Diabetic ketoacidosis in paediatrics: A 10-year retrospective study comparing children with known diabetes and those with newly diagnosed diabetes at presentation

Abstract:

Introduction:

Diabetic ketoacidosis (DKA) is a serious complication of diabetes mellitus (DM), with increased risk of morbidity and mortality in paediatric population. This study aims to determine the prevalence of DKA in paediatric patients and to analyse the clinical features and biological outcomes during the management of DKA in intensive care unit.

Methods:

We conducted a retrospective study involving children under the age of 15 who were admitted for DKA in the paediatric intensive care unit at Mohammed VI University Hospital in Marrakech, Morocco, from January 2010 to December 2020. We carried out a comparative study between 2 groups of patients with DKA: those with a known history of diabetes and those with inaugural DKA.

Results:

Over a 10-year period, 240 cases of DKA were identified among 8,222 admissions, representing 2.91% of total admissions. The average age of patients was 7,49 +/-4,44 years, with a higher incidence 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 seen in children with newly diagnosed T1DM. The majority of patients had a favourable outcome. However, 20.60% of cases experienced complications, and one death was recorded.

Discussion:

This study highlights the significant burden of DKA in children, particularly those with newly diagnosed type 1 diabetes. The high prevalence of infections as a triggering factor emphasizes the need for improved infection management in diabetic children. Early diagnosis and effective treatment are crucial in reducing the morbidity and mortality associated with DKA.

Conclusion:

DKA remains a severe complication of paediatric diabetes, with significant risks of serious consequences. Increasing awareness among healthcare professionals, ensuring early diagnosis, and implementing comprehensive management are essential to improve clinical outcomes and reduce the incidence of complications.

Keywords: Diabetic Ketoacidosis, children, type 1 diabetes mellitus

Introduction:

Diabetic ketoacidosis (DKA) is a serious complication of diabetes mellitus (DM) especially in paediatric population with increased risk of morbidity and mortality[1]. DKA is mainly associated with newly diagnosed type 1 diabetes mellitus (T1DM), but can also occur in type 2 diabetes mellitus (T2DM) at lower rates [2]. DKA is an acute complication due to relative or absolute insulin deficiency, which leads to 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].

The incidence of T1DM has increased significantly worldwide in the past few decades[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-electrolytic disorders 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, the aim of this study is to determine the prevalence of DKA in our population, to describe the clinical aspects and laboratory findings during the management of DKA in children in intensive care unit. Also, to evaluate the complications associated with DKA after the use of a standardized management protocol.

Patients and methods:

A retrospective study was performed in the paediatric intensive care unit at the university hospital: Mohammed VI in Marrakech-Morocco between January 2010 and December 2020.

In our study, we included any child under 15 years of age with DKA defined by: hyperglycaemia ≥ 2,5 g/l, ketonuria at 2 crosses or more on urine dipstick or positive ketonemia ≥ 3mmol/l and Ph< 7.3 or bicarbonates <18 mmol/l.

DKA was classified by arterial blood gas 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) score was used to identify cases with renal failure:

- Stage 1: Increased serum creatinine x 1.5 – 1.9 baseline
- Stage 2: Increased serum creatinine x 2 – 2.9 baseline
- Stage 3: Increased serum creatinine ≥ 3 or 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.

We used the International Society for Paediatric and Adolescent Diabetes (ISPAD) recommendations in the treatment of all cases of DKA [3].

The Data collected from medical records were organised in 5 main themes: epidemiological Data (age, gender, socio-economic conditions, origin), clinical and paraclinical Data (symptoms and laboratory findings), triggering factors, management and outcome of cases. The patients were divided into 2 groups: the group of patients with known diabetes presenting with DKA and the group of patients with unknown diabetes presenting with DKA for the first time. Analysis was done using Microsoft Excel® and SPSS Statistics for Windows, Version 25. Continuous variables (such as age, duration of symptoms, venous glycaemia, natremia, etc.) were expressed as mean with standard deviation (Mean +/- SD). Qualitative variables were expressed as percentages or frequencies. Pearson's χ2-test or Fisher's exact test were used for comparing proportions, and the independent samples t-test to compare means. A 5% significance level was applied.

The study was approved by Cadi Ayyad Institutional Ethics Committee of the Faculty of Medicine of Marrakech. Informed and written consent from parents / guardian was obtained

- **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 the paediatric 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** • **Male**	85 (36,48%) 73 (31,33%)	49 (21,03%) 26 (11,15%)	134 (57,51%) 99 (42,48%)	0,063

Origin: • **Urbain** • **Rural**	84 (36,05%) 74 (31,75%)	41 (17,59%) 34 (14,59%)	108 (46,35%) 125 (53,64%)	0,830
Socio-economic level : • **Medium** • **Low**	99 (42,48%) 49 (21,03%)	41 (17,59%) 34 (14,59%)	140 (60,08%) 83 (35,62%)	0,246

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. Children under 5 years of age were the 2nd most affected age group by DKA accounting for 35,62% of cases (n=83). In this age group, All DKA events were first episodes. The calculated p value was less than 0.001 indicating that younger age increases the risk of first-onset DKA (See Figure 1).
In all, DKA was inaugural in 158 cases (67.81%), and all cases of known diabetes were T1DM (n=75 or 33.19%).

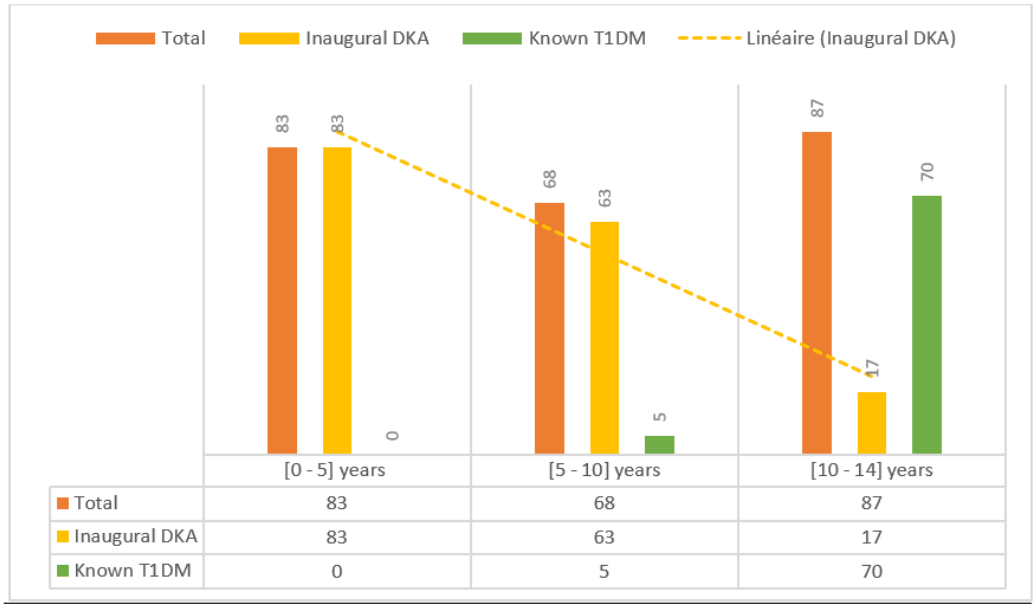

Figure 1: Distribution of children with DKA by age group

- **Clinical and paraclinical Data :**

The average delay between the onset of symptoms and hospitalisation was 2.95 +/- 1,27 days, with a maximum delay of 7 days and a minimum of 1 day. The presentation symptoms in our patients were: Polyuria-polydipsia syndrome in 219 of cases (93.99%), Kussmaul dyspnoea in 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 135 of cases (57.93%), visual disorders in 3 cases (1.29%), respiratory failure in 2 cases (0.86%). When comparing the two groups, there was a significant difference in the symptoms experienced and duration of symptoms before hospitalisation. Patients with first-time DKA had a longer time to presentation (p-value < 0,001) and experienced more severe symptoms than patients with known 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 +/-1,38 meq/l with a tendency to hyperkalaemia (K+≥5) in 84 cases (36.05%) versus 45 cases (19.31%) of hypokalaemia (K+<3.5).

According to KDIGO classification: 17 cases of acute kidney injury (AKI) were found representing a percentage of 7.3%: 5 cases (29.42%) were stage 1, 10 cases of stage 2 (58.82%), and 2 cases of stage 3 (11,76%), one patient required Renal replacement therapy (RRT). Children with first-time DKA had higher glycaemia (p-value < 0,001), severe metabolic acidosis (p-value =< 0,001) and higher osmolality (p-value < 0,001) than children with known diabetes (See Table 2).

Table 2: Clinical and biochemical results between DM debut group and known T1DM group

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 syndrome N(%)	149 (63,98%)	70 (30,04%)	219 (93,99%)	0,773
Kussmaul dyspnea N(%)	150 (64,37%)	48 (20,60%)	198 (84,97%)	< 0,001
Vomiting N(%)	108 (46,35%)	67 (28,75%)	175 (75,10%)	0,001
Alertness disorders N(%)	123 (52,78%)	31 (13,30%)	154 (66,09%)	< 0,001
Abdominal pain N(%)	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 +/- 6,10	297,97 +/- 7,06	299,81 +/- 6,54	0,005
Days of hospital stay - Mean ± SD	3,52 +/-1,05	1,82 +/- 0,76	2.97 +/- 1,25	< 0,001

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+6/-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.

- **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:

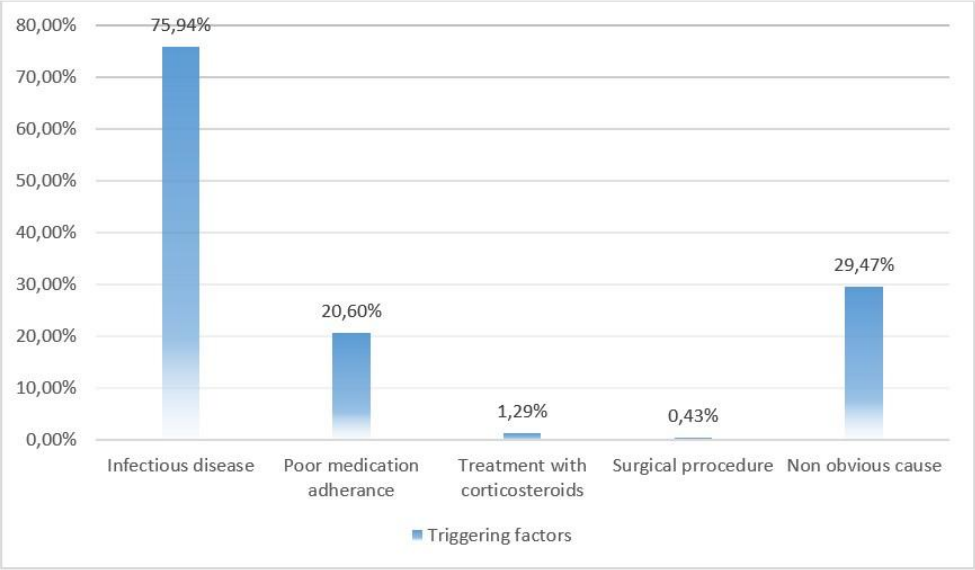

Figure 2: Triggering factors of DKA in our study

- **Management :**

The recommendations of ISPAD are based on two main components: rehydration and insulinotherapy [3]. All of the studied patients received intravenous hydration before starting the insulin administration.

We started rehydration with 0.9% isotonic sodium solution to replace the fluid deficit. Rehydration was then maintained by 5% 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 (79.40%) 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:

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

Discussion:

Over the past few decades, the incidence of T1DM in children has increased significantly[5]. Several studies have also observed higher rates of DKA at diagnosis of T1DM in children under 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 could be explained by the difficulty of verbalising symptoms at this age and the lack of awareness of the early symptoms of DM among parents and health professionals. In our study, the two most 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 mean duration of symptoms was significantly shorter in the group already diagnosed. 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. Increased awareness of early signs of T1DM among non-diabetic parents and healthcare professionals may reduce the risk of morbidity and mortality associated with DKA. The biological impact of the difference in clinical presentation was evident. The results of the analyses showed higher glycaemia and osmolality and more severe acidosis in children with first-onset DKA.

The frequency of infection as a triggering factor is still a constant fact in Africa, sometimes accounting for 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-nose and throat (ENT)infections, cutaneous, urinary, and gynecological were 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.

Delayed diagnosis of diabetes is an important factor, increasing the risk of DKA[18]. Delayed diagnosis is related to lack of parental and physicians' 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 heterolytic 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 is a potentially devastating complication of DKA that occurs almost exclusively in children [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]. Other complications of DKA include: hypokalaemia, hypoglycaemia, Hypocalcaemia, hypomagnesemia, severe hypophosphatemia, hyperchloremic acidosis, hypochloraemia alkalosis, other central nervous system complications including cerebral, venous sinus thrombosis, basilar artery thrombosis, intracranial haemorrhage, cerebral infarction…

Mortality in DKA is currently less than 1% in developed countries. However, in developing countries, this rate can reach between 3% and 13%[25]. In our study, we observed only one case of death, representing 0.43% of the cases studied. The cause of death was 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 was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Cady Ayyad University.

Declaration of patient consent:

Authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given their consent for images and other clinical information to be published in the journal.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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