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Is Phosphorus Supplementation Systematic in Diabetic Ketoacidosis?

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Abstract

Diabetic ketoacidosis (DKA) is a severe acute complication of diabetes, resulting from an insulin deficiency that leads to hyperglycemia, metabolic acidosis, and significant fluid and electrolyte losses, particularly phosphorus. This element plays a crucial role in energy metabolism and bone mineralization. Our study aims to assess the frequency of hypophosphatemia in patients with DKA, analyze the impact of phosphorus supplementation on insulin requirements, and examine its influence on the length of hospitalization in the intensive care unit. This prospective study was conducted over 12 months and included 55 cases of diabetic ketoacidosis admitted to the medical intensive care unit at CHU Ibn Rochd in Casablanca. Serum phosphate levels were measured in all patients, with a median value of 18 mg/L. Based on these levels, our sample was divided into two groups: one with normal phosphatemia and the other with hypophosphatemia. The average age of patients was 43.85 years, with a female predominance. Hypophosphatemia was observed in 56% of patients at admission, requiring systematic intravenous correction, with an average supplementation duration of 8.6 ± 5.4 days. In these patients, a significant reduction in insulin requirements was noted. The average length of hospital stay was 8.9 ± 6.1 days, with a longer stay in the hypophosphatemic group. The overall mortality rate was 29.1%. Hypophosphatemia is frequent in DKA. Its correction through phosphorus supplementation improves glycemic control and may contribute to an optimized management of patients in intensive care by reducing insulin requirements and potentially influencing the length of hospitalization.

Introduction

Diabetes mellitus is a major chronic public health disease, affecting 537 million people in 2021, with projections reaching 783 million by 2045 (1). It is characterized by hyperglycemia due to either insulin deficiency or impaired insulin effectiveness (2).

Diabetic ketoacidosis (DKA) is a severe acute complication primarily observed in patients with type 1 diabetes but can also occur in type 2 diabetes (3). It results from an insulin deficiency leading to hyperglycemia, excessive ketone body production, and metabolic acidosis (4). This condition causes water and electrolyte loss, including hypophosphatemia, through various pathophysiological mechanisms. Hypophosphatemia is defined as a serum phosphate level below 0.8 mmol/L (5) and plays a crucial role in bone mineralization and energy metabolism (6). However, its clinical implications in DKA remain insufficiently explored.

The aim of our study is to evaluate the incidence of hypophosphatemia in patients with DKA, analyze its impact on insulin requirements and intensive care unit (ICU) length of stay, and identify prognostic factors associated with DKA in this context.

Patients and Methods

We conducted a prospective study on a cohort of patients admitted for diabetic ketoacidosis to the medical intensive care unit of CHU Ibn Rochd in Casablanca over a 12-month period. The study included 55 patients, all of whom underwent phosphate level measurement upon admission.

Hypophosphatemia at admission was considered as a dependent variable, allowing the formation of two groups:

- **Group 1:** Patients with normal phosphatemia (23–47 mg/L or 0.74–1.52 mmol/L).
- **Group 2:** Patients with hypophosphatemia (<23 mg/L or <0.74 mmol/L), who systematically received phosphorus supplementation.

Comparisons between the two groups were performed using the chi-square test, Fisher's exact test for percentages, and Student's t-test, analysis of variance (ANOVA), and Friedman test for means. The length of hospitalization was analyzed at four time points (Day 1, Day 2, Day 3, and discharge). Predictive factors for mortality were assessed using a stepwise conditional logistic regression for variables with a p-value < 0.2 in univariate analysis. A difference was considered statistically significant for p-value ≤ 0.05.

Results

Epidemiological Aspects

During the study period, 292 admissions were recorded in the medical intensive care unit, of which 79 were related to diabetic ketoacidosis (DKA), representing an incidence of 27.05%. After excluding 24 patients due to the absence of phosphate measurement, the remaining 55 patients constituted the study population.

The mean age of the patients was 43.85 ± 18.89 years, ranging from 16 to 80 years, with a female predominance in 70.9% of cases. Pre-existing type 1 diabetes was observed in 38.2% of cases, while type 2 diabetes was present in 50.9% of cases. In 10.9% of cases, the DKA was the initial presentation of diabetes. The average duration of diabetes progression in our cohort was 8.5 ± 6.3 years.

Clinical and Etiological Presentation

The clinical presentation was mainly characterized by an exacerbation of the polyuria-polydipsia syndrome, reported in 91% of patients, followed by tachypnea in 83.6%, altered consciousness in 65.5%, abdominal pain in 56.4%, and nausea and vomiting in 45.5% of cases. The mean venous blood glucose level at admission was 3.04 ± 1.12 g/L. Urine dipstick tests were positive in all patients, with an average glycosuria of 2.13 ± 0.5 crosses and an average ketonuria of 2.36 ± 0.6 crosses.

Arterial blood gas analysis revealed metabolic acidosis in all patients, with a pH ranging from 6.6 to 7.30 and a bicarbonate level ranging from 4 mmol/L to 25 mmol/L. Clinical and paraclinical data analysis identified the causes of diabetic decompensation. Infection was the leading cause in 58.2% of cases, with urinary tract infections being the most common (50%). Non-infectious causes accounted for 41.8% of cases, including non-adherence to treatment (14.5%) and organic pathologies (27.3%).

Hydroelectrolytic Profile

At admission, 50.9% of patients had normal sodium levels, while 29.1% had hypernatremia and 20% had hyponatremia. Potassium levels were normal in 41.8% of cases, while 41.8% had hypokalemia and 16.4% had hyperkalemia. The mean blood urea level was 0.85 ± 0.67 g/L, and the mean creatinine level was 20.5 ± 12.4 mg/L.

The median phosphate level was 18 mg/L, with extreme values ranging from 6 to 47 mg/L. Phosphate levels were normal in 24 patients (43.6% of cases), while hypophosphatemia was detected in 31 patients (56.4%), all of whom systematically received intravenous phosphorus supplementation. Their phosphate levels normalized during their ICU stay, except for two patients at discharge.

Therapeutic Management

The management of DKA in our cohort was based on four key components: rehydration, insulin therapy, correction of hydroelectrolytic imbalances, and treatment of the underlying cause.

Sixteen patients (29.1%) required mechanical ventilation, with an average duration of 6.7 ± 5.4 days, ranging from 2 to 17 days.

Rehydration protocols were individually adjusted based on the patient's clinical condition, particularly the degree of dehydration, cardiac status, and comorbidities. Specifically, 1 to 2 liters of 0.9% saline solution were administered during the first two hours, with a total daily intake of 3 to 5 liters, considering blood glucose monitoring and urinary losses.

Correction of hydroelectrolytic imbalances included management of dyskalemia and dysnatremia, as

well as systematic phosphorus supplementation for all patients with hypophosphatemia at admission. The average duration of phosphorus supplementation was 8.6 ± 5.4 days, with a range of 3 to 29 days.

Daily insulin requirements varied between the two groups. Patients with normal phosphate levels at admission showed an increase in insulin needs from 35.5 IU to 37 IU at discharge. Conversely, those with hypophosphatemia who received intravenous phosphorus supplementation exhibited a significant decrease in insulin requirements, from 40.0 IU at admission to 26.5 IU at discharge, as illustrated in **Figure 1**.

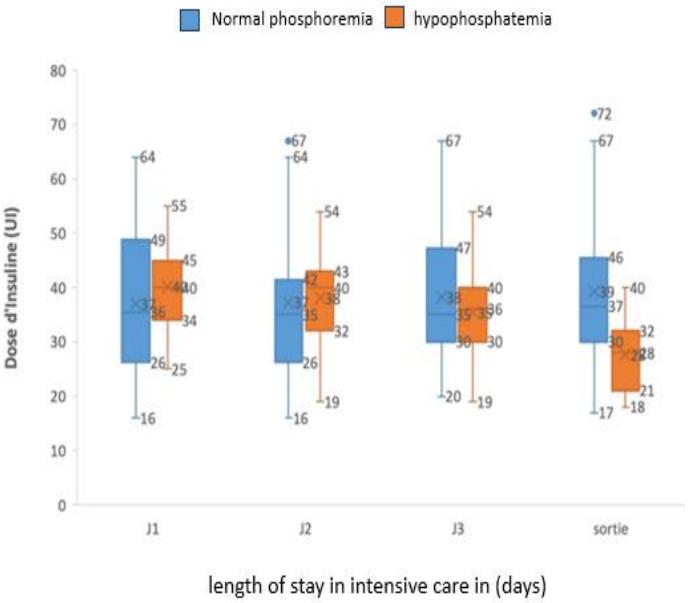

Figure 1: Evolution of Insulin Requirements by Group (Blue: Patients with normal phosphate levels**, Orange**: Patients with hypophosphatemia)

Evolution and Prognosis

In our study, the overall outcome was favorable in 71% of cases, while 29% of patients died.

The length of hospital stay was slightly longer in patients with hypophosphatemia (9.8 ± 6.9 days) compared to those with normal phosphate levels (7.6 ± 4.5 days). However, this difference was not statistically significant (p-value = 0.184).

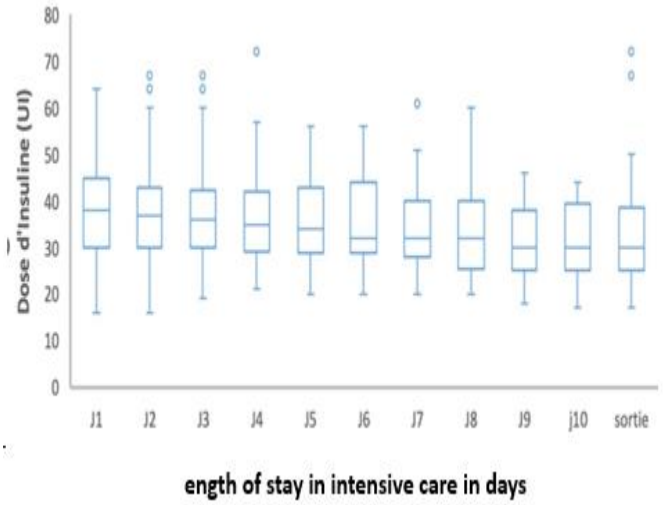

Figure 2: Insulin Requirements in Patients with DKA During Their ICU Stay

This figure illustrates the variation in daily insulin needs among patients with diabetic ketoacidosis (DKA) throughout their stay in the intensive care unit (ICU).

Parameters	Survivors (n=39)	Deceased (n=18)	P-value
APACHE Score, mean ± standard deviation (SD)	10.72 ± 3.83	14.63 ± 4.41	0.002*
SOFA Score, mean ± SD	3.26 ± 2.41	7.19 ± 3.69	0.001*
Nosocomial infection	5 (35.7%)	9 (64.3%)	0.0001 *
Age, mean ± SD	42.9 ± 18.4	46.1 ± 20.5	0.522
Hypophosphatemia at admission			0.227
Yes	24 (77.4%)	7 (22.6%)	
No	15 (62.5%)	9 (37.5%)	
Albuminemia, mean ± SD	27.1 ± 5.8	20.8 ± 2.8	0.005*

Table 1: Factors Associated with Mortality in Patients with DKA

This table summarizes the significant factors associated with mortality in our sample. Univariate analysis identified the following variables as significantly linked to fatal outcomes: Higher mean

SOFA scores (**p = 0.001**),Higher mean APACHE II scores (**p = 0.002**),Presence of nosocomial infection (**p=0.0001**),Hypoalbuminemia at discharge (**p = 0.005**)

These findings highlight the prognostic value of these factors in the management of diabetic ketoacidosis in ICU settings.

Discussion

Diabetes mellitus is a chronic disease and a major public health issue, being a priority for healthcare systems. In 2021, the International Diabetes Federation estimated that there were 537 million diabetics worldwide, with an alarming projection of 783 million by 2045 if preventive measures are not taken (1).

Diabetes can lead to various complications, including diabetic ketoacidosis (DKA), a serious medical emergency that primarily affects patients with type 1 diabetes but can also occur in type 2 diabetes. It results from an absolute or relative insulin deficiency combined with an elevation of counter-regulatory hormones. The diagnosis of DKA is made with a venous glucose level greater than 2.5 g/L (13.8 mmol/L), an arterial pH below 7.30, and plasma bicarbonate levels lower than 15 mmol/L, with the presence of ketone bodies in the blood or urine (7,8).

Patients with DKA typically present after several hours or days of symptoms such as polyuria, polydipsia, and weight loss. Nearly 40 to 75% also exhibit nausea, vomiting, and abdominal pain. Examination reveals dehydration, and in cases of severe acidosis, consciousness disturbances and Kussmaul breathing are frequently observed (9). Infection and non-compliance with medical treatments are identified as the two main triggers of diabetic ketoacidosis (10,11).

During diabetic ketoacidosis (DKA), several electrolyte disturbances occur due to the metabolic disruptions caused by insulin deficiency and hyperglycemia.

Sodium is often affected, with frequent hyponatremia due to the shift of water into the extracellular compartment in response to hyperglycemia. Hypernatremia may also occur in severe dehydration cases, leading to a contraction of the extracellular volume (12). Potassium levels undergo significant variations. Initially, hyperkalemia may be observed due to acidosis, which promotes the release of potassium from cells. However, with insulin therapy and correction of acidosis, secondary hypokalemia may develop, requiring close monitoring and appropriate correction to prevent cardiac and neuromuscular complications (13). Hypophosphatemia is another common abnormality, especially after insulin therapy. Its incidence varies across studies. In comparison to studies conducted in the Netherlands, a frequency of 74% was reported in 2021 (14). A similar figure of 77% was also noted in a 2022 U.S. study (15), while a recent study in Spain in 2024 noted a frequency of 36% (16). In our series, we observed a 56% frequency of hypophosphatemia at admission in patients with diabetic ketoacidosis.

Although its clinical impact remains controversial, severe hypophosphatemia can lead to muscular, neurological, and respiratory complications. In the context of diabetic ketoacidosis, it results from several mechanisms: transcellular phosphorus transfer, osmotic diuresis causing excessive urinary losses, reduced renal reabsorption, and insulin deficiency limiting its cellular entry. Additionally, insulin therapy causes intracellular redistribution of phosphorus, further aggravating its depletion. A decrease in phosphorus reserves is also associated with insulin resistance (17,18), resulting from a defect in insulin binding to its receptors. Moreover, hypophosphatemia can impair insulin secretion by the pancreas (19). The study by Gargouri O et al. (20) conducted in Turkey compared the insulin doses administered to patients based on their phosphorus levels. Patients with hypophosphatemia received a higher average dose (80.85 ± 40.88 UI) than those with normal phosphorus levels (62.25 ± 40.72 UI). In our study, insulin requirements increased in patients with normal phosphorus levels, while they decreased in those with hypophosphatemia, which may be explained by the systematic phosphorus supplementation of these patients, promoting the correction of hypophosphatemia and the restoration of associated energy metabolism. Furthermore, an Indian study by Raul K. et al. (21) conducted in 2015 showed that hypophosphatemia in DKA was associated with prolonged hospitalization, with an average of 10 days compared to 5.45 days in patients with normal phosphorus levels, this difference being statistically

significant (p = 0.00). In our series, the length of hospitalization was slightly longer in patients with hypophosphatemia (9.8 ± 6.9 days) compared to those with normal phosphorus levels (7.6 ± 4.5 days), but this difference was not statistically significant (p = 0.184).

To date, few studies have assessed the clinical value of phosphorus supplementation. A study conducted on 34 sepsis patients in intensive care showed a significant reduction in cardiac arrhythmias compared to a previous cohort of 16 unsupplemented patients (22). Moreover, an improvement in cardiac performance was observed in seven hypophosphatemic patients after correction of their phosphorus levels (23).

In our study, phosphorus supplementation led to the normalization of phosphorus levels in most hypophosphatemic patients, with the exception of two patients at discharge. It also seemed to contribute to the reduction of insulin requirements in these patients.

Conclusion

Among the electrolyte imbalances that occur during DKA, hypophosphatemia is common and correlated with the severity of acidosis. Although its clinical consequences remain poorly defined, it could have a significant impact on the progression of patients.

Phosphorus supplementation, although rarely associated with adverse effects and allowing for rapid correction of phosphorus levels, remains controversial due to the lack of large-scale studies evaluating its benefit. This scientific gap explains the heterogeneity of practices in its management. A better understanding of the effects of hypophosphatemia and the benefits of targeted supplementation could thus help optimize the management of patients with DKA and improve their prognosis.

Références

1. F A. A. H. Inna et al., « Le Diabète Sucré en Milieu Hospitalier Dans le Nord du Cameroun : Aspects Épidémiocliniques, Paracliniques et Thérapeutiques: Diabetes Mellitus in Hospital Settings in Northern Cameroon: Epidemiology, Clinical Features and Management », Health Sci. Dis., vol. 25, no 9, Art. no 9, août 2024, doi: 10.5281/hsd.v25i9.6033.
2. agot-Campagna A, Romon I, Fosse S, Roudier C. Prévalence et incidence du diabète, et mortalité liée au diabète en France. Synthèse Épidémiologique Inst Veille Sanit [Internet]. 2010
3. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. Nat Rev Dis Primer. 2020;6(1):40.
4. Yasuda K, Tanahashi H, Hayashi M, Yamakita N. Hyperglycemic Crises in Adult Patients With Diabetes: Response to Kitabchi et al. Diabetes Care. 1 déc 2009;32(12):e157.
5. Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE, Schultz MJ. Treatment of hypophosphatemia in the intensive care unit: a review. Crit Care. 3 août 2010;14(4):R147.
6. Penido MGMG, Alon US. Phosphate homeostasis and its role in bone health. Pediatr Nephrol. 1 nov 2012;27(11):2039-48.
7. Islam T, Sherani K, Surani S, Vakil A. Guidelines and controversies in the management of diabetic ketoacidosis – A mini-review. World J Diabetes. 15 déc 2018;9(12):226-9.
8. Kemperman F a. W, Weber JA, Gorgels J, Van Zanten AP, Krediet RT, Arisz L. The influence of ketoacids on plasma creatinine assays in diabetic ketoacidosis. J Intern Med. 2000;248(6):511-7.
9. G. Umpierrez et M. Korytkowski, « Diabetic emergencies — ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia », Nat. Rev. Endocrinol., vol. 12, no 4, p. 222-232, avr. 2016, doi: 10.1038/nrendo.2016.15.
10. Elkituni A, Elshwekh H, Bendala NM, Atwear WS, Aldaba FA, Fellah AM. Profile of diabetic ketoacidosis at the National Diabetes and Endocrine Center in Tripoli, Libya, 2015. Diabetes Metab Syndr Clin Res Rev. 1 mai 2021;15(3):771-5.
11. Galm BP, Bagshaw SM, Senior PA. Acute Management of Diabetic Ketoacidosis in Adults at 3 Teaching Hospitals in Canada: A Multicentre, Retrospective Cohort Study. Can J Diabetes. 1 juill 2019;43(5):309-315.e2.
12. A. O. Ogbera, J. Awobusuyi, C. Unachukwu, et O. Fasanmade, « Clinical features, predictive factors and outcome of hyperglycaemic emergencies in a developing country », BMC Endocr. Disord., vol. 9, p. 9, mars 2009, doi: 10.1186/1472-6823-9-9

13. Khai A. La place des biomarqueurs de l'infection chez le diabétique en acidocétose en milieu de réanimation. Thèse médicale, Casablanca.; 2020
14. Vaart A van der, Waanders F, Beek AP van, Vriesendorp TM, Wolffenbuttel BHR, Dijk PR van. Incidence and determinants of hypophosphatemia in diabetic ketoacidosis: an observational study. BMJ Open Diabetes Res Care. 1 févr 2021;9(1):e002018.
15. Hasan RA, Hesen JZ, Millican N, Pederson JM, Agus MSD. Serum Phosphorus and Hypophosphatemia During Therapy of Diabetic Ketoacidosis in Children: Single-Center, Retrospective Cohort 2016-2022. Pediatr Crit Care Med J Soc Crit Care Med World Fed Pediatr Intensive Crit Care Soc. 1 janv 2025;26(1):e77-85
16. Sanluis Fenelli G, Bechara Aded C, Lagger J, Widmer J, Zucaro F, Aparo V, et al. [Prevalence of hypophosphatemia in children with diabetic ketoacidosis and treatment with subcutaneous regular insulin. Observational study]. Andes Pediatr Rev Chil Pediatr. avr 2024;95(2):183-9
17. DeFronzo RA, Lang R. Hypophosphatemia and glucose intolerance: evidence for tissue insensitivity to insulin. N Engl J Med. 27 nov 1980;303(22):1259-63.
18. Harter HR, Santiago JV, Rutherford WE, Slatopolsky E, Klahr S. The relative roles of calcium, phosphorus, and parathyroid hormone in glucose- and tolbutamide-mediated insulin release. J Clin Invest. 1 août 1976;58(2):359-67.
19. Zhou XJ, Fadda GZ, Perna AF, Massry SG. Phosphate depletion impairs insulin secretion by pancreatic islets. Kidney Int. 1 janv 1991;39(1):120-8.
20. Gargouri O, Marrakchi R, Chbili S, Boudaya M, Jamoussi K, Turki M, et al. Prevalence and determinants of hypophosphatemia during the treatment of diabetic ketoacidosis. In: Endocrine Abstracts [Internet]. Bioscientifica; 2023 [cité 13 janv 2025]. Disponible sur: https://www.endocrine-abstracts.org/ea/0090/ea0090ep369
21. Raul K, Tungikar S, Soni DN, Deshpande S, Raundal S. Study of Serum Phosphorus Levels and Its Correlation with Clinical Profile in Patients with Diabetic Ketoacidosis [Internet]. IOSRJDMS; 2015 [cité 13 janv 2025]. Disponible sur: https://www.academia.edu/download/88317334/A014540110.pdf
22. Andrei S, Evgeni B, Leonid K, Ruslan K, Shaun EG, Moti K, et al. Association between Hypophosphatemia and Cardiac Arrhythmias in the Early Stage of Sepsis: Could Phosphorus Replacement Treatment Reduce the Incidence of Arrhythmias? Electrolytes Blood Press. 2014;12(1):19-25.
23. O'Connor LR, Wheeler WS, Bethune JE. Effect of Hypophosphatemia on Myocardial Performance in Man. N Engl J Med. 27 oct 1977;297(17):901-3.