional study including children diagnosed with T1DM based on the International Society for Pediatric and Adolescent Diabetes guidelines. Patients with T1DM aged 0–16 years who were hospitalised in or visited the Pediatric Endocrinology Outpatient Clinic at Dr. Soetomo General Hospital in Surabaya between January 1, 2016 and June 30, 2021 were included, and patients with incomplete medical records during recruitment were excluded. A total 50 patients signed informed consent and joined the study. Data for the study were obtained from the medical records of the Pediatric Endocrinology Outpatient Clinic and from interviews with the parents of inpatients.

Data Analysis

All statistical analyses were performed using SPSS version 21. Univariate analyses were performed to determine frequency of variables, and chi-squared test (Fisher's exact test) was performed to analyse the association between independent and dependent variables. Multivariate logistic regression analysis was performed to analyse risk factors that affect in DKA in children. The results were reported as odd ratios (ORs) with 95% confidence intervals (CIs). A p value of <0.05 was considered to indicate statistical significance.

Results and Discussion

The baseline characteristics of 50 patients with T1DM included in the study are summarised in Table 1. Briefly, the male/female ratio was 1:1.5, 32 patients experienced at least one DKA episode, and 6 patients experienced DKA more than once.

Table 1. Baseline characteristics of the patients with T1DM included in the study

Variable	N = 50
Sex	
Female	30
Male	20
Family history of DM	
Yes	4
No	46
DKA	
Yes	32
Never	18
Sex of patients experiencing DKA	
Female	14
Male	18
Socioeconomic status	
Low	10
Moderate	40
Maternal occupation	
Working	25
Nonworking	25
DKA frequency	
Once	26
More than once	6
Parent age (years)	
- Father	
20–40	22
40–60	27
>60	1
- Mother	
20–40	33
40–60	17
>60	0
Parental educational level	
- Father	
Elementary school	9
Junior high school	6
Senior high school	26
Academic	9
- Mother	
Elementary	10
Junior high school	10
Senior high school	22
Academic	8

Bivariate analysis revealed that there was an association between working mothers and DKA (OR 9.33, 95% CI 2.168– to 40.182, $p = 0.003$), indicating an increased DKA risk among children with working mothers.

Multivariate analysis revealed significant correlation between maternal age below 40 years and DKA frequency (OR 1.73, 95% CI 8.684–3.478, $p = 0.000$). The highest DKA frequency was among the patients with low parental educational level. However, there was no statistically significant correlation between parental educational level and DKA.

The present study, which aimed to provide updated information on potential factors associated with the development of DKA, revealed a number of key findings: parental occupation, sex, family history of DM, DKA frequency, socioeconomic status and parental educational level.

First, we found that parental occupation was association with the risk of DKA in children with T1DM. Specifically, children with working mothers were at higher risk of DKA. The signs and symptoms suggesting DKA might have been recognised earlier in the children with nonworking mothers included in the study. Two studies examined the effect of parental employment on the frequency of DKA. A study in Sweden found that the risk of DKA was higher in children with nonworking mothers (OR 4.8, 95% CI 1.8–13.1), whereas another study in Lithuania reported that the paternal employment status did not have an effect on the rate of DKA (OR 1.17, 95% CI 0.53–2.57).⁴

In the present study, the educational level was senior high school in majority of the fathers and mothers of the children who experienced DKA (52% and 44%, respectively). Several studies reported that higher parental educational level was a protective factor in DKA.^{6,7,8} As suggested in other studies, better parental educational level may aid in the improvement of metabolic regulation in children with T1DM.^{9,10}

The current study cohort was predominantly composed of female children with T1DM, whereas DKA developed predominantly in male children, with a male/female ratio of 1.3:1. A systematic review of 21 studies revealed that sex did not have an effect on the frequency of DKA in 20 studies and that only one study including 2121 subjects reported a small, albeit statistically significant, increase in the frequency of DKA in female patients (OR 1.30, 95% CI 1.07–1.58, $p = 0.0079$).⁴

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Numerous studies demonstrated that younger age was associated with increased DKA risk at onset. In some studies, most of the patients with newly diagnosed T1DM and DKA were younger than two years of age,¹³ which may be due to the lower efficacy to control metabolic deterioration and/or low speech ability in expressing issues in younger children.⁷ In contrast, only 6 (12%) patients with T1DM who were 5 years of age or younger experienced DKA.

One major study limitation of the present study is the small sample size because of the lower rates of T1DM in Asian populations compared with Caucasian populations; therefore, the current study findings might not be representative of other populations.

Conclusion

The present single-center, cross-sectional study in Indonesia has identified several factors associated with DKA in children with T1DM, which might be considered as important targets to reduce the incidence of DKA at diagnosis in Indonesia, especially East Java. The risk of DKA was influenced by local culture. Young and poor children were disproportionately affected, although DKA occurred even in children from affluent and well-educated families.

Increased public awareness and greater medical alertness concerning the symptoms and signs of DKA are warranted. Additionally, improved access to care may additionally reduce the severity and cost of initial T1DM treatment in children.

Acknowledgements

The authors would like to thank the patients who participated in the study and the endocrine teams of Dr. Soetomo General Hospital in Surabaya, Indonesia.

Ethical clearance

We sought approval of this research from the Clinical Research Unit of Dr. Soetomo General Hospital Surabaya, Indonesia, as our Ethical Committee Review Board. The ethical clearance was issued by the Clinical Research Unit of Dr. Soetomo General Hospital Surabaya (number 1023/KEPK/III/ 2019).

Source for funding

This study was funded by the authors' personal fund. No other parties are involved in financing this research.

Conflict of Interest

The author reports no conflict of interest in this work

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