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ORIGINAL ARTICLE

Incidence of hypophosphatemia in children with diabetic ketoacidosis and treatment with subcutaneous regular insulin. Observational study

Incidencia de Hipofosfatemia en niños con cetoacidosis diabética y tratamiento con insulina regular subcutánea. Estudio observacional

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What do we know about the subject matter of this study?

In diabetic ketoacidosis, the initial treatment with intravenous fluids and insulin causes the sudden entry of plasma glucose and phosphate into the tissues, producing hypophosphatemia. This results in significant respiratory, cardiac, and neuromuscular alterations, rhabdomyolysis, seizures, coma, and death.

What does this study contribute to what is already known?

Our study demonstrates that patients hospitalized due to diabetic ketoacidosis (DKA) who presented with hypophosphatemia can be treated early and safely with subcutaneous insulin without clinical complications associated with the hypophosphatemia these patients presented. Considering that in many centers the standard of care for the treatment of DKA is the use of regular intravenous insulin, we believe that our study provides a safe alternative for the treatment of DKA in pediatric patients.

Abstract

Diabetic ketoacidosis (DKA) is one of the most serious complications of type 1 diabetes mellitus. Its treatment requires fluid and electrolyte replacement and insulin. Hypophosphatemia as a complication of treatment has been scarcely evaluated. **Objectives:** To estimate the incidence of hypophosphatemia in children with DKA, treated with subcutaneous regular insulin (IRS), and to explore factors associated with this complication. **Patients and Method:** Prospective, observational study. Patients diagnosed with DKA hospitalized in the general care ward were included. Data on phosphatemia, glycemia, acid-base status, and IRS amount (U/kg) received were recorded at baseline and after 24 h of treatment. Hypophosphatemia was defined as values below 2.5 mg/dl. The correlation between initial phosphate and at 24 h of treatment was evaluated; the incidence of hypophosphatemia at 24

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h was expressed as a percentage of the total number of patients. **Results:** 30 patients were included, 15 were female, mean age 11.4 ± 3.2 years. At 24 h of treatment with IRS, 36.7% (95%CI 22-55%) presented hypophosphatemia, mean value 1.9 ± 1.5 mg/dl. Initial bicarbonate < 10 mmol/L acted as a predictor of hypophosphatemia (OR 7.5; 95%CI 1.4-39.8%; p = 0.01). No patient required intravenous phosphate correction, and no associated clinical complications were observed. **Conclusion:** In the group studied, the incidence of hypophosphatemia reached 36.7% at 24 hours of treatment. Initial bicarbonate lower than 10 mmol/L was significantly associated with hypophosphatemia. No complications associated with hypophosphatemia were observed.

Introduction

Diabetic ketoacidosis (DKA) is one of the acute, possibly the most severe complications of type 1 diabetes mellitus. It presents with hyperglycemia (≥ 200 mg/dl), ketonemia, metabolic acidosis (bicarbonate ≤ 15 mmol/L and/or pH≤ 7.30), glycosuria, and ketonuria. This situation requires emergency treatment with the administration of insulin and intravenous fluids[1]. In 30-40% of patients with type 1 diabetes mellitus (T1DM), DKA is the presenting form[2]. Hypophosphatemia, hypokalemia, hypoglycemia, alkalosis, hyperchloremic acidosis, and cerebral edema have been reported as complications of DKA[3].

Regarding the alteration of phosphatemia concentration during DKA, it should be recognized that it is frequently normal or slightly increased initially, due to the redistribution of intracellular phosphate into the extracellular fluid generated by metabolic acidosis and cell lysis. Insulin deficiency and hypercatabolic state also contribute to the outflow of phosphate into the extracellular space. As the condition progresses, patients may present phosphatemia depletion secondary to osmotic diuresis, decreased proximal tubular reabsorption due to increased glycemia, and acidosis[3]. In addition, treatment with intravenous fluids and insulin promotes phosphate entry into the tissues. All the above-mentioned can cause severe hypophosphatemia, with values < 1 mg/dl, which can cause important respiratory, cardiac, and neuromuscular alterations, rhabdomyolysis, seizures, coma, and death[1,4].

In patients with DKA treated with intravenous (IV) insulin, an incidence of hypophosphatemia of 11-42% has been reported 24-36 hours after initiating treatment[5,6]. Although the administration of IV insulin for the treatment of DKA is standard of care in many centers, the use of subcutaneous regular insulin (IRS) is an accepted treatment modality with good results, being an excellent alternative for the management of uncomplicated DKA, especially in resource-limited settings[7]. There are few reports on complications associated with hypophosphatemia in patients with DKA treated with IRS[8].

Knowing the incidence of hypophosphatemia after treatment with IRS in children with DKA, and whether there are associated factors, could be important to propose modifications in its control and eventually in its management.

The objective of this study was to estimate the incidence of hypophosphatemia in children with DKA under treatment with IRS and to explore related factors.

Patients and Method

Observational, longitudinal, descriptive study, with prospective data collection.

All patients with a diagnosis of DKA (glycemia ≥ 200 mg/dl, bicarbonate ≤ 15 mmol/L, and/or pH ≤ 7.30) aged 1 to 18 years, hospitalized in the general hospitalization ward of the *Hospital General de Niños Pedro de Elizalde* between December 1, 2018, and March 31, 2020, were included. Patients with renal failure, with exogenous phosphate contributions, and with a diagnosis of severe DKA who, due to their clinical situation (cerebral edema, shock, severe renal failure, etc.), required intensive care unit management (due to receiving treatment with IV insulin) were excluded.

Sample size estimation

Considering a reported incidence of hypophosphatemia in patients with DKA of 14%[5-6], assuming a 5% margin of error, and a confidence level of 95%, a minimum sample size of 29 subjects was estimated. Epi Info Stat Calc 7.1.1

Study procedure

All patients were treated according to the standard of care for DKA of the Nutrition and Diabetes Service of the institution. The results of the blood analysis (glycemia, uremia, creatinine, phosphatemia, creatine phosphokinase (CPK), acid-base status, and electrolytes) were recorded at hour 0 and 24 hours after initiation of treatment with IRS.

The treatment standard of the institution contemplates: initial expansion with 20 ml/kg according to

body weight of saline solution; then 0.1 IU/kg of IRS is administered, which is repeated every hour until metabolic stabilization conditions are achieved. A hydration plan (two-bag system) consisting of 2,000 ml/m^2 according to body surface area (BSA) of fluids is administered over 6 hours, including 70 mEq/L sodium chloride, 30 mEq/L potassium chloride, and initial glucose flow of 3.5 mg/kg/minute. In the following 18 hours, 2000 ml/m^2 according to BSA will be administered with 70 mEq/L sodium chloride, 40 mEq/L potassium chloride, and a glucose flow of 3.25 mg/kg/minute[9]. In addition, in all patients with phosphate < 1 mg/dl, a correction is established with intravenous potassium or sodium phosphate at 10 mg/kg within 4-6 hours and then repeated until obtaining a phosphatemia > 2 mg/dl[1].

Variables

Biochemical

- Phosphatemia after 24 hours of treatment (mg/dl), which was classified according to the reference values provided by the equipment manufacturer, as hypophosphatemia (< 2.5), normal (2.6 to 5.9), and hyperphosphatemia (> 6)[10].
- Basal phosphate difference - measured at 24 hours (deltaP): calculated from the difference between the initial phosphate values before treatment with insulin and after 24 hours of treatment with IRS.
- Other biochemical determinations, before and 24 hours after starting treatment: glycemia (mg/dl), uremia (mg/dl), creatinine (mg/dl), CPK (mg/dl), acid-base status, and electrolytes (mmol/L). The values determination was performed with the Cobas® 6000 analyzer with the c501 module (Roche Diagnostics, USA).

Other variables: age, sex, DKA as the onset of T1DM, number of previous DKA episodes, the amount of IRS administered (IU/kg) after 24 hrs. of treatment, and the severity of ketoacidosis. The latter was classified according to pH and bicarbonate values (mmol/L) (mild: pH < 7.30- ≥ 7.20 and bicarbonate < 15- ≥ 10; moderate: pH< 7.20- ≥ 7.10 and bicarbonate < 10- ≥ , and severe: pH < 7.10 and bicarbonate < 5)[1].

Statistical evaluation

The description of the variables studied was performed using absolute values for categorical variables and mean with standard deviation or median with interquartile range for continuous variables, according to adjustment or not to normality (Kolmogorov-Smirnov test). The correlation between initial phosphate and phosphate after 24 hours of treatment was evaluated with the Pearson correlation coefficient.

The incidence of hypophosphatemia at 24 hours was expressed as a percentage of the total number of patients. All percentages are expressed with their 95% Confidence Interval (95%CI).

To explore possible factors associated with hypophosphatemia after 24 hours of treatment, baseline values (glycemia, uremia, creatinine, CPK, acid-base state, and electrolytes), history of diabetes, number of previous DKA episodes, and severity of DKA were analyzed as predictor variables. Cross Product Ratio (OR) and t-test for independent samples were used. A $p < 0.05$ value was considered significant. The analysis was performed with the IBM SPSS 20.0 software.

Ethical considerations

This work is subject to the legal regulations of the Nuremberg Code and the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the *Hospital General de Niños Pedro de Elizalde*. It is listed in the Public Research Registry of the Government of the City of Buenos Aires (No. 316/15).

Results

During the study period, 45 subjects with DKA were hospitalized, of which 15 were excluded (6 due to admission to the ICU and 9 due to difficulties in processing laboratory samples) (figure 1). Regarding the patients included, they were 11.4 ± 3.2 years old, half were females, and in 9 patients, DKA was the form of disease onset. According to severity at admission, 9 were considered mild, 13 moderate, and 8 severe. Phosphatemia at baseline was normal in most patients and elevated in only 26% of them. After 24 hours of treatment, phosphatemia (mg/dl) was 3.1 ± 0.8, and 36.7% presented hypophosphatemia (table 1).

When analyzing the baseline values in patients with hypophosphatemia and normal phosphatemia at 24 hours, significant differences were found between both groups, both in pH (p = 0.01), bicarbonate (p = 0.02), and remaining anion (p = 0.04). In the rest of the variables analyzed at the beginning of the treatment, there were no significant differences (table 2).

When considering the severity of DKA, it was observed that those who presented moderate forms with a pH < 7.20 (OR 3.8; 95%CI 0.8-18.2) and bicarbonate < 10 mmol/L (OR 7.5; 95%CI 1.4-39.8), and severe ones with a pH < 7.10 (OR 4.4; 95%CI 0.8-24) and bicarbonate < 5 mmol/L (OR 4; 95%CI 0.31-50.2), were more likely to develop hypophosphatemia than those with a mild form (table 3).

The variation of phosphatemia (deltaP) mean was -1.9 ± 1.5, only 2 patients had increased phosphatemia after treatment.

Table 1. Characteristics of the study population

Variable	n (%)	Mean and standard deviation
Female	15 (50)	
Age (years)		11.4 ± 3.2
Weight (Kg)		37.8 ± 13.4
Size (cm)		142.4 ± 15.9
BMI*	27 (90)	17 ± 4
DKA** debut	9 (30)	7.7 ± 2.8 años
DKA previous diagnosis	21 (70)	1.3 ± 2.2 años
Moderate acidosis (Baseline) (pH < 7,20; bicarbonate < 10)	13 (43)	
Severe acidosis (Baseline) (pH < 7,10; bicarbonate < 5)	8 (26)	
Baseline Hypophosphatemia	8 (26)	
Hypophosphatemia at 24 hours	11 (36)	

*BMI: body max index; **DKA: diabetic ketoacidosis.

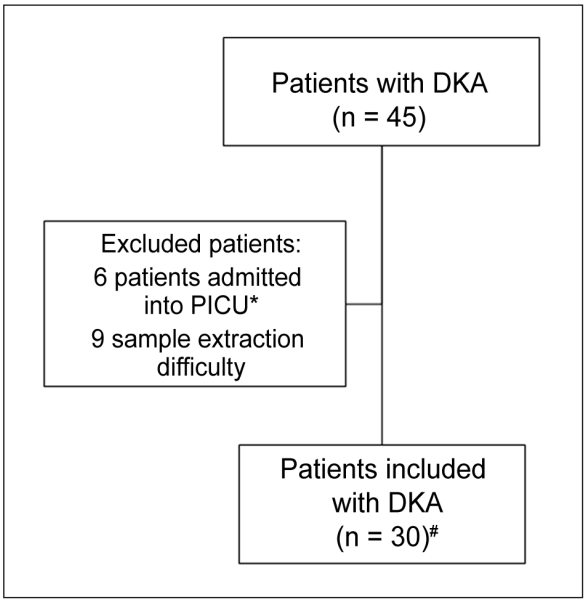

Figure 1. Flowchart patients with Diabetic Ketoacidosis (DKA). *1 patient died in the PICU (Pediatric Intensive Care Unit). ca), 5 were admitted to the PICU with regular IV insulin treatment. Clinic room: it is the general patient admission room pediatrics.

Table 2. Comparison of variables in patients at the income of treatment with DKA with subcutaneous regular insulin

Variables (Income of treatment)	After 24 hours of starting treatment		p
	Patients with Hypophosphatemia (n = 11)	Patients with Normophosphatemia (n = 19)	
Glucose (mg/dl)	550 ± 200	418 ± 154	0.079
Urea (mg/dl)	38 ± 13	35 ± 15	0.535
Creatinemia (mg/dl)	0.98 ± 0.27	0.83 ±0.28	0.176
Phosphatemia (mg/dl)	4.9 ± 1.54	5 ± 1.6	0.807
CPK (mg/dl)	82 ± 57	72 ± 35	0.622
Na+ (mmol/L)	135 ± 4.8	136 ± 3.3	0.478
K+ (mmol/L)	4.5 ±1.26	4.5 ± 0.72	0.98
Cl+ (mmol/L)	103 ± 5	103 ± 2.7	0.862
pH	7.11 ± 0.11	7.22 ± 0.09	0.014
pCO2 (mm Hg)	25.6 ± 7.76	29.9 ± 7.5	0.271
Bicarbonate (mmol/L)	8.43 ± 3.9	12 ± 4.1	0.023
GAP	23 ± 1	20 ± 3.7	0.041

CPK: creatine phosphokinase. GAP: Anion GAP.

Table 3. Association between the severity of acidosis and phosphatemia after 24 hours of treatment

Metabolic acidosis	Variables	Hypophosphatemia n, (%)	Normophosphatemia n, (%)	OR	IC95%	p
Moderate	pH < 7,20	7/11 (63%)	6/19 (32%)	3.8	0.8-18.2	0.13
	Bicarbonate < 10 (mmol/L)	8/11 (73%)	5/19 (26%)	7.5	1.4-39.8	0.018
Serious	pH < 7,10	5/11 (45%)	3/19 (16%)	4.4	0.8-24	0.1
	Bicarbonate < 5 (mmol/L)	2/11 (18%)	1/19 (5%)	4	0.31-50.2	0.613

An indirect linear correlation was verified between deltaP and basal pH (r = 0.58; p = < 0.001) and between deltaP and basal bicarbonate (r = 0.52; p = 0.003). In addition, a direct linear correlation was observed between deltaP and the amount of insulin received (r = 0.49; p = 0.005) (figure 2).

When evaluating the association of BMI in patients with a diagnosis of DKA and hypophosphatemia, we observed that those with BMI > 97th percentile were more likely to present hypophosphatemia (OR 4; 95%CI 0.31-50; p = 0.61).

Discussion

In this study, 36.7% of patients with DKA presented hypophosphatemia after 24 hours of treatment with IRS, with no other associated complications in any of the patients. These results are similar to those described by Nirmalya et al. in patients treated with IV insulin, reporting an incidence of hypophosphatemia of 42.4% and no associated complications[6].

Ditzel et al. state that, in patients with DKA, there would be initial hyperphosphatemia due to the outflow of intracellular phosphate to the extracellular medium, and then, with the start of insulin treatment, the inverse mechanism would occur, leading to hypophosphatemia associated with the treatment. They also describe clinical complications when phosphatemia values < 1 mmol/L are reached, such as respiratory depression, cardiomyopathies, arrhythmias, neuromuscular alterations, rhabdomyolysis, seizures, coma, and death[11].

The International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines mention that phosphatemia decreases with insulin treatment of DKA. This phenomenon starts in the first 24 hours of treatment and reaches its maximum decrease between 24 and 36 hrs., coinciding with the results of our work[12].

In patients who developed hypophosphatemia (24 hours), we observed a direct correlation between the decrease in bicarbonate and pH with the decrease in phosphatemia. This correlation was only verified in those with moderate or severe DKA. The same phenomenon was described by Shen and Braude, in 43 patients with 64 episodes of severe DKA, who showed a significant decrease in phosphatemia during insulin treatment[5].

In this study, an inverse linear relationship was found between deltaP, bicarbonate, and pH. This phenomenon is consistent with the pathophysiology of metabolic acidosis observed in DKA and would be related to phosphate redistribution. Likewise, a direct linear correlation was observed between deltaP and the amount of IRS received. This result would be a con-

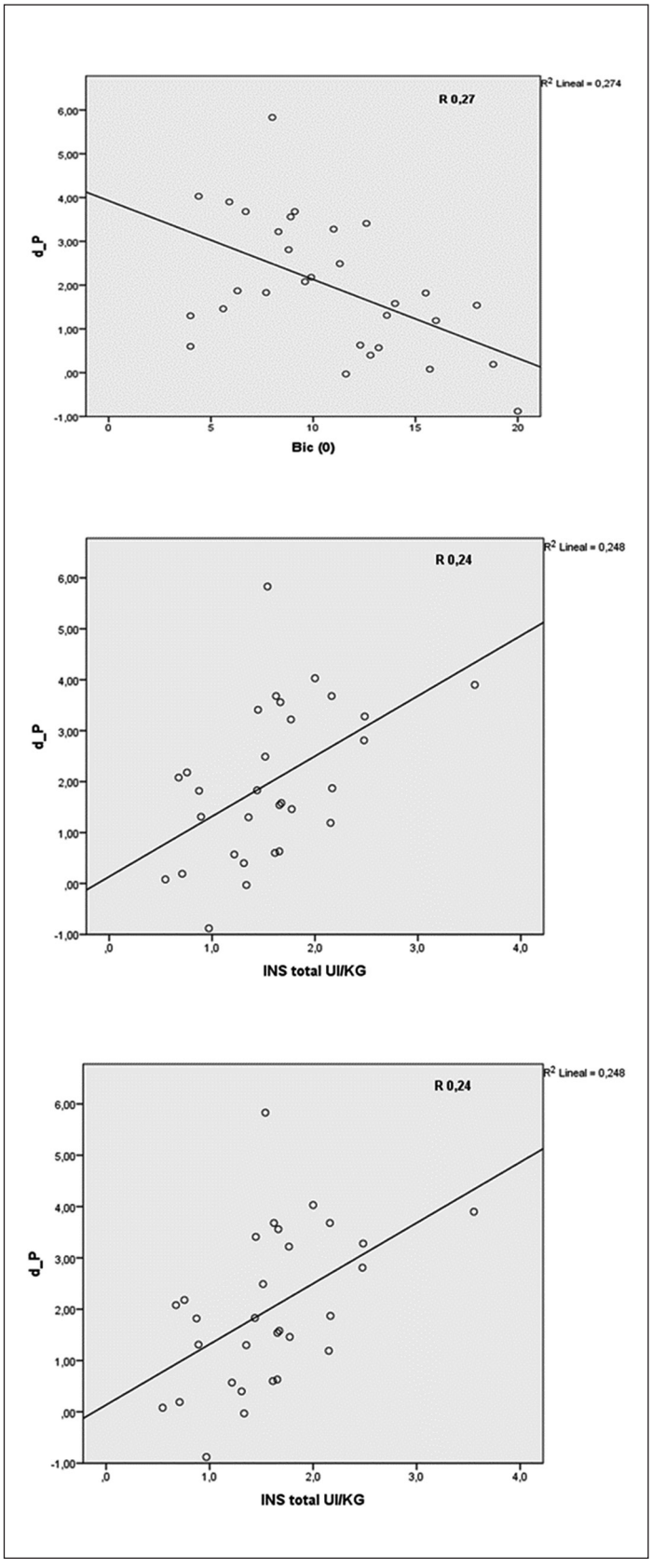

Figure 2. Pearson correlation comparing delta phosphorus (d_P) and bicarbonate (Bic); delta phosphorus and received insulin (INS) dose; delta phosphorus and Ph.

sequence of insulin activity at the cellular level, determining the entry of phosphate into the intracellular space[4].

Our study is limited by the fact that patients hospitalized in the ICU were not included since the severity of these patients requires the use of intravenous insulin and a different fluid and electrolyte therapy, elements that could bias the results. However, the objective of this study was to analyze the incidence of hypophosphatemia and the factors associated with it, using IRS in the general care ward, which is where this type of treatment has demonstrated its efficacy and safety[13,14]. Another limitation of our study is the inclusion criteria of hospitalized patients with a diagnosis of DKA, which was used with the cut-off points of bicarbonate concentration of the ISPAD 2018 guidelines[1]. Considering the change of definition for the diagnostic criterion of DKA, in the ISPAD 2022 guidelines (bicarbonate < 18 mmol/L), the data that our study would develop would be different[15].

On the other hand, our study includes prospective data collection, the use of standardized treatment for all patients, and the processing of all samples in the same laboratory, favoring the internal validity of our observations.

Finally, in this study, we were able to verify that, even using IRS for the treatment of DKA, complications associated with hypophosphatemia do not occur either, as has already been verified when using IV insulin[16].

Conclusion

In our study, the incidence of hypophosphatemia in patients diagnosed with DKA after 24 hours of treatment with IRS was 36.7%. This incidence was higher in patients with moderate or severe DKA. We evaluated the changes in phosphatemia in the first 24 hours of treatment with IRS in a general hospital ward, where we did not observe any complications associated with phosphate deficiency. Further studies are needed to confirm these results and it would be of great interest to evaluate phosphatemia in patients where IV insulin is administered compared with the use of IRS.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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