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Determining Factors of Mortality by Ketoacidosis as Seen in the Unit of Endocrinology at Joseph Raseta Befelatanana Teaching Hospital, Antananarivo-Madagascar

Thierry Razanamparany[1, 2, *], Sitraka Angelo Raharinavalona[1], Haritsiky Robertini Ramalanjaona[1], Rija Eric Raherison[1, 2], Miora Maeva Arielle Andrianiaina[1, 2], Tsikinirina Valisoa Randrianomanana[1, 2], Fenitrasoa Randrianarizao[2], Andrianirina Dave Patrick Rakotomalala[1, 2], Hanta Marie Danielle Vololontiana[1], Radonirina Lazasoa Andrianasolo[1, 2]

[1]Faculty of Medicine, University of Antananarivo, Antananarivo, Madagascar

[2]Unit of Endocrinology, Joseph Raseta Befelatanana Teaching Hospital, Antananarivo, Madagascar

Email address:

thierryrazanamparany@gmail.com (T. Razanamparany)

[*]Corresponding author

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Abstract: *Introduction*: Ketoacidosis is one of the acute metabolic complications of diabetes. It is more common and has a higher death rate in sub-Saharan Africa. To our knowledge, there are very few studies done on diabetic ketoacidosis in Madagascar. The aim of our study was to determine the hospital prevalence of diabetic ketoacidosis, to describe their epidemioclinical features as well as to look for determinants of hospital mortality in patients with ketoacidosis in the unit of endocrinology at Joseph Raseta Befelatanana University Hospital, Antananarivo. *Methods*: This is a descriptive retrospective study of diabetics admitted to this unit for ketoacidosis, over a period of 15 months (from January 1, 2017, to March 30, 2018). *Results*: Sixty-four patients were selected for the study. The hospital prevalence of ketoacidosis was 5.61%. The mean age of the patients was 46.3 years with a sex ratio of 0.94. Type 2 diabetes predominated in terms of frequency (62.5%). In 37.5% of cases, ketoacidosis was the inaugural diabetes. For patients known to be diabetic before admission, infection was the most common etiologic factor (48.44%), followed by discontinuation of treatment (31.25%). The death rate was 3.13%. Epidemioclinical variables: age [50-60 years], disturbance of consciousness, Glasgow scale < 10 as well as paraclinical variables: glycemia > 500 mg/dl, hyperkalaemia and ketonuria at 4+ at entry are determinants of mortality. *Conclusion*: Ketoacidosis exposes people to mortality, the rate of which is not negligible. There are determinants of hospital mortality from this complication of diabetes. The therapeutic education of patients and the improvement of screening tools are very important for prevention.

Keywords: Diabetes Mellitus, Ketoacidosis, Madagascar, Mortality

1. Introduction

Diabetes mellitus is a multifactorial and complex chronic disease affecting a large fraction of the worldwide population [1]. It constitutes a major public health problem, given its increasing prevalence, the frequency, and the severity of its acute and chronic complications [2].

Ketoacidosis is one of the acute metabolic complications of diabetes mellitus. It is defined by capillary ketonemia greater than 0.5 mmol/L and frank ketonuria, associated with

high anion gap metabolic acidosis and blood glucose greater than 250 mg/dl. It occurs mainly in type 1 diabetics, but also in type 2 diabetics, especially in black Africans [3]. Its incidence is estimated to be between 4.6 and 8 episodes per 1000 worldwide patients [4]. In addition, it represents approximately 4 to 9% of the causes of hospitalization of diabetics [5]. The prognosis can be severe with an estimated mortality rate of 5% [6].

In sub-Saharan Africa, epidemiological studies show that the frequency of diabetic ketoacidosis (DK) is higher, varying from 12.4 to 25.5%, with a higher mortality rate varying from 29.8 to 40% [7]. In the case of Madagascar, few data is available on this subject, hence the conduct of this study, which aimed to determine the prevalence of DK in hospitalized diabetics, to describe their clinical features as well as to search for determining factors of hospital mortality in these patients.

2. Methods

Our study was carried out at the Unit of Endocrinology of Joseph Raseta Befelatanana Teaching Hospital of Antananarivo. This is a descriptive retrospective study, extending from January 1, 2017, to March 30, 2018, or lasting fifteen (15) months. Were included all diabetics admitted to the unit for ketoacidosis whose diagnostic criteria that we have retained are the following: a glycemia greater than or equal to 250 mg/dL (13.8 mmol/L), and a ketonuria greater than or equal to 2 ++ with the urine test strip.

Data were collected from the medical records of the patients included. The parameters studied were the duration of diabetes, the type of diabetes, the antidiabetic drug treatment(s) before hospitalization (for previously known cases of diabetes), the known preexisting complications, the clinical and paraclinical features of ketoacidosis presented at the admission (glycemia, ketonuria), the precipitating factors of ketoacidosis, duration of hospitalization (in days) and mode of discharge from hospitalization (deceased, cured, discharge). The data were processed using Excel 2013 and Epi-info 7 software, with a significant p-value less than 0.05.

3. Results

During the study period, 1228 patients were hospitalized in our department, of whom 1140 were diabetic. We selected a total of 64 patients who presented with DK according to our inclusion criteria. The prevalence of DK among diabetics was therefore 5.61%. The mean age of our patients was 46.3 ± 17.3 years (range ages 5 to 89) and the sex ratio M/F was 0.94 (33 males and 31 females). We found that type 2 diabetes cases (62.5%) were the most represented (Table 1).

Table 1. *Distribution of DK cases by type of diabetes.*

Type of diabetes	Number of cases (N=64)
Type 1	21 (32, 81%)
Type 2	40 (62, 5%)
Diabetes due to specific cause	1 (1, 56%)
Gestational Diabetes	2 (3, 13%)

Among our cases of DK, those with inaugural diabetes and those whose diabetes progressed between 1 and 5 years were the most represented, the frequency of which is respectively 37.5% and 26.57%. The mean duration of their diabetes was 6.7 ± 1.7 years with extremes of 2 months and 40 years.

Thirty-one patients (48.44%) had no previous drug treatments. Among the known diabetics, 4.48% were without any drug treatment, 29.68% treated with oral antidiabetics and 21.88% treated with insulin before their hospitalization.

The mean time to hospitalization after the onset of the first signs of DK was 11 ± 15.20 days (2 to 90 days).

The main reasons for hospitalization of our patients were nausea and vomiting, asthenia, abdominal pain and disturbance of consciousness in 54.7%, 20.3%, 14.1%, and 10.9% of cases, respectively.

Regarding the clinical features presented on admission: all patients presented with polyuro-polydipsia syndrome. Dehydration (87.5%), nausea and/or vomiting (79.7%) were the most common clinical signs after polyuro-polydipsia syndrome, which was present in all patients. Obnubilation and coma were present in 3 patients (4.69%). Twenty-five percent of patients presented with arterial hypotension on admission. The characteristics of vital parameters at entry are shown in Table 2.

Table 2. *Distribution of DK cases according to their vital signs at entry (N = 64).*

Vital signs	Mean (± Standard deviation)	Minimum	Maximum
Systolic blood pressure (mm Hg)	113,73 (± 31,90)	70	220
Diastolic blood pressure (mm Hg)	75,55 (± 22,60)	50	160
Heart rate (bpm)	82,51 (± 35,10)	49	140
Respiration rate (cpm)	24,79 (± 3,18)	18	50
Temperature (°C)	36,7 (± 1,56)	35,7	38,3

The mean capillary blood glucose at admission was 389 mg/dL ± 85 with extremes ranging from 250 and 500 mg/dL. In 65.63% of cases, it was between 300 and 500 mg/dl. According to the urine dipstick examination, twenty-six patients (40.62%) had 3+ ketonuria, twenty-four patients (37.5%) at 2+, the rest (21.88%) at 4+. 3+ glycosuria was the most common (70.31%).

Electrolyte disturbances such as hyponatremia (96.87%), hypokalaemia (45.31%) or hyperkalaemia (14.06%) were present in our patients. Our patients had not benefited from the measurement of blood pH by arterial gas measurement, which was very difficult to access.

In our study, retinopathy was the most common degenerative complication found during hospitalization, 4.70% of cases, followed by ischemic stroke in 3.2% of cases. Although 85.94% of our patients had no known degenerative complications.

Apart from the cases of inaugural DK (37, 5%), one or more diabetes decompensating factors were found (Table 3). Infections were the most common (48.44%), especially respiratory and urinary tract infections, the frequencies of which are 45.2% and 29% respectively.

The mean hospital stay was 9.1 days ± 4.95 with extremes of 1 day and 23 days. Eighty-seven-point five percent of inpatients were cured of their DK and the death rate was 3.13%. Nine-point thirty-eight percent was released against medical advice.

Table 3. *Etiologic factors of ketoacidosis (N=64).*

Decompensating factors	Number of cases (%)
Infections	31 (48,44)
Inaugural diabetes	24 (37,5)
Discontinuation of treatment	20 (31,25)
Ischemic stroke	2 (3,13)
Pregnancy	2 (3,13)
Acute pancreatitis	1 (1,56)
Acute coronary syndrome	1 (1,56)

Epidemioclinical variables: age [50-60 years], disturbance of consciousness, Glasgow scale < 10 as well as paraclinical variables: glycemia > 500 mg/dl, hyperkalemia and ketonuria at 4+ at entry were significantly correlated with hospital mortality (Tables 3 and 4).

Table 4. *Correlations between epidemioclinical variables and hospital mortality (N=64).*

Variables	Living (%)	Deceased (%)	p-value
Age range (years)			
< 10	1 (1,56)	0 (0)	---
[10 – 20]	2 (3,13)	0 (0)	---
[20 – 30]	9 (14,06)	0 (0)	---
[30 – 40]	13 (20,31)	0 (0)	---
[40 – 50]	12 (18,87)	0 (0)	---
[50 – 60]	9 (14,06)	2 (3,13)	0,027
[60 – 70]	12 (18,87)	0 (0)	---
≥ 70	4 (6,25)	0 (0)	---
Gender			
Male	30 (46,87)	1 (1,56)	0,738
Female	32 (50)	1 (1,56)	---
Reason for entry			
Vomiting	35 (54,68)	0 (0)	---
Asthenia	13 (20,96)	0 (0)	---
Abdominal pain	9 (14,06)	0 (0)	---
Glasgow scale at admission			
[10-14]	5 (7,81)	2 (3,13)	0,0104
< 10	1 (1,56)	2 (3,13)	0,00001

4. Discussion

Despite the monocentric nature of the study and given the small size of the unrepresentative sample, recruitment bias could arise but also a more in-depth statistical analysis was not possible. Our study was also limited by our method, which was the urine dipstick, to diagnose ketosis. We also did not have access to more convenient and sensitive blood test kits [8]. It still allowed us to establish the epidemiological and paraclinical profile of diabetics admitted for DK at our study site and to determine certain factors determining the in-hospital mortality of these patients.

Table 5. *Correlations between biological variables and hospital mortality (N=64).*

Variables	Living (%)	Deceased (%)	p-value
Blood glucose at admission (mg/dl)			
≤ 300	14 (21,87)	0 (0)	---
[300 – 500]	42 (65,62)	0 (0)	---
>500	6 (9, 38)	2 (3,13)	0,0007
Glycated haemoglobin (%)			
< 7	0 (0)	0 (0)	---
[7 – 10]	7 (10,94)	0 (0)	---
≥ 10	25 (39,06)	2 (3,13)	0,62
Glycosuria at admission			
2+	9 (14,06)	0 (0)	---
3+	45 (70,31)	1 (1,56)	---
4+	8 (12,50)	1 (1,56)	0,3
Ketonuria at admission			
2+	24 (37,50)	0 (0)	---
3+	26 (40,63)	0 (0)	---
4+	12 (18,75)	2 (3,20)	0,025
Hypokalaemia	25 (39,06)	0 (0)	---
Hyperkalaemia	7 (10,93)	2 (3,13)	0,017

In our series, the prevalence of diabetic ketoacidosis was 5.6%. It is similar to that found by a Congolese series [9]. However, it was significantly lower than that of Alijanpour et al in Iran, who found a prevalence of 55.5% [10]. According to Choleau et al, the prevalence of DK ranged from 15 to 65% in Europe and North America [11]. These differences could be explained not only by the diversity of the populations studied but also by the criteria used to diagnose ketoacidosis. With a more sensitive diagnostic method such as capillary ketonemia, this prevalence that we objectified in our study could be different. However, the higher proportion of type 2 diabetes (which carries a lower risk of ketoacidosis) compared to other types could explain this difference.

The average age, which was 46.3 ± 17.3 years in our study, was similar to those made in Congo, the United States of America and Scotland, where the mean ages of their patients were respectively 44.8 years [9], 45 years [12] and 44 years [13]. On the other hand, the average age of our patients was lower than that of the study by Ridouane et al, conducted in Morocco, 56 years old [14].

Our study population consisted of 33 women (51.56%) and 31 men (48.44%) giving a sex ratio of 0.94. A female predominance which was also found by Hafanawy et al (59.6% of women and 40.4% of men) [15], Ridouane et al (52.3% of women and 47.7% of men) [14]. Although other authors, Kakoma et al, and Alijanpour et al had found male predominance with respective sex ratios of 1.42 [9] and 1.21 [10]. Tenoutasse et al had a result that could be superimposed on that of ours [16]. Therefore, diabetic ketoacidosis affects, without distinction, both general [9].

In our series, type 2 diabetes was represented in 62.5% of

cases, type 1 diabetes in 32.81% of cases and other types in 4.69% of cases (Table 1). This was in line with the results of literature where there was always a predominance of type 2 diabetes [17, 18]. However, some authors found different results in which type 1 diabetes was the most prevalent type in their series. In fact, diabetic ketoacidosis was a complication preferentially affecting type 1 diabetics [19, 20]. The literature has stated that in the past, ketoacidosis was known as an acute metabolic complication of type 1 diabetes. However, since 1980, authors have demonstrated the presence of DK in patients with type 2 diabetes [3, 20].

This clinical picture then became more and more frequent. Thus, the prevalence of DK in type 2 diabetics has increased considerably for several years. It most often involved people of African, African American, or Hispanic descent [12, 19]. But also given the predominant number of cases of type 2 diabetes on the epidemiological level (with improvement of the cases detected, problem of treatment of which the cost, especially in countries with limited resources like Madagascar). This could explain this predominance of cases of type 2 diabetes.

In our study, diabetes was already known in 62.5% of cases with a mean duration of 6.7 years. This approached the mean duration of diabetes in the patients of Kruljac et al, which was 7.7 years [21]. Yet it was lower than that of Sarr et al in Dakar who was 10 years old [22]. The delay in screening for diabetes in Madagascar could be the explanation for this shorter development time. Moreover, according to the World Health Organization, patients with diabetes mellitus generally develop acute metabolic complications such as ketoacidosis after 5 years of progress [23]. The diabetes of our patients was discovered incidentally in 36.5% of cases. This was in line with the findings of studies carried out in China [24] where ketoacidosis was the mode of discovery of diabetes in 49.7% of cases.

In our series, 51.56% of diabetic patients had received previous treatment for diabetes, of which 29.68% were on oral antidiabetics and 21.88% on insulin. And 48.44% had not received treatment before admission. Despite their previous treatment, therefore, our diabetics suffered from DK.

No patient had controlled diabetes (HbA1c < 7%) and the average HbA1c level of the patients was 11.3%. This was similar to that of the study by Ekpebegh et al, in South Africa, where the average glycated hemoglobin of their patients was 12.4% [25]. Indeed, an average blood sugar level of 269 mg/dL (217 - 314) corresponds to a glycated haemoglobin level of 11%, according to the literature [26]. We must therefore optimize the management of all of our patients to have a well-balanced diabetes in order to avoid the occurrence of ketoacidosis. Because according to the literature, this complication can still occur if diabetes mellitus is not controlled [27]. This underlines the importance of optimizing the care of our patients. In fact, our patients all had a glycated hemoglobin level above 7%.

In our study, retinopathy was the most common degenerative complication in 4.70% of cases, followed by stroke in 3.2% of cases.

In the United Kingdom, Wright et al also reported that in patients with DK microvascular complications were more common than macrovascular complications. Their patients suffered from retinopathy, nephropathy, neuropathy, stroke, and cardiovascular disease in 12%, 5%, 5%, 2%, and 1% of cases, respectively. Indeed, microangiopathies generally occur before macroangiopathies in diabetes [28].

On average, our patients did not come to the hospital until the eleventh day after the onset of clinical symptoms of ketoacidosis. This was similar to the result of the study by Alijanpour et al, in Iran, whose average consultation time for their patients was 14.5 days [10].

In type 2 diabetics, ketoacidosis is clinically progressive in most cases. While in type 1 diabetics, the set-up is often abrupt and noisier [8]. Regardless of the method of installation, therapeutic education on the clinical manifestations of ketoacidosis and blood glucose self-monitoring is the rule in order to minimize this consultation time and improve their prognosis.

Our patients came to the hospital for nausea and vomiting, asthenia, abdominal pain, and disturbance of consciousness in 54.7%, 20.3%, 14.1%, and 10.9% of cases, respectively. Other authors had found reasons for hospitalization as follows: Polyuria and polydipsia (54.5%), persistent vomiting (52.7%), altered sensorium (50.9%), abdominal pains (47.3%) were common presenting symptoms [29]. In our series, on average, the systolic blood pressure of the patients was 113.73 mmHg and the diastolic blood pressure 75.55 mmHg. One in four patients (25%) presented with arterial hypotension (blood pressure less than 90/60 mmHg) on admission. Tenoutasse et al also found that 25.5% of their study population had low blood pressure [16]. Indeed, during DK, this arterial hypotension is linked both to the major dehydration responsible for hypovolemia and to the acidosis responsible for a decrease in myocardial contractility, vascular tone, and sensitivity to endogenous catecholamine [30]. The average respiratory rate of our patients was 24.79 cycles per minute. Indeed, polypnea is a physiological response of the body to eliminate excess ketone bodies [30]. On average, the body temperature of our patients was 36.7°C (Table 2). It did not exceed 38.3°C, although infections were the most common cause of ketoacidosis decompensation in our patients. This could be explained by the fact that hypothermia is common in DK, favored by acidosis and peripheral vasodilation [30].

On admission, all our patients had presented with polyuropolydipsia. Then mucosal dryness was the second clinical sign presented by our patients (87.50%), followed by nausea and vomiting (79.70%). Only one patient was comatose. In a study conducted in Congo, Kakoma et al found that 80.4% of their patients had Küssmaul breathing, 76.5% dehydration, 58.8% coma, 56.9% ketone breath and 25%. 5% a polyuro-polydypsia syndrome [9]. Seth and colleagues in India had shown that vomiting was the most common clinical sign (57.7%), followed by abdominal pain (42.2%) and dehydration (42.2%). Polyuro-polydipsia was seen in only in 28.1% and Küssmaul breathing in 14% [31]. These differences in clinical presentations could be explained by the

difference in the populations studied and that in the severity of DK at the time of admission. Nevertheless, all the clinical signs raised are manifestations of ketoacidosis. A capillary blood sugar level greater than or equal to 250 mg/dL (13.8 mmol/L) is one of the criteria we used to make the diagnosis of DK [32]. At the end of our series, the mean capillary blood glucose of our patients was 389 mg/dL on entry. It was said to be "high" or very high (greater than or equal to 600 mg/dL) in 12.5%.

Given the mean capillary blood glucose levels of our patients, their blood glucose levels sought by the urine dipstick were 2+ and 4+ in 14.06% of cases each. It was 3+ in 71.88% of cases. According to the literature, the renal threshold for glucose reabsorption is 180 mg/dL. However, one of the criteria for making the diagnosis of diabetic ketoacidosis is blood glucose greater than or equal to 250 mg/dL [30]. Which could explain this massive glycosuria.

During ketoacidosis, the ketone body is produced in three forms: acetone, acetoacetate, and beta hydroxybutyrate (β-OHB). Acetoacetate can be measured in the urine using a urine dipstick and in the capillaries while β-OHB is measured primarily in the capillary to give ketonemia [8]. In our series, we used the urine dipstick to diagnose diabetic ketoacidosis. Half of our patients had 4+ ketonuria on admission.

In our study, 96.88% of patients had blood ionogram hyponatremia. This situation could be explained by the high frequency of vomiting and polyuria in our patients, thus promoting a massive loss of sodium causing hyponatremia [30, 33].

In addition, according to the literature, pseudo-hyponatremia is often found to compensate for extracellular hyperosmolarity caused by the osmotic flow of water from the intracellular space to the extracellular space associated with hyperglycemia [30]. In our study, the patients presented with hypokalaemia, normal kalaemia and hyperkalaemia respectively in 45.31%, 40.63% and 14.06% of cases. Most of the time, the blood ionogram was done during or even at the end of the ketoacidosis correction. This could explain the high frequency of hypokalaemia, linked to insulin therapy. On the one hand, Sarr et al found that 78.5% of their patients were in normokaliemia, 19% in hypokalaemia and 2.5% in hyperkalaemia after the correction of ketoacidosis [22]. hyperkalemia may well occur and be fatal to the heart during ketoacidosis [34, 35]. It is secondary, on the one hand to insulin deficiency leading to a blockage of the sodium-potassium pump causing the transfer of potassium from the intracellular compartment to the extracellular compartment [36]. It is only after insulin therapy that hypokalaemia occurs, hence the value of potassium supplementation [30].

In our study, the main etiology of patients' ketoacidosis was infections (48.44%), followed by unrecognized diabetes (37.50%) and treatment discontinuation (31.25%) (Table 2). Similarly, in China and Pakistan, infections remained the most common triggering factor for ketoacidosis (in 39.16% and 69.0% of cases respectively), followed by inaugural diabetes (25.86% in China) and non-compliance of treatment (in 25.5% and 53.5% of cases respectively) [24, 31]. In addition, other authors have shown that discontinuation of treatment is mainly a cause of recurrent diabetic ketoacidosis [37]. The World Health Organization has also confirmed that only half of patients with chronic illnesses, such as diabetes, are truly observant [38]. This explains the frequency of DK cases following a treatment problem in diabetics, because many of these patients are not observing their treatment.

In our study, as in the literature, urinary tract and respiratory infections were the leading infectious causes of ketotic decompensation in diabetes [31].

The risk of developing urinary tract infections (especially pyelonephritis) [39], acute community-acquired pneumonia, pneumococcal bacteremia [39] is higher in diabetics, especially if their diabetes is unbalanced, hence their frequency during DK.

On average, our patients were hospitalized for 9.1 days. This result was superimposed on the studies carried out in India, where the average length of hospitalization of subjects admitted for diabetic ketoacidosis was 10 days [9]. A shorter hospital stay has been reported by an american author [40].

In our series, the mortality rate for diabetic ketoacidosis was 3.13%. This result was slightly higher than that of the study done in China and the United Kingdoms with a death rate of 1.7% and 2% [24, 28]. On the other hand, other authors said that the mortality rate from diabetic ketoacidosis was very high worldwide, at around 5% [6]. In Africa this mortality rate remains high according to authors [6, 7]. Lack of regular follow-up was found to be a factor associated with DK mortality in African diabetics [28].

Regarding the determining factors of mortality, age was significantly associated with in-hospital mortality ($p = 0.027$) (Table 4). There was no significant correlation between gender and in-hospital mortality ($p = 0.7380$) (Table 4). Disorder of consciousness was significantly correlated with in-hospital mortality ($p = 0.0104$) (Table 4). Which joins that found in the series of Kakoma and his collaborators [9].

We found a correlation between coma and intra-hospital mortality ($p = 0.0001$) (Table 4). Tenoutasse et al, Xu et al reported the same finding in their series [16, 24].

The significant correlation that we found between very high blood sugar and intra-hospital mortality ($p = 0.0007$) (Table 5) was not in the Chinese study by Xu et al [24]. This discrepancy in results was explained by the difference in blood glucose measurement. Since, in their study, the measurement of blood glucose at entry was venous [24]. But with regard to glycosuria, neither our study (Table 5) nor the Chinese study found a significant correlation with in-hospital mortality [24]. There was no significant correlation between ketonuria and in-hospital mortality ($p = 0.025$) (Table 5). The Chinese study did not find this correlation either [24].

In our series (Table 5), as in the literature [16, 34, 35], there was a significant correlation between hyperkalaemia and in-hospital mortality. Indeed, hyperkalaemia is a cause of cardiac arrhythmias leading to death, especially in the presence of underlying heart disease.

5. Conclusion

Ketoacidosis occupies a place among the complications motivating the hospitalization of diabetic patients, it is often indicative of diabetes mellitus. Despite a low prevalence, this pathology deserves attention because its mortality rate is not negligible. Accessibility to more efficient methods for the diagnosis of ketoacidosis would be desirable in Madagascar, because not only can this help to detect more correctly and treat early. Education about the clinical signs and what to do with the patient in the face of ketoacidosis is certainly essential to avoid delay in admission and a poor prognosis. Regular monitoring and availability of treatment for diabetes mellitus will surely reduce the occurrence of this complication.

Competing Interests

The authors declare that they have no competing interests.

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