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Characteristics of Type 2 Diabetes Mellitus Patients With Diabetic Ketoacidosis: A Study in A National Referral Hospital in Indonesia

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Abstract

Background: Diabetic ketoacidosis (DKA) is one of the acute complication of diabetes mellitus (DM) with high mortality and morbidity rates. Research data regarding the characteristics of patients with type 2 diabetes mellitus (T2DM) with and without DKA are not yet widely available. Therefore, further research is needed to minimize the annual morbidity and mortality rate and prevent complications at the earliest possible moment. This study was carried out to determine the differences in the characteristics of T2DM patients with and without DKA in Dr. M. Djamil Central General Hospital Padang period 1st January 2018 to 31st December 2020.
Methods: This study used a comparative analytic study with a cross-sectional approach using the medical records of T2DM patients with and without DKA in Dr. M. Djamil Central General Hospital Padang period 1st January to 31st December 2020 with total sampling. Data analysis calculated by chi-square test, unpaired T-test, and Mann-Whitney test.
Results: Most of T2DM patients with DKA were aged ≥ 40 years (62.1%), female (65.5%), secondary level of education (72.4%), DM diagnosis duration was ≤ 5 years (75.9%), had infection precipitating factors (65.5%), on insulin (58.6%), Body Mass Index (BMI) in overweight-obese criteria (55%), fasting blood glucose (FBG) < 250 mg/dl (62.1%), and post-prandial glucose (PPG) 250-600 mg/dl (51.7%). This study found that the association of age, DM diagnosis duration, precipitating factors, medication use, and PPG with DKA in T2DM patients ($p<0.05$).
Conclusion: This study confirmed significant differences in age, DM diagnosis duration, precipitation factors, type of antidiabetic therapy, and PPG between T2DM patients with and without DKA in Dr. M. Djamil Central General Hospital Padang.

Keywords: diabetic ketoacidosis, patient characteristics, type 2 diabetes mellitus.

Introduction

Diabetes is undoubtedly one of the most challenging health problems in this era. Diabetes mellitus (DM) is a chronic metabolic disorder that occurs when blood glucose rises persistently due to the body's inability to produce adequate insulin, no insulin at all, or ineffective use of insulin that the body has produced. The incidence of diabetes continues to increase every year. Based on International Diabetes Federation (IDF) estimates, 425 million people in the world had diabetes in 2017, and increased to 463 million people in 2019. This number is predicted to increase up to 578 million people by 2030.[1]

Type 2 diabetes mellitus (T2DM) accounting for around 90% of all diabetes worldwide.[1] Uncontrolled blood glucose levels in T2DM patients increase the risk of complications, both acute and chronic complications. Chronic complications include microvascular and macrovascular damage, while acute complications include hypoglycemia, non-ketotic hyperosmolar hyperglycemia, and diabetic ketoacidosis (DKA). DKA is one of a

frequent and life-threatening acute complications of diabetes, with the triad of hyperglycemia, metabolic acidosis, and ketosis. Although DKA is globally more common in patients with type 1 diabetes mellitus (T1DM), T2DM patients are also susceptible to DKA. Complications pose significant problems to quality of life and increase mortality and morbidity rates.[2]

Although the incidence of DKA in T2DM may be less, but since prevalence of T2DM exceeds T1DM, DKA is thus more or less observed equally in both arms.[3] T2DM patients with DKA predominantly with severe DKA with worse outcomes and higher mortality compared to T1DM.[4] Based on reviewed, we found that studies about DKA especially in Indonesia were not yet widely available or still rarely studied.[5] More studies is needed in order to know valuable information about ketoacidosis. This information will help in increasing the knowledge and understanding of various factors related to DKA and help in differentiating the various characteristics of both T2DM patients with and without DKA. Hopefully, DKA morbidity and mortality rate each year can be minimized and complications can be prevented at the earliest possible moment.

Methods

Study Design

This study was a retrospective study with a cross-sectional approach using secondary data of the patients from medical records that was obtained from the Medical Records Installation of Dr. M. Djamil Central General Hospital in Padang.

Study Population

The population in this study were all T2DM patients recorded in medical records period 1st January 2018 to 31st December 2020 and the sample were all population who met the inclusion and exclusion criteria. The inclusion criteria for this study were all T2DM patients with and without DKA who had complete medical record data including age, gender, education level, DM diagnosis duration, precipitating factors, Body Mass Index (BMI), medication use, fasting blood glucose (FBG), and post-prandial blood glucose (PPG). The independent variables consist of nine variables: Age (<40 y; ≥ 40 y),[6] sex (male; female),[5] education level (primary, elementary school or below; secondary, junior or senior high school; tertiary, university or equivalent),[7] DM diagnosis duration (≤ 5 y, 6-10 y, >10 y),[7,8] precipitation factors (infection; non-infection; infection and non-infection; unknown),[5] BMI (underweight; normal; overweight; obese),[9] medication use (without medication; oral antihyperglycemia (OAH); OAH+insulin; insulin). In fasting blood glucose (FBG) and post-prandial blood glucose (PPG) variables we categorized the blood glucose range into <250 mg/dL, 250-600 mg/dL, and >600 mg/dl.[5] The dependent variables consist of two variables: T2DM with DKA and without DKA. Patients with incomplete data in the medical records or the writing of the required data could not be read were excluded from the study. The sampling method in this study was total sampling with 65 patients in total who met the inclusion and exclusion criteria.

Statistical Analysis

Patients data was reviewed retrospectively. Data was analyzed by using SPSS. Univariate analysis was performed to describe each variable in this study presented in the form of a frequency distribution table. Bivariate analysis was performed to see if there were differences in the characteristics of patients with and without DKA. In this study, chi-square test was used to compare the categorical variables between T2DM patients with and without DKA. We omitted the classification for primary-secondary schools level of education, infection-unknown precipitating factors, and OAH-OAH+insulin of medication use to identified low level of education, infection precipitating factors, and patients without medication use. P-value less than 0.05, was considered as statistically significant. In fasting blood glucose and post-prandial blood glucose variables, normality test was performed with Kolmogorov-Smirnov test. Data were normally distributed if the p-value > 0.05. Furthermore, if normally distributed, data were analyzed using unpaired T-test. However, if not normally distributed, the Mann-Whitney test was performed. If the p-value less than 0.05, there was a significant difference between fasting blood glucose and post prandial glucose of patients with and without DKA.

Ethical Clearance

The protocol of this study was approved by the Institutional Review Board of Dr. M. Djamil Central General Hospital (No. LB.02.02/5.7/02/2022).

Results

The results of the study are presented in table 1 and 2. In this study, we found that T2DM patients with DKA mostly aged ≥ 40 years, female, secondary level of education, DM diagnosis duration ≤ 5 years, mostly with precipitating factors of infection and using insulin, and the majority of patients were with underweight-obesity BMI criteria. The fasting blood glucose of T2DM patients with DKA were mostly <250 mg/dl, while the post-prandial blood glucose mostly in the range of 250-600 mg/dl.

In the group of T2DM patients without DKA, there were also mostly aged ≥ 40 years, female gender, secondary level of education, DM diagnosis duration ≤ 5 years, but most of the precipitating factors were not found in the medical record or unknown. The majority of T2DM patients without DKA were also taking insulin with the majority of BMI also in the underweight-obesity category. Fasting blood glucose and post-prandial blood glucose in T2DM patients without DKA were mostly < 250 mg/dl.

This study showed that T2DM patients aged < 40 years were more likely to have DKA (84.65%) than those without DKA (15.4%). Meanwhile, T2DM patients aged ≥ 40 years were mostly in the group of patients without DKA (65.4%) compared to those with DKA (34.6%). DKA were mostly diagnosed with DM less than 5 years. Meanwhile, the majority of patients who did not have DKA had been diagnosed with DM for 6-10 years or more than 10 years. In this study, infection was the common precipitating factor in T2DM patients with DKA than patients without DKA. The combination of infectious and non-infectious precipitating factors was also more common in T2DM patients with DKA. In both subject groups showed that 90% of subjects who had not received diabetes treatment had DKA. The majority of T2DM patients with DKA in this study were used insulin, and the rest used oral antihyperglycemic (OAH) alone or a combination of OAH and insulin (20%). Study on the post-prandial glucose (PPG) showed that the median of PPG in T2DM patients with DKA was also higher. PPG's data were not normally distributed. There was a statistically significant difference in the variable of age, DM diagnosis duration, precipitation factors, medication use, and PPG in the two subject groups (p<0.05).

Table 1. Differences in Characteristics of T2DM Patients With and Without DKA

Variables		Complication Status				p-value
		With DKA		Without DKA		
		n	%	n	%	
Age	< 40 years	11	84.6%	2	15.4%	0.003
	≥ 40 years	18	34.6%	34	65.4%	
Sex	Male	10	50%	10	50%	0.755
	Female	19	42.2%	26	57.8%	
Education Level	Primary-secondary	22	44.0%	28	56%	1.000
	Tertiary	7	46.7%	8	53.3%	
DM Diagnosis Duration	≤ 5 years	15	65.2%	8	34,8%	0.039
	6-10 years	6	28.6%	15	71.4%	
	>10 years	8	38.1%	13	61.9%	
Precipitation Factors	Infection	19	57.6%	14	42.4%	0.005
	Infection and non-infection	7	77.8%	2	22.2%	
	Unknown	3	13%	20	87%	
BMI	Underweight	6	66.7%	3	33.3%	0.497
	Normal	7	36.8%	12	63.2%	
	Overweight-obese	16	43.2%	21	56.8%	
Medication Use	Without medication	9	90%	1	10%	0.002
	OAH-OAH+insulin	3	20%	12	80%	
	Insulin	17	42.5%	23	57%	

Based on gender variable, this study showed that 50% of male patients had DKA and 50% without DKA. Meanwhile, in female, 42.2% with DKA and 57.8% without DKA. The study on education level variables showed that 56% of patients with primary-secondary education level did not experience DKA and 44% with DKA. Meanwhile, 53.3% of patients with tertiary education did not experience DKA and 46.7% with DKA. We found that most T2DM patients with DKA were overweight-obese (55%). The results of the mean fasting blood glucose (FBG) of T2DM patients with DKA was higher than patients without DKA. Previously, Kolmogorov-Smirnov normality test was conducted and the data were normally distributed. There was no significant difference between the gender, education levels, BMI, and FBG of T2DM patients with and without DKA ($p>0.05$).

Table 2. Differences in Fasting Blood Glucose (FDG) and Post-Prandial Glucose (PPG) of T2DM Patients With and Without DKA

Variables	T2DM with DKA	T2DM without DKA	p-value
FBG (mg/dl) Mean ±SD	231.76 ±119.58	189.94 ±74.289	0.089
PPG (mg/dl) Median (Min-Max)	275(116-662)	220(116-662)	0.034

Discussions

As highlighted earlier the aim of this study was to compared the characteristics between T2DM patients with and without DKA. In our study, T2DM patients aged < 40 years tend to experienced DKA (84.6%). However, both T2DM patients with and without DKA mostly aged ≥ 40 years. It might caused by the samples of this study were T2DM patients which mostly diagnosed at aged > 40 years, while type 1 diabetes mellitus (T1DM) is usually diagnosed at young age. Prevalence of T2DM was also exceeds T1DM.[5] A study showed that among T2DM patients, incidence rates of DKA were low up to an age of 40 years and rose in adults aged 60-90 years. The risk for DKA steadily increased with age.[4] In addition, T2DM patients with aged < 40 years in this study might be T1DM or atypical DM which most likely to experienced DKA.[5]

The aging process reduced the ability of pancreatic beta cells to release insulin, thus increasing the risk of T2DM. In addition, in old age there are also more stressful conditions in the body such as infection, inflammation, intoxication, infarction, and iatrogenic.[10] Stressful conditions in T2DM patients can be as a precipitating factor for DKA. Stress in the body increases counter-regulatory hormones such as cortisol, growth hormone, glucagon, and catecholamines. Increased levels of these hormones can interfere with glucose metabolism and can increase lipolysis and the production of ketone bodies.[11] Furthermore, the compliance to treatment in old age is also decreasing which also as a precipitating factor for DKA.[12]

This study found that the majority of T2DM patients with and without DKA were female. This was similar with previous studies.[7,13,14] In contrast, a study showed that in T2DM patients there was an increase in DKA cases among elderly male patients. The study concluded that in adolescence, females were predominantly prone to develop DKA, however in adults there was a switch towards higher rates in males.[4] A study explained that majority T2DM patients were female because they more prone to obesity due to a higher proportion of body fat than male.[15] Obesity triggers and increase in lipolysis in adipose tissue so that a lot of acetyl Co-A will be produced. There will be a shift to another metabolic pathway if acetyl Co-A can not be compensated by the Krebs cycle, namely ketogenesis. Ketones are acidic which can cause acidosis. The occurrence of ketosis, acidosis, and hyperglycemia can causes the clinical manifestations of DKA.[11]

In this study, there was no significant difference between the education levels of T2DM patiens with and without DKA. There was a study that showed education levels can affect patient compliance with the therapy. Low compliance are at risk of developing DKA.[16] Previous study found that low levels of education and socioeconomic status were associated with the incidence of DKA in patients with DM.[7]

Most T2DM patients with DKA were diagnosed with DM less than 5 years. Based on the theory, DKA can occur in T2DM patients due to insulopenia caused by beta cell dysfunction over a long period of time.[11] This study result were different from the theory. This can be caused by many factors, for example, patients who were included in the study were diagnosed with diabetes when they had already experienced DKA or there was a diagnostic delay. The duration of DM diagnosis does not indicate how long the patient has DM because the onset of DM can occur years before the diagnosis. Patients diagnosed with DM ≤ 5 years in this study could have been suffering from diabetes for a long time and were recognized with DM within the last 5 years.

The majority of T2DM patents with DKA in this study had infection as the precipitating factors. This results are the same as the study conducted at Dr. Soetomo Hospital in Surabaya which showed that 88.9% of DM patients with DKA having infection.[5] Research conducted by Shahid *et al* in 2020 showed similar results. Most common precipitating factor in DKA patients in the study was infection (69%).[17] Another study showed that the most common precipitating factors for DKA are related to insulin noncompliance an comorbidities.[14] The precipitating factor of DKA causes an increase in the body's need for insulin, while T2DM patients experience insulin deficiency due to beta cell dysfunction. Insulin deficiency stimulates an increase in the levels of counter-regulatory hormones which in turn can trigger the occurrence of DKA.[18]

This study found that the majority of T2DM patients with DKA were overweight-obesity (55%) so did in patients without DKA (58,3%). This was similar with previous studies.[8,10] Research conducted by Frankie B from the endocrinology division of University of Tennessee in the USA found that lean DKA patients exhibited as much of an increase in cardiovascular risk markers, oxidative stress, counter-regulatory hormones, and cytokines as obese ketoacidotic patients. The only exception to this statement was the level of TNF-α which was significantly greater in obese DKA than either lean DKA. Although TNF-α values exhibited high correlation with BMI ($r=0.81$, $p < 0.05$).[19] Obesity contributes to increased beta cell destruction.[20] The higher the BMI of DM patients, the higher the risk of developing DKA. DKA patients with obesity require longer hospitalization time. The group of T2DM patients with DKA tends to be overweight.[21]

In this study, most T2DM patients who did not receive diabetes treatment experienced DKA (90%). A study reported that DKA can be caused when patients forget or knowingly do not take diabetic medications.[8] Another study concluded that higher frequency of DKA was associated with discontinuation and/or inadequate dose of diabetic medication.[7] T2DM patients who have not received treatment or non-compliance in taking DM medication are at risk of developing DKA due to insulin deficiency. Insulin deficiency causes less glucose to enter the cells, resulting in less ATP being produced. The body tries to find alternative energy resources, fat and lipolysis will be increased. Triglycerides in adipose tissue will be broken down into free fatty acids and glycerol. Fatty acids will undergo beta oxidation into acetyl Co-A which will enter the Krebs cycle for ATP production. However, if there is too much acetyl Co-A, there will be a shift to another metabolic pathway, namely ketogenesis. Acetyl Co-A will be condensed with the help of the thiolase enzyme into acetoacetyl Co-A. Then it will undergo condensation again with acetyl Co-A with the help of HMG Co-A synthase into HMG Co-A which furthermore will be processed into ketone bodies. Ketone bodies enter the circulation cause ketosis and acidosis. T2DM patients experience hyperglycemia. Thus, there is a triad of DKA namely ketosis, acidosis, and hyperglycemia.[11,22]

This study found that the mean of FBG and median of PPG were higher in T2DM patients with DKA. Hyperglycemia causes pro-inflammatory status and proved by the increase in oxidative stress markers and pro-inflammatory cytokines which can inhibit insulit signalling and increases the incidence of lipolysis which can lead to DKA.[19] Several studies demonstrated that acute post-prandial hyperglycemia induces increased oxidative stress due to the production of more ROS.[23]

This study has several limitations. First, our study was used paper-based medical records with disadvantages including poor handwriting and the potential for incomplete data. Hence, several patients were excluded and causes the sample was reduced. Second, we cannot exclude risk of misclassification since administrative data were used in our analyses and we were not able to validate the diagnoses, thus it is possible that patients with atypical diabetes mellitus may have been misclassified. Third, the sample of T2DM patients without DKA was much more than patients without DKA in this study. We recommend to use the same amount in both groups or

larger amount of samples for the next similar studies. Expanding study in the future is highly recommended and might help explore different trends.

There were several strength of this study. First, the study of DKA in T2DM patients were not widely available, most study about DKA were in T1DM patients. This study will give the information and supporting the policy for DKA in T2DM patients. Second, the results highlight the need for further studies especially on national incidences of DKA.

Conclusions

DKA appears to be life-threatening that can occur at all ages and caused by many factors such as non-compliance in medication use, under infection or stress condition, etc. Infections in diabetic patients should be carefully monitored as they are most common precipitating factors of DKA. More attention and prevention strategies are needed to narrowing down the incidence rates of DKA.

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Conflict of Interest

There was no conflict of interest in this study.

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