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ORIGINAL ARTICLE

The Prevalence of Hypophosphatemia and its Associated Risk Factors in Diabetic Ketoacidosis Patients

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Abstract

Objective. We aimed to study the prevalence of hypophosphatemia and its associated risk factors in Diabetic Ketoacidosis (DKA) patients in the pediatric population.

Methodology. We included 65 subjects aged 7 months to 18 years old who were admitted to Hospital Universiti Sains Malaysia (HUSM) for DKA. Patients' socio-demographic and clinical characteristics, and biochemical examinations from their first admission for DKA were analyzed. The diagnosis of DKA was based on the International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria. Multiple logistic regression models examined associations between different variables and hypophosphatemia.

Result. The prevalence of hypophosphatemia in DKA was highest on day 1, at 70.8%, with a mean age of 11 on presentation. Multiple logistic regression analysis showed plasma bicarbonate at day 3 [adjusted odds ratio (OR) 1.2, with a p-value of 0.027] and baseline hemoglobin [adjusted OR 0.62, with p-value 0.009] were significantly associated with hypophosphatemia during DKA.

Conclusion. The prevalence of hypophosphatemia in DKA pediatric patients admitted to our center was highest on day 1 of admission. There were many factors associated with hypophosphatemia from simple logistic regression analysis. However, our final model revealed that plasma bicarbonate on day 3 and baseline Hb were the only significant risk factors for hypophosphatemia in DKA patients in the pediatric population.

Key words: diabetes mellitus, prevalence, hypophosphatemia, risk factors, diabetic ketoacidosis, children

INTRODUCTION

Diabetes Mellitus (DM) is a primary public health concern worldwide.[1] It leads to significant morbidity and mortality.[2] According to the World Health Organization, the prevalence of DM among pediatrics and adolescents worldwide has increased from 4.7% to 8.5% from 1980 to 2014. Diabetes in Children and Adolescents Registry (DiCARE) found that 71.8% of children under the age of 20 years old had type 1 DM while 18% suffered from type 2 DM.[3]

DKA is a complication of poorly controlled diabetes. However, more than half, or 58% of newly diagnosed DM in Malaysia presented with DKA as the first presentation because of low awareness among the public.[2-4]

Most of the electrolyte management in DKA focused mainly on potassium replacement. Until recently, the latest ISPAD consensus guidelines have emphasized other electrolyte derangements such as phosphate, calcium, and magnesium.[2,5] Hypophosphatemia can lead to complications such as anemia, metabolic encephalopathy, seizures, rhabdomyolysis, myocardial infarction, acute respiratory failure, and renal failure.[5-11]

Several important factors are associated with hypophosphatemia in DKA patients, such as metabolic acidosis, anemia, other electrolyte imbalances, fluid resuscitation, timing to start–insulin, poor glycemic control, fasting time, and length of hospital stay.[5, 12-16] There are not many publications related to hypophosphatemia among DKA patients in our region, and considering its clinical significance and serious acute complications, we conducted a retrospective review of all DKA admissions to study the prevalence of hypophosphatemia and its associated risk factors in DKA involving pediatric patients in Hospital Universiti Sains Malaysia (HUSM), Kelantan.

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METHODOLOGY

Study design and setting

This retrospective cohort study included all DKA pediatric cases admitted from January 2010 to December 2023 (13 years duration) at HUSM.

Patient and data collection

This study included 65 patients from one study site (HUSM). No sampling method was conducted as we included all the available records of patients aged 18 years and below diagnosed with DKA and excluded those with underlying primary phosphate synthesis and regulation disorders, records that are missing more than 20% of the required information, and those whose case notes were not available from the record system.

DKA was diagnosed based on ISPAD 2017 criteria (hyperglycemia more than 11 mmol/L, acidosis on blood gas [pH<7.3 or HCO3 <15 mmol/L], significant ketonuria [more or equal 2+] or ketonemia [more or equal 3 mmol/L]) and was categorized into mild, moderate, and severe DKA. Meanwhile, the hypophosphatemia level was based on HUSM laboratory references according to the age and gender of the patient.[17] For patients with recurrent DKA, only the first episode of DKA was analyzed to ensure a homogenous sample type.

Data collection was made using proforma comprising socio-demographic data, past medical history, family history of DM, history of presenting illness, summary of hospital admissions, clinical examination, and biochemical results related to DKA and hypophosphatemia (Tables 1-3). Patients' records were extracted from the HUSM record system from 2010 to 2023. A total of 92 patients were admitted for DKA within the specified time period, and 27 were excluded for the following reasons: case notes not available, admission was not the first event of DKA, and incomplete essential data (i.e., phosphate level and blood gas). This left 65 cases that were included in the final analysis of data. The search term used for tracing the patients' medical records were based on ICD10 of DM, DKA, and Hypophosphatemia.

Sample size estimation

The sample size was calculated by using a single proportion formula based on the sample size calculator web[20] to estimate the prevalence of hypophosphatemia in DKA patients as the primary objective of this study. The power and sample size program were as follows: (a) the prevalence of hypophosphatemia in DKA patients based on the previous study was 78%;[21] (b) the margin of error was set at 5%; and (c) the confidence level was set at 95%. This resulted in a sample size of 264 patients. Anticipating a 10% dropout rate, the sample size was adjusted to 294 patients. However, due to the limited sample size based on the previous record of admissions to our center, we decided to use a finite population correction calculator. Using this formula with previous details of the power and sample size program, margin of error of 6.1% and the population size set at 92 samples, the final sample size required after finite population correction calculations was 65.

Table 1. Demographic and clinical parameters

Variables	n (%)
Gender	
Male	28 (43.1)
Female	37 (56.9)
Race	
Malay	62 (95.4)
Others	3 (4.6)
Parents income status	
Higher income	15 (23)
Lower income	50 (76.9)
Parents education status	
Lower education	36 (55.4)
Higher education	29 (44.6)
****Age***	11.0 ± 4.3
Mother antenatal GDM	
Yes	1 (1.5)
No	64 (98.5)
Family History	
None	43 (66.2)
DM	18 (27.7)
DM + HPT	3 (4.6)
HPT + heart disease	1 (1.5)
Newly diagnosed DM	
No	31 (47.7)
Yes	34 (52.3)
Type of DM	
Type 1	47 (72.3)
Type 2	12 (18.5)
Others	6 (9.2)
Type of Insulin	
Human insulin	24 (37.0)
Analog insulin	5 (7.6)
****Onset of DM (years)***	4.0 ± 5.0
****Duration of DM (years)***	1.8 ± 2.9
****Total insulin/day (unit/kg)***	0.56 ± 0.79
****Total Metformin dose (g/day)***	0.06 ± 0.30
****HbA1c (%)***	11.2 ± 3.35

Parents income: Higher income (M40+T20), Lower income (B40), Malaysian household income update 2023[18]

Parents education: Higher education (Diploma and above), Lower education (Primary and secondary school), Categorical n (%), Mean ± SD*, Median (min, max)#

Statistical analysis

The categorical variables were expressed as frequencies and percentages, while data for numerical variables were either presented as mean (SD) or median (IQR), depending on whether the data was normally distributed. The distribution of numerical (quantitative) variables was determined by multiple tests, including the visual method (histogram) and the normality test (to examine the skewness, kurtosis, Kolmogorov–Smirnov test, and Shapiro-Wilk test). Data with normal distribution was presented as median with SD, whereas non-normally distributed data were presented as median and IQR.

Factors associated with hypophosphatemia were determined by logistic regression. We used simple logistic regression

analysis to identify the factors to be included in the multiple regression analysis. We used the cut-off point of p <0.25 in choosing the variables to be included in the final model. The forward selection technique was used for the variable selection method. The probability of entering the model was set at p <0.05. All the assumptions of the tests were examined. There were no interactions and multicollinearity with a variance inflation factor of less than 10.

Table 2. Clinical parameters

Variables	n (%)
DKA Severity	
Mild	10 (15.4)
Moderate	17 (26.2)
Severe	38 (58.5)
#Duration of hospital stay(days)	8.0 (3.0, 20.0)
****Total fluid bolus (ml/kg)***	21.1 ± 13.5
#Insulin infusion dose(u/kg/hour)	0.1 (0.02, 0.1)
#Duration of insulin infusion(hours)	24.0 (5.0, 168.0)
#Timing of infusion insulin on admission (hours)	2.0 (1.0, 96.0)
#Duration of NBM (hours)	22.0 (0.0, 144.0)
#DKA resolution timing (hours)	24.0 (5.0, 120.0)
****Duration of fluid correction(hours)***	40.8 ± 16.2
Tanner staging	
Prepubertal	45 (69.2)
Pubertal	20 (30.8)
#Weight (kg)	32.0 (6.7, 93.0)
****Weight (z-score)***	-0.72 ± 1.58
#Height(m)	1.4 (0.6, 1.8)
****Height (z-score)***	-0.58 ± 1.13
#BMI (kg/m²)	16.4 (11.1, 46.5)
BMI (z-score)	-0.54 ± 1.67
****SBP (mm Hg)***	116.0 ± 15.94
****DBP (mm Hg)***	70.6 ± 12.92
****HR***	122.6 ± 23.31
#GCS	15 (3,15)

Anthropometry (weight, height, and BMI in z-score) CDC growth chart, 2000[19]

Categorical n (%), Mean ± SD,* Median (min, max)#

Table 3. Biochemical data

Variables	Mean*/Median#
****RBS (mmol/L)***	26.5 ± 9.64
#Serum ketone(mmol/L)	3.9 (0.0, 7.8)
****Urine ketone (+)***	3.1 ± 0.76
#pH on admission	7.0 (6.7, 7.3)
#HCO3 on admission	8.3 (1.0, 20.6)
#BE on admission	-22.8 (-30.8, -1.8)
****pH on day 1***	7.2 ± 0.08
****HCO3 on day 1***	13.4 ± 4.20
#BE on day 1	-15.0 (-27.0, -2.6)
#pH on day 3	7.3 (0.0, 7.4)
****HCO3 on day 3***	16.7 ± 5.74
#BE on day 3	-7.2 (-21.6, 7.8)
****Hb (g/dL)***	16.7 ± 5.74
#Urea (mmol/L)	5.1 (1.0, 18.3)
****Creatinine (micromol/L)***	98.0 ± 41.47
****Sodium (mmol/L)***	132.1 ± 7.00
****Potassium (mmol/L)***	4.4 ± 0.92
#Mg (mmol/L)	0.8 (0.0, 1.3)
****Calcium (mmol/L)***	2.3 ± 0.32
#Phosphate on admission (mmol/L)	0.9 (0.2, 1.9)
#Phosphate day 1	0.7 (0.0, 2.7)
#Phosphate day 3	0.9 (0.0, 2.7)
#AST (U/L)	19.0 (5.0, 4474.0)
#ALT (U/L)	15.0 (6.0, 795.0)
#ALP (U/L)	235.0 (37.0,934.0)
#Albumin (g/L)	43.0 (27.0, 72.0)

Categorical n (%), Mean ± SD*, Median (min, max)#

Ethical approval

The study was approved by the Human Research Ethics Committee USM (USM/JEPeM/KK/23010132).

RESULTS

Majority of the included patients were female (56.9%), and predominantly Malay (95.4%). Most of the patients' parents were from a lower income status (76.9%), and about half (55.4%) had lower educational backgrounds (primary and secondary school). The mean age was 11 ± 4.37 years, with onset of DM at a mean of 4.0 ± 5.0 years old and duration of 1.8 ± 2.9 years. Most subjects did not have a history of maternal GDM (98.5%), and did not have a combined family history of DM, HPT, or heart disease (66.2%). Twenty-seven percent were positive for the family history of DM. DKA occurred in both newly diagnosed DM (52.3%) and those previously diagnosed with DM (47.7%). Thirty-seven percent were on human insulin, while only 5 (7.6%) were on analog insulin. Human insulin brands Insulatard and Actrapid were most often used (37.0%), at a mean dosage of 0.56 ± 0.79 unit per kg per day.

In terms of DKA severity, 58.5% had severe DKA, 26.2% had moderate DKA, and 15.4% had mild DKA. The mean fluid bolus during initial resuscitation was 21.1 ± 13.52 ml/kg, and the duration of fluid correction was 40.8 ± 16.22 hours. The dose of insulin infusion was 0.1 (0.02, 0.1) u/kg/hour with a median duration of 24 (5.0, 168.0) hours, and it was initiated at 2 (1.0, 96.0) hours post-hospital admission.

Other pertinent clinical parameters such as blood pressure, GCS, weight, height and BMI are tabulated in Table 2.

Mean RBS was 26.5 ± 9.64 mmol/L and HbA1c was 11.2 ± 3.3 %. Serum ketone and urine ketone levels were 3.9 (0.0,7.8) mmol/L and 3.1 ± 0.76, respectively. Blood gas on admission showed pH 7.0 (6.7, 7.3), HCO3 8.3 (1.0,20.6) and BE -22.8 (-30.8, -1.8). Blood gas on day 1 of admission improved with pH 7.2 ± 0.08, HCO3 13.4 ± 4.20, and BE -15.0 (-27, -2.6). Subsequently, the blood gas on day 3 admission was pH 7.3 (0.0,7.4), HCO3 16.7 ± 5.74, and BE -7.2(-21.6, 7.8), which were consistent with DKA resolution.

Regarding renal functions and other electrolytes, blood urea nitrogen was 5.1 (1.0, 18.3) mmol/L, serum creatinine 98.0 ± 41.47 micromol/L, sodium 132 ± 7.0 mmol/L, potassium 4.4 ± 0.92 mmol/L, Mg 0.8 (0.0,1.3) mmol/L, and calcium of 2.3 ± 0.32 mmol/L. The liver transaminases were AST 19.0 (5,4474) U/L, ALT 15.0 (6,795) U/L. Whereas, ALP was 235.0 (37,934) U/L and serum albumin 43 (27,72) g/L. The mean Hb of our patients was 16.7 ± 5.74 g/dL.

Table 4. Simple and multiple logistic regression analyses to determine factors associated with Hypophosphatemia in DKA

Variables	Crude OR (95% CI)	*P*-value	Adjusted OR (95%)	*P*-value
Family history				
DM	0.3 (0.1,1.0)	0.069		
DM + HPT	0.6 (0.05,8.3)	0.769		
HPT + heart disease	1.0			
Severity of DKA				
Mild	1.0			
Moderate	2.6 (0.5, 13.7)	0.253		
Severe	10.3 (2.12, 50.2)	0.004		
Heart rate	1.03 (1.002, 1.051)	0.035		
Duration of fluid correction	1.03 (0.9, 1.0)	0.069		
Urine ketone	2.0 (1.0, 4.2)	0.042		
pH on admission	0.003 (0.0, 0.2)	0.007		
HCO3 on admission	0.7 (0.6, 0.9)	0.003		
BE on admission	0.8 (0.7, 0.9)	0.002		
pH day 3	1.3 (1.0, 1.8)	0.049		
HCO3 day 3	1.1 (1.0, 1.2)	0.017	1.2 (1.0, 1.3)	0.027
Hb	0.7 (0.5, 0.9)	0.039	0.62 (0.4, 0.8)	0.009
Calcium	0.2 (0.02, 1.2)	0.080		
Albumin	0.9 (0.8, 1.0)	0.081		

On the day of admission, serum phosphate was noted to be 0.9 (0.2, 1.9) mmol/L, which then dropped to 0.7 (0.0, 1.7) mmol/L on day 1 of admission and improved with a median of 0.9 (0.0,2.7) mmol/L on day 3 of admission. The prevalence of hypophosphatemia among DKA patients on presentation was 66.2% (CI 0.5, 0.70), and it increased to 70.8% (CI 0.5,0.8) while patients were receiving treatment on day 1 and later reduced to 56.9% (CI 0.4,0.6) on the third hospital day.

Based on simple logistic regression analysis, family history of DM (Crude OR 0.3 (0.1,1.0), *p*-value 0.069), severe DKA (Crude OR 10.3 (2.12, 50.2), *p*-value 0.004), heart rate (Crude OR 1.03 (1.002, 1.051), *p*-value 0.035), duration of fluid correction (Crude OR 1.03 (1.002, 1.051), *p*-value 0.069), urine ketone (Crude OR 2.0 (1.0, 4.2), blood gas on admission (pH on admission Crude OR 0.003 (0.0,0.2) *p*-value 0.007), (HCO3 on admission Crude OR 0.7 (0.6,0.9) *p*-value 0.003), (BE on admission Crude OR 0.8 (0.7, 0.9) *p*-value 0.002), pH on day 3 (Crude OR 1.3 (1.0, 1.8), *p*-value 0.049), HCO3 on day 3 (Crude OR 1.1 (1.0,1.2), *p*-value 0.017), baseline Hb (Crude OR 0.7 (0.5, 0.9), *p*-value 0.039), serum calcium (Crude OR 0.2 (0.02, 1.2), *p*-value 0.080) and albumin (Crude OR 0.9 (0.8,1.0), *p*-value 0.081) were significantly associated with hypophosphatemia among DKA patients. However, only HCO3 on day 3 [adjusted OR 1.2 (1.0,1.3), a *p*-value of 0.027], and baseline Hb [adjusted OR 0.62 (0.4, 0.8), a *p*-value of 0.009] proved to be significantly associated with hypophosphatemia using multiple logistic regression analysis (Table 4).

There were no interactions and multicollinearity with a variance inflation factor of less than 10. The Hosmer-Lemeshow test assessed the model's fitness, and 76.9% of cases were predicted correctly. The area under the curve (AUC) was 83% with 95% CI (0.72,0.93). There were no significant outliers, high leverage points or highly influential points as checked by Cook's influential statistics.

DISCUSSION

We managed to review 65 DKA patients, aged 7 months to 18 years old, admitted to our hospital from 2010 to 2023. The prevalence of hypophosphatemia in DKA patients was highest on day 1 (70.8%) and lowest on day 3 admission (56.9%), which was consistent with another local study by Anand et al., that had a prevalence of hypophosphatemia among DKA patients of 78%.[21] A study by Van Der Vaart et al., also showed the prevalence of hypophosphatemia in DKA patients to be similar, at about 74%.[15] However, a study by Sanluis Fenelli G et al., showed a lower prevalence of hypophosphatemia on day 1 admission (after treatment) at only 36.7%.[12] Despite a difference in the prevalence from various studies, we noticed similarities in trend of phosphate levels from a lower level at baseline which further declines to reach the lowest level on day 1 and then slowly improves throughout admission.

Our study showed a female predominance at 56.9% compared to males at 43.1%. The study of Van Der Vaart et al., also showed female predominance at 50.4%.[15] In contrast, a study by El-Naggar A et al., showed male predominance at 64.7%.[16] Most of our patients were Malay since the East Coast of Malaysia is mainly populated by Malay, and they were from lower socio-economic backgrounds. The high prevalence of DKA as the first presentation in new cases of DM and in those previously diagnosed to have DM may be associated with poor public awareness or lack of education.[3]

The mean age of DKA at presentation was 11 years old, the same as a local study by Anand LA et al.[21] According to ISPAD guideline 2017, DKA at diagnosis is commonly seen in younger children aged less than 2 years old, including infants with both transient and permanent neonatal diabetes.[2] However, in the study by Hong et al., the mean age of DKA at presentation was mainly the age of more than 5.[3] It was concluded in most of the studies

that age did not show any significant association with hypophosphatemia.[12-16]

Most of the patients did not have a mother with antenatal GDM (98.5%) and did not have family history of DM, HPT, or heart disease (66.2%). Our patients were mainly type 1 DM, which explained why the family history for DM was negative. This contrasts with a local study by Hong et al., where the proportion was 56.9% for a positive family history of DM in DKA patients.[3] The study recruited patients from mainly Klang Valley with a higher proportion of type 2 DM than our cohort.

Type 1 DM predominates most of our patients (72.3%) compared to type 2 (18.5%) and other types of DM (9.2%). It showed that DKA is more common in type 1 DM since type 1 DM is due to absolute insulin deficiency, leading to increased endogenous glucose production and counter-regulatory hormones.[2] In Malaysia, the rate of DKA occurrence at the onset of T1DM was as high as 57.5% because of poor public awareness since type 1 DM is not common in our region compared to Europe.[4] The overall prevalence of T2DM is on the rise, which is consistent with an increase in the prevalence of obesity.[5] In type 2 DM, DKA occurs as a consequence of relative insulin deficiency. High adiposity in type 2 DM leads to insulin cascade signaling interference, resulting in insulin resistance syndrome. During the time of infection, the rise of counter-regulatory hormones contributes to a high glucose load, and whenever the body is unable to meet the demands, it results in relative insulin deficiency and, ultimately DKA.[22]

Hypophosphatemia correlates with the degree or severity of DKA. In DKA, there is intracellular depletion of phosphate associated with the shift of phosphate from the intracellular to the extracellular compartment associated with metabolic acidosis. Renal tubular phosphate reabsorption is impaired during DKA, resulting in hyperphosphaturia. With fluid and insulin administration during the treatment phase of DKA, phosphate is shifted back into the intracellular compartment, leading to low plasma phosphate levels. Hence, hypophosphatemia is caused by osmotic losses in the urine and secondary to fluid and insulin administration during the treatment phase of DKA.[2] We found that severe acidosis on admission had increased odd 10.3; 95% CI (2.1,50.2) from simple logistic regression analysis.

The majority of our patients were prepubertal with a low BMI of 16.4 kg/m^2 (z-score -0.54), which was typical of type 1 DM with poorly controlled DM, and this finding was similar to Hong et al.[3] They had normal BP with normal GCS on presentation, which showed that even though 58% presented with severe DKA, complications such as decompensated shock and cerebral edema were rare. Their overall HbA1c was high (11.2%), similar to Anand et al., which showed a mean HbA1c of 12.6%.[19] High HbA1c had a significant correlation with low-level serum phosphate, according to Hasan et al.,[13] which was not demonstrated in our current study.

From univariate analysis, positive predictors of hypophosphatemia in DKA were BE on admission [OR 0.8 (0.7,0.9)], HCO3 at day 3 [OR1.1 (1.0,1.2)], urine ketone [OR 2.0 (1.0,4.2)], fluid boluses [OR 1.3 (1.0,1.6)], duration of fluid correction [OR 1.03 (0.9,1.0)], heart rate [OR 1.03 (1.002,1.051)], severe DKA [OR 10.3 (2.12,50.2)], and pH at day 3 [OR 1.3 (1.0,1.8)]. In our study, the BE on admission was high (-22.6), typically seen in severe DKA, which later normalized, as evidenced by normal pH and HCO3 on day 3. This could be explained by the patient's treatment, which includes insulin infusion and fluid therapy. Insulin facilitates glucose and phosphate uptake into the cells, while fluid administration corrects the hyperosmolar state due to hyperglycemia. High levels of blood glucose that exceed the renal threshold for glucose reabsorption result in osmotic diuresis and worsening of hypophosphatemia. When DKA has been reversed, as evidenced by increasing pH and bicarbonate levels, phosphate levels will normalize, too. Protective predictors for hypophosphatemia were positive family history of DM [OR 0.3 (0.1,1.0)], serum albumin [OR 0.9 (0.8, 1.0)], calcium [OR 0.2 (0.02, 1.2)], baseline Hb [OR 0.7 (0.5,0.9)], pH admission [OR 0.003 (0.0, 0.2)] and HCO3 on admission [OR 0.7 (0.6,0.9)]. Those with normal levels of albumin, calcium, hemoglobin, and bicarbonate and a positive family history of DM were less likely to have hypophosphatemia.

There were 2 significant predictors of hypophosphatemia from the multivariate analysis: plasma bicarbonate level on day 3 [OR 1.2 (1.0,1.3)] and hemoglobin level at baseline [OR 0.62 (0.4,0.8)]. The plasma HCO3 level on day 3 admission (while the patient received ongoing treatment) increases the odds of hypophosphatemia by 1.2 times. This is due to increased intracellular glycolysis that consumes phosphate for ATP production, resulting in the reduction of intracellular phosphate, and to compensate for this, the extracellular phosphate will enter cells, leading to low serum phosphate levels. The Hb at baseline was associated with 38% decreased odds of having hypophosphatemia. This important information reflects the volume depletion secondary to osmotic diuresis leading to phosphate loss. These 2 final predictors were also reported by Van der Vaart et al., study in 2021.[15]

Limitations of the study

The study had a few limitations. The cases were limited to our centre alone. They might not truly represent DKA cases with hypophosphatemia in our state since some of the cases were managed at other hospitals. The study design in itself was a limitation as it was a retrospective cohort study which tend to have a lot of missing data. It would be ideal to perform a prospective study with a longer duration to follow the patient up and for more extensive monitoring of important laboratory parameters. In addition, to achieve a good sample size the study might need to be done in multicentre in the future.

CONCLUSION

The prevalence of hypophosphatemia in pediatric patients admitted to our center for DKA was highest on day 1 of admission. Many factors were identified to be associated with hypophosphatemia from simple logistic regression analysis, however, final model revealed that plasma bicarbonate on day 3 and baseline Hb were the only significant risk factors for hypophosphatemia in DKA patients. Nevertheless, with the small sample size of this study, our results need to be verified in larger, well-powered studies of a similar nature.

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Statement of Authorship
All authors are certified in fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

CRediT Author Statement
MHR: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **SH**: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **MHK:** Conceptualization, Methodology, Software, Validation, Investigation, Resources, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition; **NJA:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition.

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References
1. CDC. Diabetes in Youth. 2021. Accessed date, April 4, 2022. https://www.cdc.gov/diabetes/library/reports/reportcard/diabetes-in-youth.html
2. Wolfsdorf J, Craig ME, Daneman D, et al. Diabetic ketoacidosis in children and adolescents with diabetes. Pediatr Diabetes. 2009;10(Suppl 12):118–33. PMID: 19754623 DOI: 10.1111/j.1399-5448.2009.00569.x
3. Hong JYH, Jalaludin MY, Mohamad Adam B, et al. Diabetic ketoacidosis at diagnosis of type 1 diabetes mellitus in Malaysian children and adolescents. Malaysian Fam Physician. 2016;10(3):11–8. PMID: 27570603 PMCID: PMC4992349
4. Ho J, Huang C, Pacaud D. Management of type 1 diabetes mellitus in children. Malaysia Health Technology Assessment Section (MaHTAS). 2015. https://www.moh.gov.my/moh/resources/maklumat%20terkini/DRAF%20CPG/Draft_CPG_T1DM_301115.pdf
5. Lervang H-H, Ditzel J. Disturbance of inorganic phosphate metabolism in diabetes mellitus: Clinical manifestations of phosphorus-depletion syndrome during recovery from diabetic ketoacidosis. Diabetes, Metab Syndr Obes Targets Ther. 2010;3:319-24. PMID: 21437101 PMCID: PMC3047968 DOI: 10.2147/DMSOTT.S13476
6. Brunelli SM, Goldfarb S. Hypophosphatemia: Clinical consequences and management. J Am Soc Nephrol. 2007;18(7):1999–2003. PMID: 17568018 DOI: 10.1681/ASN.2007020143
7. Yoshida T, Takemoto M. Impaired cardiac and neurological function with mild hypophosphatemia during insulin therapy for diabetic ketoacidosis and marked improvement with phosphate supplementation: A case report. J Diabetes Investig. 2021;12(3):454–8. PMID: 32654423 PMCID: PMC7926208 DOI: 10.1111/jdi.13357
8. Miszczuk K, Mroczek-Wacinska J, Piekarski R, Wysocka-Lukasik B, Jawniak R, Ben-Skowronek I. Ventricular bigeminy and trigeminy caused by hypophosphataemia during diabetic ketoacidosis treatment: A case report. Ital J Pediatr. 2019;45(1):42. PMID: 30940174 PMCID: PMC6444668 DOI: 10.1186/s13052-019-0633-y
9. Choi HS, Kwon A, Chae HW, Suh J, Kim DH, Kim HS. Respiratory failure in a diabetic ketoacidosis patient with severe hypophosphatemia. Ann Pediatr Endocrinol Metab. 2018;23(2):103–6. PMID: 29969883 PMCID: PMC6057019 DOI: 10.6065/apem.2018.23.2.103
10. Shah SK, Shah L, Bhattarai S, Giri M. Rhabdomyolysis due to severe hypophosphatemia in diabetic ketoacidosis. JNMA J Nepal Med Assoc. 2015;53(198):137–40. PMID: 26994037
11. De Oliveira Iglesias SB, Pons Leite H, de Carvalho WB. Hypophosphatemia-induced seizure in a child with diabetic ketoacidosis. Pediatr Emerg Care. 2009;25(12):859–61. PMID: 20016359 DOI: 10.1097/PEC.0b013e3181c399f6
12. Fenelli GS, Aded CB, Lagger J, et al. [Prevalence of hypophosphatemia in children with diabetic ketoacidosis and treatment with subcutaneous regular insulin. Observational study]. Andes Pediatr. 2024;95(2):183-9. PMID: 38801366 DOI: 10.32641/andespediatr.v95i2.4924
13. Shen T, Braude S. Changes in serum phosphate during treatment of diabetic ketoacidosis: Predictive significance of severity of acidosis on presentation. Intern Med J. 2012;42(12):1347–50. PMID: 23252999 DOI: 10.1111/imj.12001
14. Hasan RA, Hesen JZ, Millican N, Pederson JM, Michael. Serum phosphorus and hypophosphatemia during therapy of diabetic ketoacidosis in children: Single-center, retrospective cohort 2016–2022. Pediatr Crit Care Med. 2024;26(1):e77–85. PMID: 39785552 PMCID: PMC11706349 DOI: 10.1097/PCC.0000000000003649
15. Van Der Vaart A, Waanders F, Van Beek AP, Vriesendorp TM, Wolffenbutel BHR, Van Dijk PR. Incidence and determinants of hypophosphatemia in diabetic ketoacidosis: An observational study. BMJ Open Diabetes Res Care. 2021;9(1):e002018. PMID: 33597187 PMCID: PMC7893606 DOI: 10.1136/bmjdrc-2020-002018
16. El-Naggar A, Sameer G, Sadek A. Impact of hypophosphatemia and hypomagnesaemia on diabetic ketoacidosis patient's outcome in medical intensive care unit. Zagazig Univ Med J. 2021. DOI: 10.21608/zumj.2021.65424.2156
17. Colantonio DA, Kyriakopoulou L, Chan MK, et al. Closing the gaps in pediatric laboratory reference intervals: A caliper database of 40 biochemical markers in a healthy and multiethnic population of children. Clin Chem. 2012;58(5):854–68. PMID: 22371482 DOI: 10.1373/clinchem.2011.177741
18. Lim JL. T20, M40, B40 Household income update 2023. Malaysian Employers Federation. 2023 https://mefacademy.mef.org.my/Attachments/MSN20230731a.pdf
19. Centers for Disease Control and Prevention, National Center for Health Statistics. CDC growth charts. Accessed May 30, 2000. http://www.cdc.gov/growthcharts/.
20. Arifin WN. Sample size calculator; 2024. http://wnarifin.github.io
21. Anand LA, Syahirah MN, Jalaludin MY, Zaini AA. Prevalence of hypophosphatemia in children with diabetic ketoacidosis. J ASEAN Fed Endocr Soc. 2022;37:10. DOI: 10.15605/jafes.037.S2.96
22. Puttanna A, Padinkakara RNK. Diabetic ketoacidosis in type 2 diabetes mellitus. Pract Diabetes. 2014;31(4):155–8.