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RESEARCH ARTICLE

DIABETIC KETOACIDOSIS IN PEDIATRICPATIENTS: A 10-YEAR RETROSPECTIVE STUDY COMPARING PREVIOUSLY DIAGNOSED AND NEWLY DIAGNOSED CASES AT PRESENTATION

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Abstract

Background: Diabetic ketoacidosis (DKA) represents a severe metabolic disorder associated with diabetes mellitus (DM), posing a heightened risk of morbidity and mortality in children. This research aims to evaluate the prevalence of DKA in pediatric patients and to explore its clinical characteristics and biological consequences during intensive care management.

Patients and Methods: A retrospective study was carried out on children younger than 15 years who were hospitalized for DKA in the pediatric intensive care unit of Mohammed VI University Hospital, Marrakech, Morocco, spanning the period from January 2010 to December 2020. A comparative analysis was performed between two groups: patients with a known history of diabetes and those experiencing DKA as the initial presentation of diabetes.

Results: Over a 10-year period, 240 cases of DKA were identified among 8,222 admissions, representing 2.91% of total admissions. The mean age of patients was 7.49 ± 4.44 years, with a higher prevalence observed in children over 10 years old. The most common clinical signs included polyuria-polydipsia syndrome, Kussmaul breathing, vomiting, and altered consciousness. The most severe symptoms were observed in children with newly diagnosed type 1 diabetes mellitus (T1DM). The majority of patients had a favourable outcome. However, 20.6% of cases experienced complications, and one death was recorded.

Discussion: This study highlights the significant burden of DKA in pediatric patients, especially among those newly diagnosed with T1DM. The high prevalence of infections as a triggering factor emphasizes the need for improved infection management in diabetic children. Prompt recognition and appropriate management play a key role in mitigating the morbidity and mortality linked to DKA.

Conclusion:DKA remains a severe complication of pediatric diabetes, with significant risks of serious consequences. Raising awareness among healthcare providers, facilitating early detection, and adopting a

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comprehensive approach to management are fundamental for enhancing clinical outcomes and minimizing complications.

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Introduction:

Diabetic ketoacidosis (DKA) is a severe metabolic complication of diabetes mellitus (DM) that significantly increases morbidity and mortality risks, particularly in children[1]. DKA is predominantly observed in newly diagnosed cases of type 1 diabetes mellitus (T1DM), though it may also manifest in type 2 diabetes mellitus (T2DM), albeit at a lower frequency[2].DKA arises as an acute condition resulting from either partial or complete insulin deficiency, triggering hyperglycaemia and osmotic diuresis.In the absence of insulin, cells use lipids instead of glucose as a source of energy and leads to ketone body accumulation or ketogenesis.All these processes, lead to dehydration and metabolic acidosis[3-4].

Over the past few decades, there has been a notable global rise in the incidence of T1DM[5]. In Morocco, we have limited epidemiological data concerning diabetic children.In 2021 in Morocco, T1DM in young people under 19 years of age was estimated at 43.3 thousand, with an annual increase of 5.1 thousand[6].

In developing countries, DKA-related mortality in children is higher than in western countries. This is due to the lack of information among parents and healthcare professionals about the early symptoms of T1DM. Also, difficult access to healthcare and poor socio-economic conditions delay diagnosis of T1DM and increase mortality of DKA.The severity of DKA is related to hydro-electrolyticdisorders and cerebral oedema which occurs in 0.3% to 0,9% of cases and accounts for 21 to 24% of all deaths linked to DKA' not to mention the permanent neurocognitive sequelae that can results[3-7].

Aim of the study:

Given the importance of this public health problem, this study aims to assess the prevalence of DKA in our population, examine its clinical characteristics and laboratory findings in pediatric intensive care cases, and analyze complications following the implementation of a standardized management protocol.

Patients and Methods:

This study employed a retrospective design and was conducted in the pediatric intensive care unit of Mohammed VI University Hospital in Marrakech, Morocco, spanning the period from January 2010 to December 2020.This study included children younger than 15 years diagnosed with DKA, characterized by hyperglycaemia (≥ 2 g/L), ketonuria (≥ 2 crosses on urine dipstick) or positive ketonemia (≥ 3 mmol/L), and an arterial pH below 7.3 or bicarbonate levels under 18 mmol/L.

DKA was classified based on arterial blood gas analysis according to the severity of acidosis:

- Mild DKA: pH <7.3 or bicarbonates<18 mmol/L
- Moderate DKA: pH <7.2 or bicarbonates <10 mmol/L
- Severe DKA: pH <7.1 or bicarbonates<5 mmol/L.

The Kidney Disease Improving Global Outcomes (KDIGO) criteria were applied to identify cases of renal failure:

- Stage1: Increased serum creatinine x 1.5 – 1.9 baseline
- Stage2: Increased serum creatinine x 2 – 2.9 baseline
- Stage 3: Increased serum creatinine ≥x3baselineor initiating renal replacement therapy

Cases of isolated hyperglycaemia with no other clinical or biological signs, essentially the presence of ketonuria or ketonemia, as well as incomplete or untraceable records, were excluded from the study.

The management of all DKA cases in this study followed the guidelines established by the International Society for Paediatric and Adolescent Diabetes (ISPAD)[3].

Medical records were reviewed and categorized into five principal themes: epidemiological characteristics (including age, gender, socio-economic background, and origin), clinical and paraclinical findings (symptoms and

laboratory results), triggering factors, therapeutic interventions, and patient outcomes. Patients were classified into two categories: those with a prior diagnosis of diabetes who developed DKA, and those experiencing DKA as the first manifestation of diabetes. Data analysis was performed using Microsoft Excel® and SPSS Statistics for Windows, Version 25. Continuous variables (e.g., age, symptom duration, venous glycaemia, and natremia) were reported as mean ± standard deviation (Mean ± SD). Qualitative variables were presented as percentages or frequencies. Comparative analyses of proportions were conducted using Pearson's $\chi 2$-test or Fisher's exact test, while the independent samples t-test was employed for mean comparisons. Statistical significance was set at a 5% threshold.

Ethical approval for this study was granted by the Institutional Ethics Committee of the Faculty of Medicine at Cadi Ayyad University, Marrakech. Writteninformed consent wasobtainedfrom parents or legalguardians.

Epidemiology:
Over 10 years, 240 cases of DKA were observed among 8222 admissions corresponding to 2.91% of all admissions. Of the 240 cases of DKA, 233 were included while 7 cases were excluded because of lack of records.

The average age of our patients was 7,49 ±4,44 years. 134 females (57,51%) and 99 males (42,48%) were affected. 125 children (53,64%) were from rural areas and 108(46,35%) from urban areas. It should be noted that 30,04% of the children had visited at least 2 health institutions before being admitted to thepediatric intensive care unit (See Table 1).

Table 1: Epidemiological characteristics of patients with DKA.

Characteristics	Inaugural DM	Known T1DM	Total	P-value
Age (years) - mean ± SD	5,11 ± 3,25	12,52 ± 1,26	7,49 ±4,44	< 0,001
Gender:				
• **Female**	85 (36,48%)	49 (21,03%)	134 (57,51%)	0,063
• **Male**	73 (31,33%)	26 (11,15%)	99 (42,48%)	
Origin:				
• **Urbain**	84 (36,05%)	41 (17,59%)	108 (46,35%)	0,830
• **Rural**	74 (31,75%)	34 (14,59%)	125 (53,64%)	
Socio-economiclevel :				
• **Medium**	99 (42,48%)	41 (17,59%)	140 (60,08%)	0,246
• **Low**	49 (21,03%)	34 (14,59%)	83 (35,62%)	

There was a peak in the frequency of cases among children aged over 10 years who accounted for 37.34% of cases (n=87).In this age group, only 17 children presented with DKA for the first time, whereas 70 children were already known to have T1DM. The second most affected group consisted of children younger than 5 years, accounting for 35.62% of cases (n=83), with all instances being inaugural DKA episodes. A statistically significant p-value (<0.001) indicated that younger age is a risk factor for first-onset DKA (See Figure 1). Overall, inaugural DKA was observed in 158 cases (67.81%), while all known diabetes cases corresponded to T1DM (n=75; 33.19%).

Clinical and paraclinical Data:
The mean time from symptom onset to hospital admission was 2.95 ± 1.27 days, with delays ranging from a minimum of 1 day to a maximum of 7 days. The presentation symptoms in our patientswere:Polyuria-polydipsia syndrome in 219 of cases (93.99%), Kussmaul dyspnoeain 198 of cases (84.98%), vomiting in 175 of cases (75.10%), alertness disorders in 154 of cases (66.09%), abdominal pain in 137 of cases (58.80%), weight loss in 135of cases (57.93%), visual disordersin 3 cases (1.29%), and respiratory failure in 2 cases (0.86%). A significant variation was observed between the two groups regarding symptom presentation and duration prior to hospitalisation. Patients experiencing DKA for the first time had a prolonged delay before admission (p-value < 0.001) and exhibited more severe clinical manifestations compared to those with pre-existing diabetes (See Table 2).

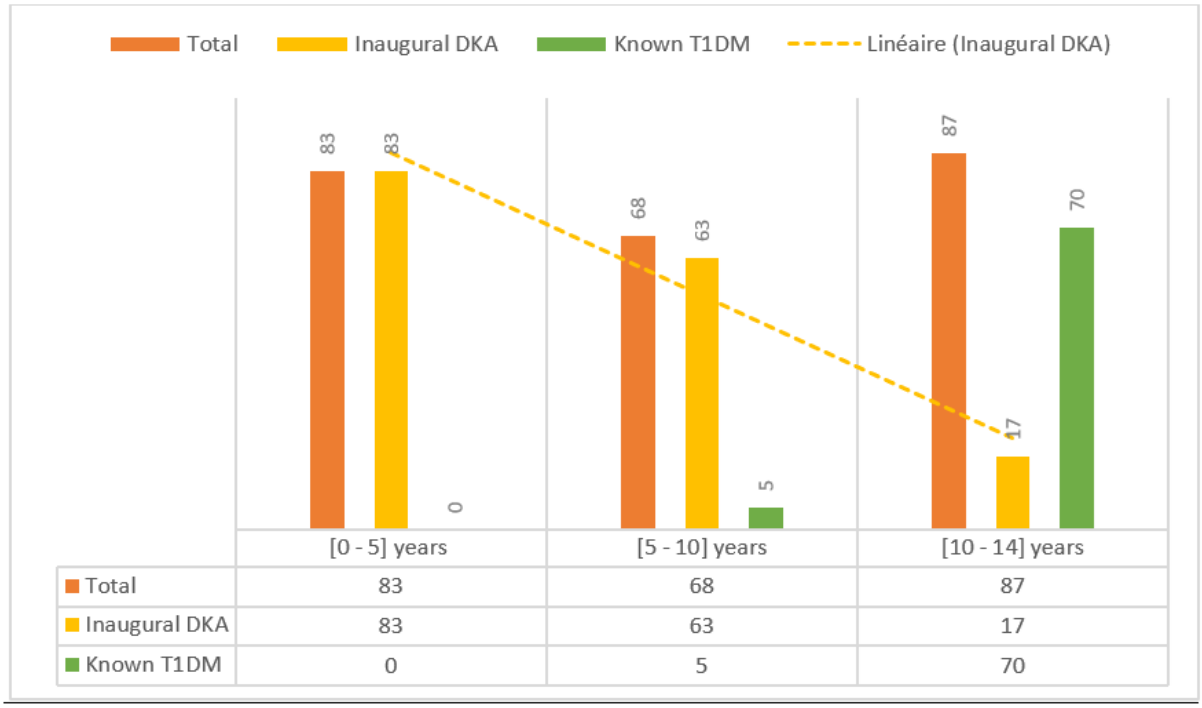
All the gas measurements taken showed a metabolic acidosis with a drop in bicarbonates. The average Ph was 7.1 with an extreme value of 6,82. Of the cases studied 48,06% showed moderate acidosis, there were also 28,32% of mild acidosis, and 23.6% of severe acidosis.

Patients in our study had a mean kaliemia of 4,70±1,38meq/l with a tendency to hyperkalaemia (K+≥5) in 84 cases (36.05%) versus 45 cases (19.31%)of hypokalaemia (K+<3.5)

Based on the KDIGO classification, acute kidney injury (AKI) was identified in 17 cases, accounting for 7.3% of the study population. Among these, 5 cases (29.42%) were classified as stage 1, 10 cases (58.82%) as stage 2, and 2 cases (11.76%) as stage 3, with one patient requiring renal replacement therapy (RRT). Compared to children with pre-existing diabetes, those experiencing their first episode of DKA exhibited significantly higher glycaemia levels (p-value < 0.001), more severe metabolic acidosis (p-value ≤ 0.001), and increased osmolarity (p-value < 0.001) (See Table 2).

All our patients, had undergone: CRP, blood culture and urine cytobacteriological examination (UCBE) as a matter of course. The mean CRP in our population was 18.87±7.28 mg/l with 139 cases of elevated CRP representing 59.66% of the cases studied. Sepsis was diagnosed in 16 cases (6.87%). The most frequent germs were staphylococcus (n=13) and Klebsiella pneumoniae (n=2). UCBE tests revealed 26 cases of urinary tract infections.

We also systematically performed chest X-rays, which showed 18 pathological cases (7.72%) with 16 cases of pneumonia and a bronchial syndrome in 2 cases. Chest X-rays were particularly useful during the global COVID-19 pandemic for detecting interstitial syndrome. In this period, all respiratory polymerase chain reaction tests (PCR) for SARS-COV2 (n=24) were negative. Thus, we did not detect any cases of DKA triggered by SARS-COV 2 infection in this period.



	[0 - 5] years	[5 - 10] years	[10 - 14] years
Total	83	68	87
Inaugural DKA	83	63	17
Known T1DM	0	5	70

Figure 1: Distribution of children with DKA by age group

Table 2: Comparison of clinical and biochemical profiles between newly diagnosed and known T1DM patients:

Characteristics	Inaugural DKA	Known DM	Total	p-value
Days of symptoms-mean±SD	3,40±1,24	2,01±0,69	2.95 ±1,27	< 0,001
Polyuria-polydipsia syndromeN(%)	149 (63,98%)	70 (30,04%)	219 (93,99%)	0,773
Kussmaul dyspneaN(%)	150 (64,37%)	48 (20,60%)	198 (84,97%)	< 0,001
VomitingN(%)	108 (46,35%)	67 (28,75%)	175 (75,10%)	0,001
Alertness disordersN(%)	123 (52,78%)	31 (13,30%)	154 (66,09%)	< 0,001
Abdominal painN(%)	98 (42,06%)	39 (16,73%)	137 (58,79%)	0,118
Weight loss N(%)	123 (52,78%)	12 (5,15%)	135 (57,93%)	< 0,001
Glycemia (g/dl) - Mean ±SD	4,75±0,74	3,73 ± 0,96	4,42 ± 0,94	< 0,001
Kalemia (meq/l) - Mean ±SD	4,70 ±1,47	4,71 ±1,19	4,70 ± 1,38	0,956
Natremia (meq/l) - Mean ±SD	135,72 ± 8,56	139,84 ± 8,52	136,84 ± 8,52	0,030
Bicarbonates (mmol/L) - Mean ± SD	6,84 ±2,34	10,77 ± 2,62	8,11 ± 3,04	< 0,001
Osmolality (mOsmol/l) - Mean ± SD	300,68 ±6,1	297,97 ± 7,06	299,81 ± 6,54	< 0,001
Days of hospital stay - Mean ± SD	3,52 ±1,05	1,82 ± 0,76	2.97 ± 1,25	< 0,001

Triggering factors:
Infections topped the list of triggers of DKA in 135 cases (57.94%). Figure 2 summarises the precipitating factors of DKA in our study:

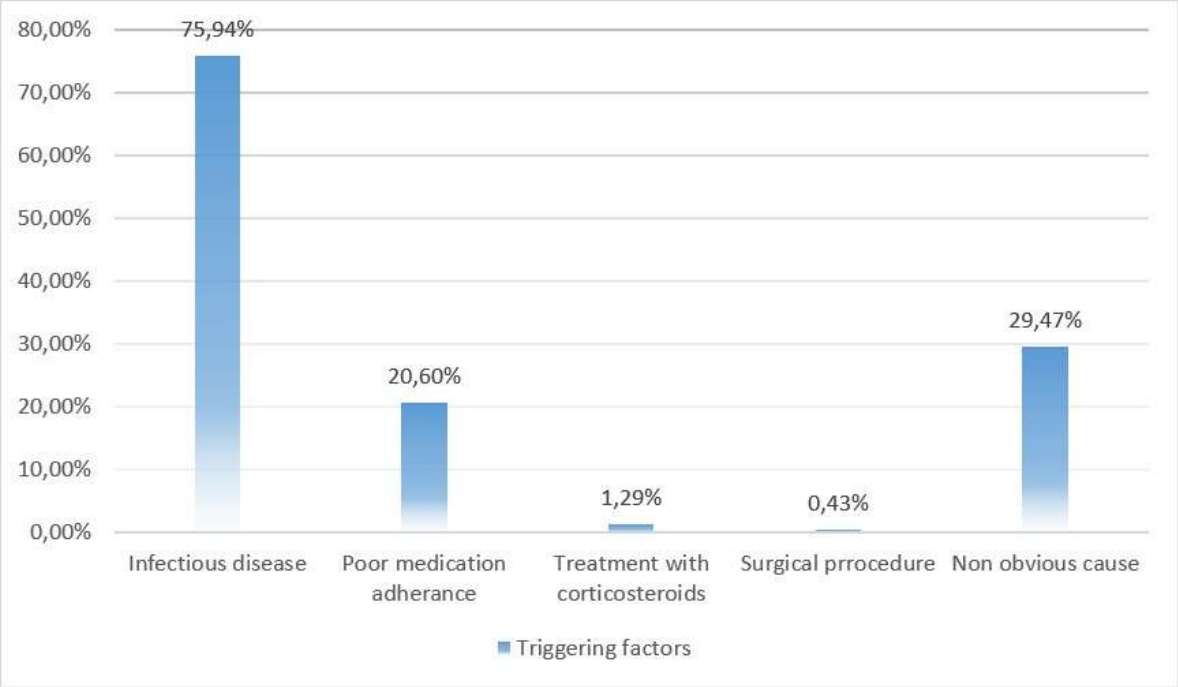


Figure 2: Triggering factors of DKA in our study

Management:
Therecommendations of ISPAD are based on two main components: rehydration and insulinotherapy[3].In this study, all patients underwent intravenous fluid administration prior to the initiation of insulin therapy.

We started rehydration with 0.9% isotonic sodium solution to replace the fluid deficit. Rehydration was then maintained by5% or 10% glucose serum, depending on the blood glucose level. Sodium supplementation was systematic for serum tonicity between 0.45% and 0.9%.

In our study, all patients received insulin therapy with rapid-acting insulin administered intravenously with a syringe pump at a flow rate adapted to age (between 0.05 and 0.1 IU/kg/h).This protocol allowed us to achieve good results within the first 24 hours, with an average blood glucose of 1.95 g/l, no ketonuria and an average pH of 7.28.

Treatment also included: Correction of ionic disorders, antibiotics when indicated. RRT was performed in 1 patient and 6 children required mechanical ventilation. None of our patients received bicarbonate alkalization.

Evolution:
The average hospital stay for our patients was 2.97 ± 1,25 days with a maximum of 7 days. The majority of patients: 185 of cases (79.4%) had a favourable outcome. However secondary complications were observed in 48 patients (20.60%).

The following table presents the secondary complications found in our patients:**(Table 3)**

Table 3: Complications of patients with DKA in our study:

Complications	Number of cases	Pourcentage (%)
Hypokalemia	32	13,73%
Hyperkalemia	4	1.72%
Hypoglycemia	4	1.72%
Renalfailure	3	1,29%
Hemodynamicshock	2	0,86%
Hospital-acquired infections	2	0 ,86%
Death	1	0,43%

Discussion:

In recent decades, there has been a significant rise in the incidence of T1DM in children. Research has consistently reported higher rates of DKA at the time of T1DM diagnosis, particularly in children younger than 5 years[8-9-10].This was also the case in our study, where all children under the age of 5 years had a first episode of DKA.In fact, younger people are more likely to have a first episode of DKA.This increased risk in younger individuals may be attributed to challenges in expressing symptoms at an early age and a general lack of awareness among parents and healthcare professionals regarding the early manifestations of T1DM.In our study, the twomost affected age groups by DKA were: children over 10 years of age n= 87(37,34%), followed by children under 5 years of age n= 83 (35,62%). The increase in cases during puberty can be explained by the hormonal changes that reduce insulin action by 30 to 50%, due to growth and sex hormones causing insulin resistance[11-12].It is also explained by the psychological changes that can accompany puberty (denial of the disease, eating disorders, etc)in those already known to be diabetic.

According to the literature, there is no significant predominance of one sex over the other, even in our study, there was a slight female predominance[13].

There was a clear difference in clinical presentation between those who had their first episode of the DKA and those who already had a diagnosis of T1DM. The average duration of symptoms was significantly shorter in children with pre-existing diabetes.In addition, children who were known to have diabetes were less likely to have alarming symptoms (i.e alertness disorders p-value< 0,001).This highlights the importance of diabetes education. Enhancing awareness of early T1DM symptoms among parents and healthcare professionals could help mitigate the risks of morbidity and mortality associated with DKA. The biological implications of these differences in clinical presentation were evident, as children with first-time DKA exhibited higher glycaemia, increased osmolality, and more severe acidosis.

The frequency of infection as a triggering factor is still a constant fact in Africa, sometimes accountingfor over 70% of cases. In our study,infectious causes accounted for 57.94 % of cases similar to other African countries[14-15-16]. The nature of these infections varied wildly: bronchopumonary, ear-noseand throat (ENT)infections, cutaneous, urinary, and gynecologicalwere the most common.In our study, ENT infections accounted for 44.45% of cases with angina in the majority.

Poor adherence to medication includes the following: voluntary or unvoluntary discontinuation of insulin therapy, inappropriate dosage of insulin, and dietary errors. The frequency of these factors found in 20.60% of our patients is higher than other African studies[16-17]. We can thus conclude, that this factor is still frequent in developing countries. Other triggers: situations of physical or psychological stress, certain medication such as corticosteroids, surgical procedures.

A delayed diagnosis of diabetes is a critical factor contributing to an increased risk of DKA[18]. Delayed diagnosis is related to lack of parental andphysicians'awareness. Also, referral to appropriate centres is one of the major risk factors of delayed diagnosis and mortality in DKA[19].

Treatment must be undertaken as a matter of urgency, without waiting for the results of further tests[3]. It consists of 4 components: rehydration and volume resuscitation, insulin therapy, correction of hydro-electrolytic disorders, and treatment of triggering cause. Properly administered, this treatment allows a gradual return to normal within 8 to 12 hours. Its aim should not be rapid normalization of blood glucose levels or cessation of urinary excretion of ketone bodies, but rather interruption of hepatic production of ketone bodies by continuous administration of low doses of insulin, and gradual correction of dehydration[20].The cause of decompensation must be treated at the same time as the ketoacidosis. In children, episodes of DKA are most often inaugural; however, precipitating causes can be found, mainly infections and poor compliance with treatment, which may justify antibiotic treatment, and a resumption of diabetes education or supportive psychotherapy in adolescents denying the disease[21].

Complications encountered during episodes of ketoacidosis are rare. Cerebral oedema represents a severe and potentially life-threatening complication of DKA, predominantly affecting paediatric patients[22]. Early warning signs of cerebral oedema include headaches (especially if first experienced during treatment), irritability or behavioural changes, followed by drowsiness and decreased level of consciousness[3-23].

Treatment of cerebral oedema must be rapid and effective, as the time during which treatment with mannitol and hyperventilation is effective is very short[3]. Therefore, when cerebral oedema is suspected, immediate treatment is essential, without waiting for the results of diagnostic tools (CT scan)[24]. DKA may lead to various complications, including electrolyte imbalances such as hypokalaemia, hypoglycaemia, hypocalcaemia, hypomagnesaemia, and severe hypophosphataemia. Acid-base disturbances, including hyperchloremic acidosis and hypochloraemic alkalosis, are also common. Additionally, central nervous system complications may arise, such as cerebral venous sinus thrombosis, basilar artery thrombosis, intracranial haemorrhage, and cerebral infarction…

In high-income countries, the mortality rate associated with DKA remains below 1%. However, in developing countries, it can range between 2% and 13%[25]. In our study, a single fatal case was recorded, accounting for 0.43% of the study population. The identified cause of death was severe hypoglycaemia.

Conclusion:

In summary, DKA is a severe complication in diabetic children. It can lead to serious consequences, including infant mortality especially in children with newly diagnosed DM. Consequently, it is imperative to raise awareness of this condition among healthcare professionals and patients. In addition, improved access to medical care and early diagnosis can help reduce the morbidity and mortality associated with DKA in children in developing countries.

Ethics:

This study adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of Cady Ayyad University.

Declaration of patient consent:

The authors confirm that all necessary patient consent forms have been obtained. Parental consent was secured for the publication of images and clinical data in this journal.

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Nil.

Conflicts of interest

The authors declare no conflicts of interest.

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