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Study of Serum Phosphate levels and its clinical significance in Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

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Abstract
Aim: *The aim of the study was to access mortality in Diabetic Keto Acidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS)with special reference to serum Phosphate levels.*
Methods: *It was a across sectional study conducted on patients with Type 1 and type 2 Diabetes Mellitus (DM), admitted with DKA and HHS in emergency ward and Intensive care unit of a tertiary care hospital in Bengaluru, during the period September 2014 to August 2015.Serum phosphate levels were measured in all the patients on day 0, day 1 and before discharge or death . Patients were treated as per the standard protocol. Type 1 and Type 2 DM patients were identified separately. Patients with DKA and HHS were also put in two separate groups. Mortality in the two groups was correlated with serum Phosphate levels by applying Chi Square test.*
Results: *We had 31 males and 19 female patients. Out of them 16 belonged to type 1 DM and 34 were type 2 DM. 39 of the 50 patients had DKA and 11 had HHS. Infection and noncompliance of treatment were the major precipitating factors of DKA /HHS. 6 patients (12%) expired. Mean phosphate level in the mortality group was 2.14 mg% and 3.03 mg% in those who survived. 93% of the patients who recovered had normal phosphate levels at discharge, where as 83% of the patients in the mortality group had low serum phosphates.*
Conclusion: *Though Phosphate therapy is not routinely required during the treatment of acute Diabetic Hyperglycemic emergencies, they should not be ignored. If hypophosphatemia is severe or if the patient develops cardio respiratory distress, phosphate should be administered under close supervision.*
Key words: *Diabetic ketoacidosis, Hyperglycemic hyperosmolar state, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Serum Phosphate levels,*

INTRODUCTION

Acute Hypophosphatemia with phosphate depletion is common in the hospital setting and results in significant morbidity and mortality. All cause mortality in patients with serum phosphate levels less than 1.0 mg % is as high as 30%.[1] Abnormalities of serum phosphate levels are more prominent in certain subsets of emergency department patients than in general population. Patients with Diabetic ketoacidosis (DKA),

Hyperosmolar Hyperglycemic State (HHS), COPD, Alcoholism, malnourishment, postoperative patients, malignancy and renal failure are at increased risk[2,3].

Hypophosphatemia though a common complication of DKA, is seldom severe and rarely causes clinical symptoms.[4] Low Phosphate levels in DKA and HHS is due to increased urinary loss as a result of osmotic diuresis and intracellular shift of PO4 during insulin therapy [5].Phosphate therapy is not an essential part of therapy for DKA in most patients.[6] and routine treatment with PO4 is not required.

However there are few reports of life threatening complications as a result of hypophosphatemia requiring urgent phosphate therapy.[4,7] Very few studies are available about the correlation of severity of hypophosphatemia and the outcome in diabetic emergencies.

This study is undertaken to assess mortality in DKA and HHS with special reference to serum phosphate levels.

MATERIAL AND METHODS

It was a cross sectional study conducted in a tertiary hospital in Bengaluru. 50 consecutive diabetic patients, above the age of 18 (both type 1and 2) admitted to emergency ward and ICU with DKA or HHS were included in the study. Approval by the Ethical committee was taken before starting the study. Written informed consent was taken in all patients. Detailed examination was done in all patients who satisfied the inclusion criteria. Relevant investigations as per the protocol were done. Patients with malnutrition, alcoholics, renal transplant recipients, patients with pancreatitis, burns, hyperparathyroidism, patients on steroids, diuretics, phosphate binding antacids were excluded from the study. Serum phosphate levels were measured on day 0, day 1 and at the time of discharge / death. Serum phosphate levels are defined as normal if it was between 2.5-4.5 mg%, mild hypophosphatemia if between 2-2.5 mg %, moderately low if between 1-2 mg % and very low if levels below 1.0 mg %. The patients were divided into two groups namely type 1 and Type 2 DM. Patients with DKA and HHS were identified separately. The duration of diabetes treatment and history of precipitating factors were taken into account. Mortality was correlated with serum phosphate levels. Statistical analysis was carried out using standard formulae. P value of <0.05 was considered as significant. Statistical significance was calculated by using Chi square test.

RESULTS

Out of 50 patients of the study group, 31 were males and 19 males. 16 and 34 patients belonged to type 1 and type2 DM respectively. Most of the patients of type 1 DM were in the age group 18-28. 65% of the patients with type2 DM were above the age of 59 and others between 39-58 age group. 66% of the patients had duration of Diabetes less than 10 years. 25 patients were on oral hypoglycemic agents (OHA) only, and 14 patients on OHA and insulin. All patients with type 1 DM were on insulin only.

Of the 50 patients, 39 had DKA and 11 patients had HHS. Infection and noncompliance were the major precipitating factors of DKA/HHS. 4 patients had acute coronary syndrome and 1 had cerebro- vascular accident. (Table 1) Most patients with infection had either urinary tract infection or lower respiratory infection. The lab values in the study group are given in table 2.Phosphate levels in the study group (n=50) are mentioned in tables 3 . Patient outcome: 6 of the 50 patients expired. 5 patients had DKA and 1 HHS.P value of 0.015 was observed at the date of discharge/ death which is statistically significant. Significant correlation was also observed after applying Chi Square test and t test.

Table 1: Precipitating causes of DKA/ HHS

Precipitating cause of DKA/HHS	No. of patients	%
Non – compliance	15	30%
Infection	26	52%
Cardiovascular event	4	8%
Cerebrovascular event	1	2%
New onset	4	8%

Table 2.. Laboratory values (No of patients = 50)

Criteria	Minimum	Maximum	Mean	Std. Deviation
Age (yrs)	18	84	50.0	20.58
Duration of DM(yrs)	0.5	30	7.42	7.33
RBS (mg%)	242	802	390.68	136.27
pH	6.7	7.424	7.147	0.174
HCO3 (mEq/l)	7.6	23.14	13.187	4.73
B.Urea (mg%)	15.6	64.2	35.16	11.21
S.Creatinine (mg%)	0.44	2.3	1.01	0.384
Na (mEq/l)	126	147.2	134.6	5.76
K (mEq/l)	3.05	5.2	4.062	0.548

Table 3 : Phosphate levels

Phosphate Levels	Day 0	Day 1	At discharge/death
Normal (2.5-4.5mg/dl)	34 (68%)	31 (62%)	42 (84%)
Mild (2-2.5mg/dl)	11 (22%)	13 (26%)	5 (10%)
Moderate (1-2.omg/dl	4 (8%)	6 (12%)	3 (6%)
Severe (< 1.0mg/dl)	1 (2%)	0	0

Table 4:

Mortality	N	Mean	Std. Deviation
No	44	3.03	0.41931
Yes	6	2.14	0.61236

Table 5 .Mean phosphate levels in the two groups

Patient Outcome	Number	%
Recovery	44	88%
Mortality	6	12%

Table 6 : Phosphate levels in the mortality group

Phosphorous levels at death	No. of patients with DKA/HHS	%
Normal (2.5 – 4.5mg/dl)	1	17%
Mild hypophosphatemia (2 – 2.5mg/dl)	2	33%
Moderate hypophosphatemia (1 – 2mg/dl)	3	50%
Severe hypophosphatemia (<1mg/dl)	0	0%

Table 7 : Phosphate levels among the patients who recovered

Phosphorous levels at discharge	No. of patients	%
Normal (2.5 – 4.5 mg/dl)	41	93%
Mild hypophosphatemia (2 – 2.5mg/dl)	3	7%
Moderate hypophotemia (1 – 2 mg/dl)	0	0%
Severe hypophosphatemia (< 1mg/dl)	0	0%

DISCUSSION

DKA and HHS are dangerous complications of DM. With appropriate treatment, the mortality rate in DKA is low (<1%) and is related more to the underlying precipitating event such as infection or Myocardial infarction. HHS has higher mortality, even with treatment (upto 15% in some clinical series)[8,9]. Appropriate treatment includes administering insulin infusion, IV fluids and monitoring blood glucose and electrolyte levels.[10] Dynamic changes occur in serum phosphate levels in DKA and hyperphosphatemia is common before initiation of therapy.[11]Later asymptomatic Hypophosphatemia is a common finding during DKA and may rarely manifest clinically. Factors responsible for hypophosphatemia are increased urinary loss of phosphate, intracellular shift of phosphate during therapy and fluid resuscitation [12]. Phosphates serve a number of crucial functions in the body. It is an essential component of the main energy currency of the cell- ATP 1 Severe Hypophosphatemia causes impaired cardiac contractility, skeletal muscle weakness, neurological and hematological abnormalities. [13,14,15] Jom Ditzel and Hans-Henrik have presented evidence of the occurrence of a paradoxical imbalance in phosphate metabolism from the early onset of Diabetes mellitus and have indicated that this may lead to a reduction of high energy phosphate and tissue hypoxia.[14] Current evidence regarding the clinical consequences of Hypophosphatemia is not straight forward. Randomized controlled trials have demonstrated that among the patients with DKA, phosphate supplementation did not improve biochemical or clinical outcome and instead it

may cause low serum ionized calcium. Howard K Wilson and others in their study [16] observed that phosphate therapy did not affect the duration of DKA, dose of insulin required, to correct acidosis or morbidity and mortality. On this basis routine repletion of Phosphate in a patient with DKA is probably not warranted.

However, if severe (<0.1mg %) hypophosphatemia can give rise to symptoms from many organ systems and it is recognized as a cause of mortality in DKA. Hence we took up this study to assess serum phosphate levels and its relation to mortality in hyperglycemic diabetic emergencies. 5 out of 39 patients with DKA and 1 out of 11 HHS patients expired. (mortality of 13% & 10% in the two groups respectively). Mean phosphate levels in the mortality group was 2.14 mg% where as it was 3.03 mg% in those who survived, which is statistically significant. Almost all patients who recovered had normal phosphate levels at discharge where as only one patient had normal values in the mortality group. Results of our study indicate that Phosphate levels during treatment of diabetic emergencies should not be ignored.

There are reports of mortality in DKA related to low phosphate levels. Hypophosphatemia induced seizures[,7] respiratory failure[4], encephalopathy[17] and severe thrombocytopenia[12] have been reported.

CONCLUSION

We conclude that although phosphate therapy is not routinely indicated in diabetic hyperglycemic emergencies, if the patient develops cardio pulmonary distress, or severe hypo phosphatemia, phosphate therapy under close monitoring is indicated.

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