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ORGINAL ARTICLE

Impact of Hypophosphatemia and Hypomagnesaemia on Diabetic Ketoacidosis patient's Outcome in Medical Intensive Care Unit

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ABSTRACT

Background: Diabetic ketoacidosis (DKA) is a life-threatening condition of biochemical derangements comprising hyperglycemia, acidosis, and ketonemia. The study aimed to explore the prognostic impact of phosphate (Po4) and magnesium (Mg) levels on DKA-associated morbidity and mortality.

Methods: Sixty-eight patients with DKA were admitted to the intensive care unit (ICU) in the Internal medicine Department in Zagazig University Hospital over the period of 6 months were evaluated serially for Po4 and Mg levels among other routine investigation. The patients were followed for the in-hospital clinical outcome.

Results: hyponatremia, HbA1c, random blood sugar (RBS), creatinine, urea, ICU stay, low pH, and hypophosphatemia showed a strong correlation with a mortality rate (P<0.001), while hypomagnesemia was insignificant. A positive correlation was noticed between Po4 and sodium (Na) level (P=0.004), whereas a negative correlation with RBS (P=0.001), HbA1c (P=0.001), creatinine (P=0.001), urea (P=0.001), and ICU stay duration (P=0.008). Hypophosphatemia had a 13-fold higher relative risk for mortality in DKA.

Conclusion: We concluded that hypophosphatemia was an independent predictor of the DKA-associated mortality rate, and serial Po4 measurement should be considered in DKA treatment protocols.

Keywords: Diabetic ketoacidosis, Hypophosphatemia, Intensive Care Units, Magnesium, Patient Outcome Assessment

INTRODUCTION

Diabetic ketoacidosis (DKA) is a deleterious sequel of uncontrolled diabetes mellitus (DM), comprising hyperglycemia, high anion gap metabolic acidosis, and ketonemia. It symbolizes a state of deficient insulin with counterregulatory hormones storm (growth hormone, glucagon, cortisol, and catecholamines), causing a deranged glucose and fatty acids homeostasis. [1]

Serum Po4 level significantly changes through the course of DKA treatment. Acidosis causes an extracellular shift of Po4, with the reversal of this process during pH level recovery. During these changes, a significant part of Po4 is lost, leading sometimes to marked hypophosphatemia with hazardous outcomes, involving nervous, respiratory, cardiac, muscular, and endocrinal systems, resembling multiorgan failure state [2, 3].

Hypomagnesemia has a known effect of increasing potassium (K) and Po4 loss in urine, causing difficulty in their replenishment. In addition to the deleterious effect on muscular

contractility especially the respiratory and cardiac muscles [3, 4, 5].

Studies on the changes of serum Po4 and Mg in patients with DKA are insufficient, with uncertain data about the link between Po4 and Mg levels with DKA outcome.

The study aimed to explore the prognostic impact of Po4 and Mg levels on DKA-associated morbidity and mortality.

2|Methods

2.1|Study design and settings

We carried out a cross-sectional cohort study conducted in the period extending from January 2018 to November 2018 in the medical intensive care unit of the internal medicine department, Zagazig University Hospitals, Egypt.

2.2|Participants

Forty-four patients were type 1 DM while the other 24 patients were known to be type 2 DM. 44 patients were males while the remaining 24 patients were females, their age ranged from 17 to 73 years with a mean age ± SD (35.35±18.38) years.

2.3|Ethical clearance

Written Informed and oral consents were taken from the relatives of patients who were participated in the study in addition to the approval of the internal medicine department, and the Institutional Review Board (IRB:4228). We comply with the code of ethics of the world medical association (Declaration of Helsinki).

2.4|Inclusion criteria

Patients aged 16 years or older, of either gender, admitted to the medical ICU (either for the first time or recurrent admission) with DKA criteria (Serum glucose >250 mg/dL, Serum bicarbonate concentration <18 mmol/L, arterial pH <7.30, ketonemia >3 mmol/L, and significant ketonuria > 2+ on standard urine sticks).

2.5|Exclusion criteria

Other metabolic acidosis states like uremia, lactic acidosis, and inborn errors of metabolism. In addition, the consumption of ethylene glycol, iron, isoniazid, methanol, paraldehyde, and salicylates.

2.6|Process

Complete medical history was obtained from the patient, families, or prior medical records including diabetes mellitus type either type I or II, use of insulin and or oral hypoglycemic agents, other accompanying medical diseases of importance like IHD, hypertension, and chronic liver disease, and the occurrence of previous DKA.

Laboratory tests including random blood glucose, urine analysis, complete blood picture, blood gases and electrolytes, kidney function tests, liver function tests, HbA1c, serum Mg, serum Po4, and urine sample in a plastic container (preservative-free) at room temperature using a reagent strip (Ketostix) for acetone. Normal range of Po4 is 2.5 to 4.5 mg/dL, Po4 level from 2-2.5 mg/dL, 1-2 mg/dL, and less than 1 mg/dL is considered mild, moderate, and severe hypophosphatemia, respectively. Normal range of Mg is 1.7 to 2.4 mg/dl, Mg level from 1.4-1.7 mg/dL, 1-1.4 mg/dL, and less than 1 mg/dL is considered mild, moderate, and severe hypomagnesemia, respectively.

2.7|Statistical analysis

Data were collected in a Microsoft Excel sheet, then imported into the Statistical Package for the Social Sciences (SPSS version 20.0, Armonk, NY: IBM Corp.) software for analysis. Qualitative data were denoted as number and percentage, and the Chi-square test is used to measure the significance of differences, and in small groups (less than five), Fisher Exact test was applied. Whereas mean ± SD signifies continuous variables that were analyzed by the Shapiro Wilk test for normality. Gaussian distributed two groups verified by Student t-test, and One-Way ANOVA in three groups. While Mann Whitney test was used for non-gaussian distributed two groups and Kruskal Wallis for three groups. Pearson's and Spearman's correlation is applied for the assessment of parametric and non-parametric variables respectively. A multivariate logistic regression model was generated to signify the independent factors of mortality. Relative risk was calculated by dividing the death risk in a specific

population group by the risk of people from all other groups. Alpha level value <0.05 was set for significance.

3|RESULTS

From all precipitating factors, infections account for about 50% of the total number of patients and the 2nd precipitating factor was poor compliance (Table1).

No significant changes in CBC, liver, and kidney functions in patients with DKA. Also, the study reveals very poor control of DM as the HbA1c Range about 9%. No significant change in sodium and potassium level. As patients with DKA PH median was 7.2 (Table2).

At (day 0) most of patients had normal phosphorus level (2.5:4.5mg/dl) while seven patients were admitted with mild hypophosphatemia (2:2.5 mg/dl), four patients admitted with moderate hypophosphatemia (1-2 mg/dl) and only one patient admitted with severe hypophosphatemia (< 1.0mg/dl). At (day 2) shows the highest number of patients with hypophosphatemia equally divided between mild and moderate hypophosphatemia. On the day of discharge, most patients 56(out of 59) were normal, two had mild hypophosphatemia and only one patient had moderate hypophosphatemia (Supplementary1).

At (day 0) 61 patients were normal, five patients had mild hypomagnesaemia (1.5-1.7 mg/dl) and two patients had moderate hypomagnesaemia (1.1- 1.5 mg/dl). On (Day 2) 60 patients were normal, six patients had mild hypomagnesemia, two patients had moderate hypomagnesemia. On the day of discharge 51 patients were normal and two patients had mild hypomagnesemia (Supplementary2).

A significantly higher RBS, creatinine, HbA1C, ICU stay, and urea with a significantly lower duration of DM, Na, PH, and phosphate were noticed in deceased patients. No significance regarding Mg also died patients associated with type 2 diabetes and comorbidities (Table 3).

There is a positive correlation between PO4 level and Na^+ and PH, while there is a negative correlation between PO4 level and random blood sugar, HbA_1c, creatinine, urea, and ICU stay (Table4).

There is a positive correlation between Mg level and age and AST, while there is a negative correlation between Mg level and creatinine (Table5).

Co-morbidity, low PH, and low PO4 level were only independent predictors for mortality (Table 6).

Also, the relative risk of mortality in patients with hypophosphatemia was higher by13 fold (Supplementary3).

Table (1) Demographic data of DKA patients in the study.

		Mean	SD	Median(range)
Age		35.35	18.38	27.0 (17-73)
Duration of DM		17.22	5.9	16.5 (5-30)
Blood pressure	**SBP**	135.25	15.35	130 (100-160)
	DBP	82.5	12.8	80.0(60-100)
Heart rate		85.0	8.5	83.0(70-95)
Temperature		37.35	2.3	37.0(36.5-38.4)
		Number		Percentage %
Gender	**Male**	44		64.7%
	Female	24		35.3%
Type of DM	**Type 1**	44		64.7%
	Type 2	24		35.3%
CO- morbidity	**No**	49		72.1%
	Hypertension	9		13.2%

		Mean	SD	Median(range)
	CVD	7		10.3%
	CVA	3		4.4%
Precipitating factors	**Infection**	34		50%
	Non-compliance	21		30.9%
	Cardio-vascular disease	13		19.1%

CVA, Cerebro-vascular accident; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; IDDM, insulin dependent DM; NIDDM, non-insulin dependent DM; SBP, systolic blood pressure; SD, standard deviation.

Table (2): Laboratory Data of DKA patients in the study:

	Mean	SD	Median (range)
Hb	11.09	1.04	11.0 (8.9-13)
WBCs	7.95	2.3	7.6 (4-12)
ALT	20.05	3.5	20.0 (12-26)
AST	20.3	3.5	19.0 (14-29)
Bilirubin	1.22	0.26	1.12 (0.98-1.7)
Albumin	3.95	1.3	4.1 (2.7-4.6)
Creatinine	2.1	0.69	2.1 (1-3.2)
Urea	35.98	10.6	32.0 (19-56)
RBS	519.05	84.9	507.0 (389-725)
HbA1c	9.15	0.51	9.05 (8-10.5)
Na	131.58	3.63	133.0 (122-135)
K	4.16	0.28	4.2 (3.5-4.5)
Ca	10.9	2.3	11.2 (9.8-13.7)
pH	7.17	0.12	7.2 (6.9-7.4)
Po_4 Day 0	3.45	0.81	3.3 (0.9-4.5)
Po_4 Day 2	3.0	0.85	3.05 (1.3-4.2)
Po_4 at the End	3.2	0.8	3.2 (1.6-4.4)
Mg Day 0	1.93	0.3	1.9 (1.3-2.5)
Mg Day 2	1.87	0.28	1.88 (1.5-2.3)
Mg at the End	1.94	0.28	1.9 (1.5-2.5)

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; Ca, Calcium; HbA1c, Glycated Hemoglobin; Hb, Hemoglobin; K, Potassium; Mg, Magnesium; Na, Sodium; PO4, Phosphate; RBS, Random Blood Sugar; WBCs, White Blood Cells.

Table (3): Comparison between survived and died of DKA patients in the study:

parameter	Died (N=9)	Survived (N=59)	t	p
Age	46.28±15.03	35.54±13.5	1.929	0.058
Duration DM	13.0±6.06	17.86±5.6	-2.368	**0.021**
RBS	640.0±75.8	500.6±70.1	5.496	**<0.001**
HbA1c	9.95±0.33	9.03±0.42	6.261	**<0.001**
Na	127.6±4.27	132.18±3.1	-3.811	**<0.001**
K	4.24±0.3	4.15±0.28	0.843	0.402
pH	7.0±0.08	7.2±0.1	-5.288	**<0.001**
HB	11.55±0.93	11.02±1.05	1.432	0.157
WBCs	7.34±2.1	8.05±2.3	-0.851	0.398

parameter		Died (N=9)	Survived (N=59)	t	p
ALT		20.44±3.2	20.0±3.6	0.349	0.728
AST		20.66±5.14	20.25±3.3	0.321	0.750
Creatinine		3.1±0.15	1.95±0.61	5.539	**<0.001**
Urea		52.0±5.26	33.54±9.0	5.969	**<0.001**
Po_4 Day 0		1.58±0.52	3.51±0.64	-8.634	**<0.001**
Po_4 Day 2		1.52±0.26	3.23±0.66	-7.603	**<0.001**
Po_4 at the End		1.77±0.24	3.42±0.61	-7.913	**<0.001**
Mg Day 0		1.96±0.13	1.93±0.32	0.325	0.746
Mg Day 2		2.06±0.13	2.01±0.27	0.586	0.560
Mg at the End		1.96±0.13	1.94±0.29	0.223	0.824
ICU Stay		8.0±1.58	6.57±1.13	3.327	**<0.001**
		N (%)	**N (%)**	**χ^2**	
Sex	**Male**	6 (66.7%)	38 (64.4%)	0.017	0.89
	Female	3 (33.3 %)	21 (35.6%)		
DM Type	**Type 1**	3 (33.3%)	41 (69.5%)	4.47	**0.034**
	Type 2	6 (66.7%)	18 (30.5%)		
CO morbidity	**NO**	3 (33.3%)	46 (78.0 %)	7.7	**0.005**
	YES	6 (66.7%)	13 (22.0%)		
Precipitating factors	**CVD**	3 (33.3%)	10 (16.9%)	4.87	0.08
	Infection	6 (66.7%)	28 (47.5%)		
	Non-compliance	0 (0.0 %)	21 (35.6%)		

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; Ca, Calcium; HbA1c, Glycated Hemoglobin; Hb, Hemoglobin; K, Potassium; Mg, Magnesium; Na, Sodium; PO4, Phosphate; RBS, Random Blood Sugar; t, t-test; WBCs, White Blood Cells; χ^2, chi square.

Table (4): correlation with PO4 with other parameters in the DKA studied patients:

		Po_4 Day 0	Po_4 Day 2	Po_4 at the End
Age	**r**	0.086	0.122	0.069
	p	0.483	0.32	0.578
Duration of DM	**r**	-0.213-	-0.167-	-0.228-
	p	0.081	0.174	0.061
RBS	**r**	-0.405-	-0.415-	-0.428-
	p	**0.001**	**<0.001**	**<0.001**
HbA1c	**r**	-0.538-	-0.545-	-0.556-
	p	**<0.001**	**<0.001**	**<0.001**
Na	**r**	0.342	0.282	0.298
	p	**0.004**	**0.02**	**0.014**
K	**r**	-0.204-	-0.196-	-0.166-
	p	0.095	0.109	0.176
pH	**r**	0.17	0.252	0.216
	p	0.167	**0.038**	0.077
Hb	**r**	-0.068-	-0.209-	-0.148-
	p	0.583	0.088	0.227
WBCs	**r**	-0.005-	0.052	0.021
	p	0.965	0.675	0.867
ALT	**r**	0.132	0.084	0.098
	p	0.284	0.498	0.428

		Po_4 Day 0	Po_4 Day 2	Po_4 at the End
AST	**r**	-0.027-	0.041	0.026
	p	0.824	0.739	0.836
Creatinine	**r**	-0.595-	-0.663-	-0.646-
	p	**<0.001**	**<0.001**	**<0.001**
Urea	**r**	-0.649-	-0.655-	-0.667-
	p	**<0.001**	**<0.001**	**<0.001**
ICU Stay	**r**	-0.318-	-0.247-	-0.244-
	p	**0.008**	**0.042**	**0.045**

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; Ca, Calcium; HbA1c, Glycated Hemoglobin; Hb, Hemoglobin; K, Potassium; Mg, Magnesium; Na, Sodium; PO4, Phosphate; RBS, Random Blood Sugar; WBCs, White Blood Cells.

Table (5): correlation with Magnesium with other parameters in the DKA studied patients:

		Mg Day 0	Mg Day 2	Mg at the End
Age	**r**	0.532	0.505	0.473
	p	**<0.001**	**<0.001**	<0.001
Duration DM	**r**	-0.126-	-0.182-	-0.158-
	p	0.307	0.138	0.199
RBS	**r**	0.072	0.157	0.178
	p	0.561	0.202	0.148
HbA1c	**r**	0.109	0.120	0.119
	p	0.375	0.330	0.334
Na	**r**	-0.169-	-0.189-	-0.178-
	p	0.168	0.122	0.146
K	**r**	-0.097-	-0.020-	-0.017-
	p	0.432	0.872	0.891
pH	**r**	-0.230-	-0.267-	-0.185-
	p	0.060	**0.028**	0.131
Hb	**r**	-0.201-	-0.174-	-0.181-
	p	0.100	0.156	0.139
WBCs	**r**	0.008	0.037	0.066
	p	0.946	0.762	0.595
ALT	**r**	0.073	0.098	0.084
	p	0.553	0.427	0.494
AST	**r**	0.246	0.236	0.211
	p	**0.043**	0.052	0.084
Creatinine	**r**	-0.339-	-0.297-	-0.360-
	p	**0.005**	**0.014**	0.003
Urea	**r**	-0.198-	-0.207-	-0.202-
	p	0.105	0.091	0.098
ICU Stay	**r**	-0.013-	0.014	0.015
	p	0.919	0.912	0.906

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; Ca, Calcium; HbA1c, Glycated Hemoglobin; Hb, Hemoglobin; K, Potassium; Mg, Magnesium; Na, Sodium; PO4, Phosphate; RBS, Random Blood Sugar; WBCs, White Blood Cells.

Table (6): multivariate logistic regression for predictors of mortality in DKA patients in the study:

Independent predictors	p	OR	95% CI	
			Lower	Upper
High Duration DM	0.124	0.237	0.000	1.214
Type II DM	0.078	2.521	0.897	12.325
CO-morbidity	**<0.001**	15.254	5.214	25.324
High RBS	0.214	1.291	0.562	7.6541
High HbA1c	0.087	9.025	0.987	16.214
Low Na	0.321	2.159	0.321	4.254
Low pH	**0.025**	10.235	3.214	18.254
High Creatinine	0.541	6.139	0.912	15.245
Low Po_4	**0.045**	7.548	2.321	26.512
ICU Stay	0.075	1.534	0.784	5.621

DM, diabetes mellitus; HbA1c, Glycated Hemoglobin; Na, Sodium; RBS, Random Blood Sugar.

4|DISCUSSION

A few little studies were done regarding the impact of hypophosphatemia and hypomagnesemia on patients with DKA outcomes. The current study enrolled 68 patients with DKA and serially measured phosphate and magnesium levels among other routine investigations through the treatment period to access their influence on mortality.

In our study mean ± SD of age was 35.35±18.38 with a minimum of 17 and a maximum of 73 years old. Most of the patients were between the age of 17 and 35 years old with a mean age of 35.35 and with a median of 27 years. This is because most patients are of IDDM of young age. Age had a marginal effect on outcome (*P*= 0.05) with more favorable outcome in younger (<40 years) ones, but the difference was insignificant.

In the present study 44 patients (64.70%) were males and 24 patients (35.30%) were females. Sex was insignificant in our study in disagreement with *Agarwal, et al.* [6] who stated that favorable outcomes in males compared to the females (33.3% vs. 66.7%), which may be due to racial and cultural differences. But our results are in agreement with *Ekpebegh, et al.* [7] who stated that sex has no significance.

About two-thirds of the patients were type one DM. Type of DM was a significant predictor of mortality. With higher mortality in type 2 DM (66 %). These results were in agreement with *Agarwal, et al.* [6] study that revealed higher mortality in type 2 DM (74 %).

In this current study, 50% of cases had sepsis as a precipitating factor of DKA, most commonly pneumonia (41.1%), urinary tract infection (29.4%), and septic shock (29.4%). The remaining factors were insulin discontinuation (non-compliance) (30.9%), and myocardial infarction (19.1%).

In our study, Po4 level at admission was normal in 56 (82.4%), mild hypophosphatemia was reported in 7 (10.2%), moderate hypophosphatemia in 4 (5.8%), while severe hypophosphatemia was reported in only one patient and he was admitted by fits followed by paresis with a dramatic response after correction of phosphate level. *Betdur, et al.* [8] reported that 34 (68%) patients had normal phosphate levels, 11(22%) showed mild hypophosphatemia, 4(8%) showed moderate and 1(2%) showed severe hypophosphatemia.

Po4 is essential for cellular ATP production. Severe hypophosphatemia, which can occur during fluid and insulin therapy of DKA, has a risky influence on nervous system, cardiac, muscular, and hematologic functions [9].

There is evidence that the early onset of DM affects Po4 metabolism leading to high energy Po4 depletion and tissue hypoxia [10].

At 2 days after admission, our study founded that 50(73.5%), 9 (13.2%) and 9 (13.2%) patients showed normal, mild, and moderate

hypophosphatemia respectively, while *Betdur, et al.* [8] founded that 31 (62%), 13 (26%), 6 (12%) patients showed normal, mild and moderate hypophosphatemia respectively at 1 day of admission.

On the day of discharge, Po4 level was normal in 56 (94.9%) patients out of 59 living patients, after exclusion of the nine dead ones, two (3.8%) patients showed mild hypophosphatemia, and one (1.6%) patient showed moderate hypophosphatemia. While *Betdur, et al.* [8] study founded that 42 (84%), 5 (10%), and 3 (6%) patients showed normal, mild, and moderate hypophosphatemia, respectively. The nine dead patients showed a mild hypophosphatemia in one patient (11%) and moderate hypophosphatemia in eight patients (89%) at the last reading before death (between 6-10 days of ICU stay).

According to the Mg level in the current study, at admission was normal in 61 patients (89.7%), mild hypomagnesemia was reported in 5 patients (7.3%), moderate hypomagnesemia in only 2 patients (3%). Mg depletion resulted possibly from osmotic diuresis by urinary glucose, in addition to the effect of acidosis, and intra-cellular shift caused by insulin [11]. The frequency of hypomagnesemia was much lower when compared to the results of *Salman et al.* [5] who revealed that 59.02% of patients had hypomagnesemia after 10 hours of treatment, this may be due to the timing of Mg measurement [3] plus the ethnic differences.

2 days after admission our study founded that 60 patients (88.2%), 6 patients (8.8%), and 2 patients (3%) showed normal, mild, and moderate hypomagnesemia, respectively.

On the day of discharge, Mg level was normal in 57(96.6%) patients out of 59 survived patients after exclusion of the 9 dead ones. While 2 patients (3.4%) patients showed mild hypomagnesemia.

Finally, out of the 68 patients, 59 (86.8%) patients were discharged, while 9 patients died (13.2%). These results were in agreement with *Betdur, et al.* [8] who showed a mortality rate of 12%. While *Agarwal, et al.* [6] had a higher mortality rate (30.0%) that was referred to limited resources in the face of large patient admissions in tertiary care hospitals plus delayed referrals. Correlations and multivariate logistic regression showed that Co-morbidity (OR, 15.254; CI, 5.214-25.324), low PH (OR, 10.235; CI, 3.214-18.254), and low PO4 level (OR, 7.548; CI, 2.321-26.512) were the independent predictors for mortality with a 13-fold increase in the relative risk of mortality in patients with hypophosphatemia. While *Agarwal, et al.* [6] showed that decrease in mean Po4 (4.38) at presentation led to 2.71-fold (OR, 2.71; 95% CI, 1.51 to 6.99) better outcomes compared to those with higher levels (Po4, 6.04), which is a strange finding that author did not explain. In addition, mortality in type 2 DM was higher as DKA is rare in these patients' category and occurs only when there a sever metabolic derangements which usually leads to a poor outcome and this was supporting the findings in other studies [6, 12]. We could say that our study is the first to address this issue in our locality in DKA patients of both type 1 and type 2 DM.

Limitations in the current study include the small number of patients enrolled and the lack of follow-up measurements after patients discharge; even though they do not compromise our results. In addition, hypophosphatemia interpretation could be confounded by multifactorial causes rather than DKA.

Longitudinal follow-up studies are needed to get more light on the impact of hypophosphatemia and hypomagnesemia on DKA.

CONCLUSION

We concluded that hypophosphatemia was an independent predictor of the DKA-associated mortality rate, and serial Po4 measurement should be considered in DKA treatment protocols.

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