IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 14, Issue 5 Ver. IV (May. 2015), PP 01-10
www.iosrjournals.org

Study of Serum Phosphorus Levels and Its Correlation with Clinical Profile in Patients with Diabetic Ketoacidosis

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Abstract:
Background And Objectives: *Diabetic ketoacidosis is one of the most common endocrinal emergency in the world. Electrolyte and fluid imbalances are known to occur in diabetic ketoacidosis. Phosphorus containing compounds have important roles in cell structure, function and acid base balance. Phosphorus depletion occurs in diabetic ketoacidosis owing trans-cellular shift and hyperphosphaturia. This study was undertaken to study phosphorus levels and its correlation to clinical profile in patients with diabetic ketoacidosis.*
Methods: *An prospective observational study is undertaken in 110 diabetic ketoacidosis patients at tertiary care centre. Serum phosphorus levels are performed at baseline, on day 1and on day 3.Ocurrence of complications of hypophosphatemia and hyperphosphatemia, outcome measures including length of hospital stay and mortality were assessed. in 48% patients on day 1. Among symptomatic hypophosphotemics , respiratory distress was the most common symptom. The mean length of stay among hypophosphatemics (10 days) was significantly higher than euphosphatemics or hyperphosphatemics (5.45 days).There was statistically significant negative correlation between HBA1C levels and serum phosphorus levels at baseline. Mortality rate was found high in hypophosphatemic group however this observation was found to be statistically insignificant.*
Interpretation And Conclusion: *This study demonstrated that phosphorus the neglected aspect of diabetic ketoacidosis needs due consideration. All patients having symptomatic hypophosphatemia in the form of unexplained respiratory distress and difficulty in weaning off from ventilator need appropriate attention for medical management of hypophosphatemia.*
Keywords: *Diabetic ketoacidosis, phosphorus, hypophosphatemia, respiratory distress, length of hospitalization.*

I. Introduction

Nationally, DKA contributes to approximately 1,00,000 hospital admissions per year[1]and accounts for 2% to 9% of hospital admissions in persons with diabetes[2]. Electrolyte disturbances and especially changes in potassium levels in diabetic ketoacidosis have been an area of interest for many decades now. There is paucity of studies regarding changes in serum phosphorous levels during diabetic ketoacidosis and its management. Phosphate is needed for bone mineralization and cellular structural components (phospholipids, nucleotides, phosphoproteins), for energy storage as ATP, for oxygen transport as 2,3-DPG and for acid base balance (as cellular and urinary buffer)[3]. Other phosphates, such as creatine phosphate are involved in many energy-intensive physiological functions, such as muscle contractility, neurological functions and electrolyte transport[4]. Dynamic changes in serum phosphorous levels take place during occurrence and management of diabetic acidosis[5]. But data regarding clinical manifestation resulting from these dynamic changes in serum phosphorus levels is very rare.

Phosphate excretion is increased in diabetics, especially those with uncontrolled one.[6] Phosphate depletion is common in diabetic ketoacidosis. Initially intracellular phosphate moves to extracellular compartment due to acidosis, dehydration.[5] So patients with diabetic ketoacidosis can present with hyperphosphatemia i.e. increased levels of serum phosphorus. Hyperphosphatemia which is usually asymptomatic can be associated with symptoms which are secondary to hypocalcemia.[7] During treatment of diabetic ketoacidosis with insulin and intravenous fluids, phosphorous is taken up intracellular with resultant hypophosphatemia. Hypophosphatemia especially moderate and severe is associated with a number of clinical sequalae including neurological, muscular, cardiac, respiratory and hematological problems[8].

The present study is designed to study serum phosphorus levels and its clinical correlation in patients with Diabetic Ketoacidosis.

II. Materials And Methods

110 patients with diabetic ketoacidosis were studied in this observational study. Adult patients (18 years and older) admitted to Intensive Care Unit and general wards. The period of study was 2 ½ years. Total 110 patients with diabetic ketoacidosis were included in the study. The diagnosis of diabetic ketoacidosis was made by presence of following laboratory findings-1) Blood sugar level of 250mg/dL or higher 2) Serum bicarbonate level of 15 mEq/L or lower 3) Arterial blood ph of 7.30 or lower or Venous blood ph of 7.25 or lower4) Presence of moderate or large urinary ketones[2].

Inclusion Criteria –

1) Patients who are > 18 years of age
2) Patients with diabetic ketoacidosis

Exclusion Criteria –

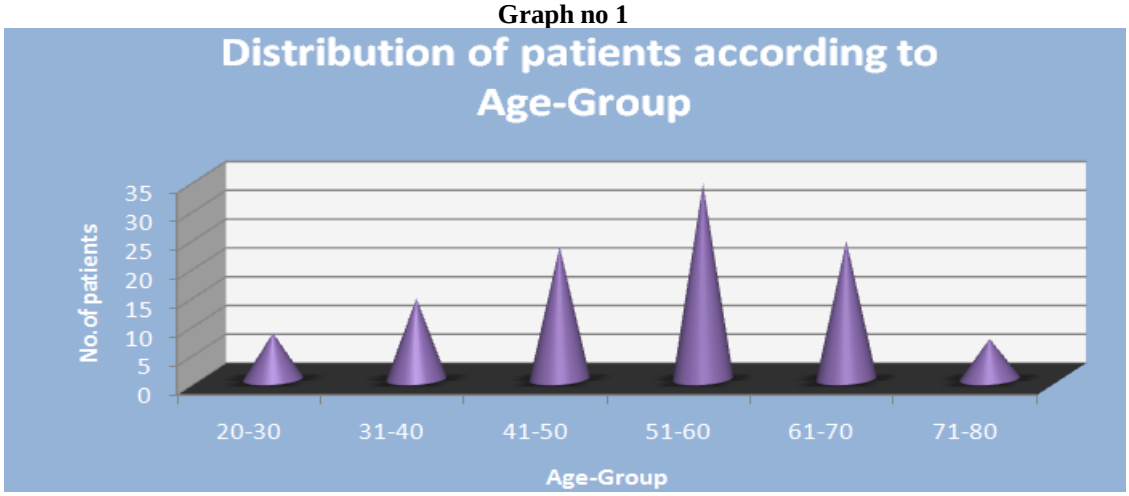
1) Patients under the age of 18 years
2) Patients with hyperglycemic hyperosmolar coma
3) Patients with hyperemesis gravidarum
4) Patients with starvation ketosis
5) Patients with renal transplantation
6) Alcoholics

a) Required routine/specific investigations including arterial blood gas analysis, blood sugar levels, urinary sugar and ketones, complete blood counts, renal function tests, serum sodium and potassium levels, glycosylated haemoglobin were carried out.
b) Serum phosphorous levels were done 3 times –1) at baseline 2) on day 1 3) on day 3.
c) Other haematological and radiological investigations were carried out as and when needed.
d) Occurrence of complications of hypophosphatemia, hyperphosphatemia, length of stay and mortality were assessed. Serum phosphorous levels were measured calorimetrically which is modified Fiske and Sub-barow method.
e) Treatment of diabetic ketoacidosis as per standard Joslin protocol[9].
f) Patients having hypophosphatemia (i.e., serum phosphorous level <2.5mg/dl) were treated with oral sodium phosphate preparation (1gm) twice daily until serum phosphorous level reached 2.5mg/dl or above[26].
g) Patients with hyperphosphatemia were treated with oral preparation of phosphate binders like calcium acetate or sevelamer[27].
h) Outcome measures including length of hospital stay and mortality were assessed Occurrence of following complications of hyperphosphatemia and hypophosphatemia was assessed like -:
1)Respiratory distress 2)Encephalopathy 3)Seizures 4)Muscle weakness 5)Tetany 6)Perioral numbness 7) ECG changes 8)Arrhythmias 9)Haemolytic anemia

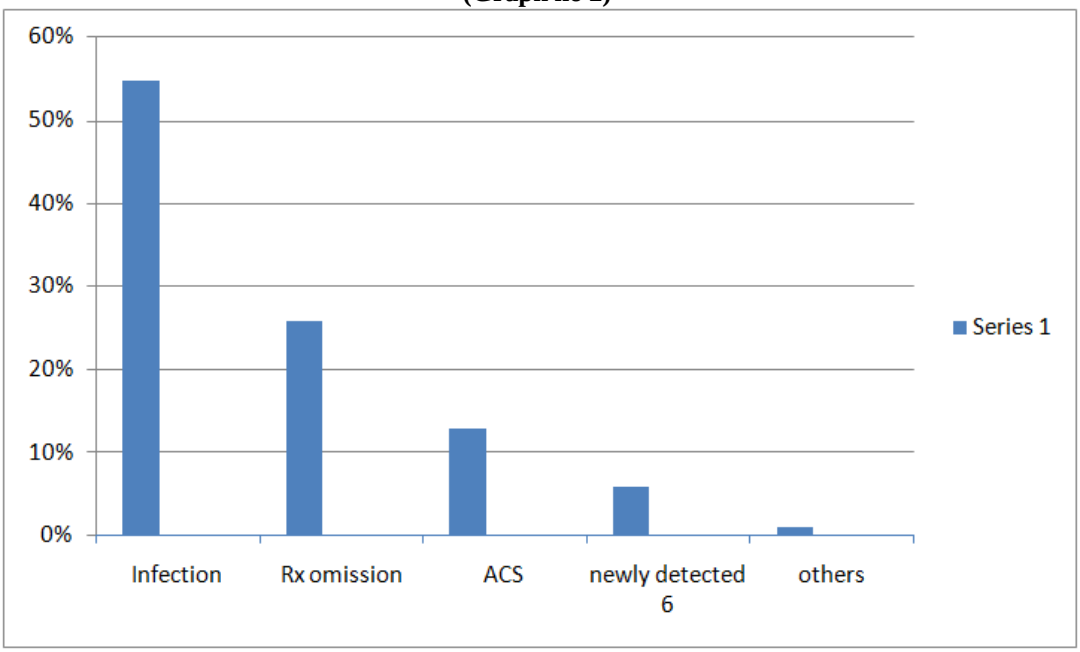
III. Results & Discussion

1) Out of the 110 patients, 58 (52.73%) were males and 52 (47.27%) were females. Maximum number of patients were found in the age group of 51-60 years, (30.91%). The mean age of patients was 52.96 ± 13.46 years.

Graph no 1



(Graph no 2)

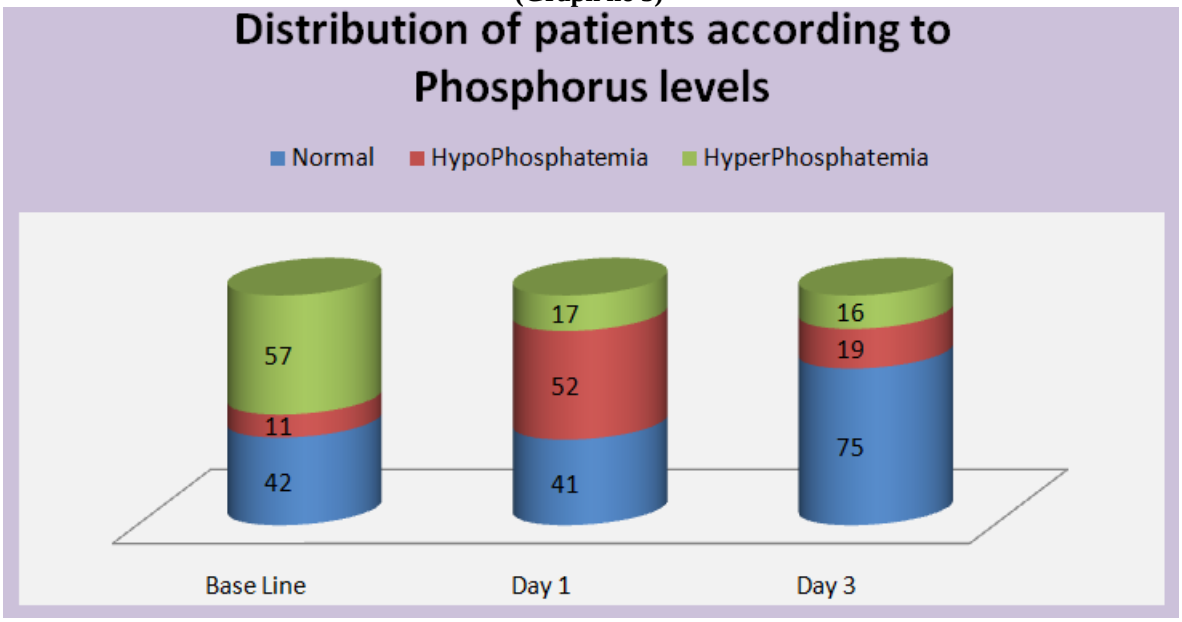


2) Infection was the most common cause of diabetic ketoacidosis(as shown in graph no.2) accounting 61 patients (55%). Second most common cause was treatment omission 29 (26%) followed by other causes14 (13%) like acute coronary syndromes, stroke, etc.

3) 6 (6%)patients in the study were newly detected diabetics. , 19 (17.27%) had type 1 diabetes mellitus and 91 (82.73%) patients had type 2 diabetes mellitus.

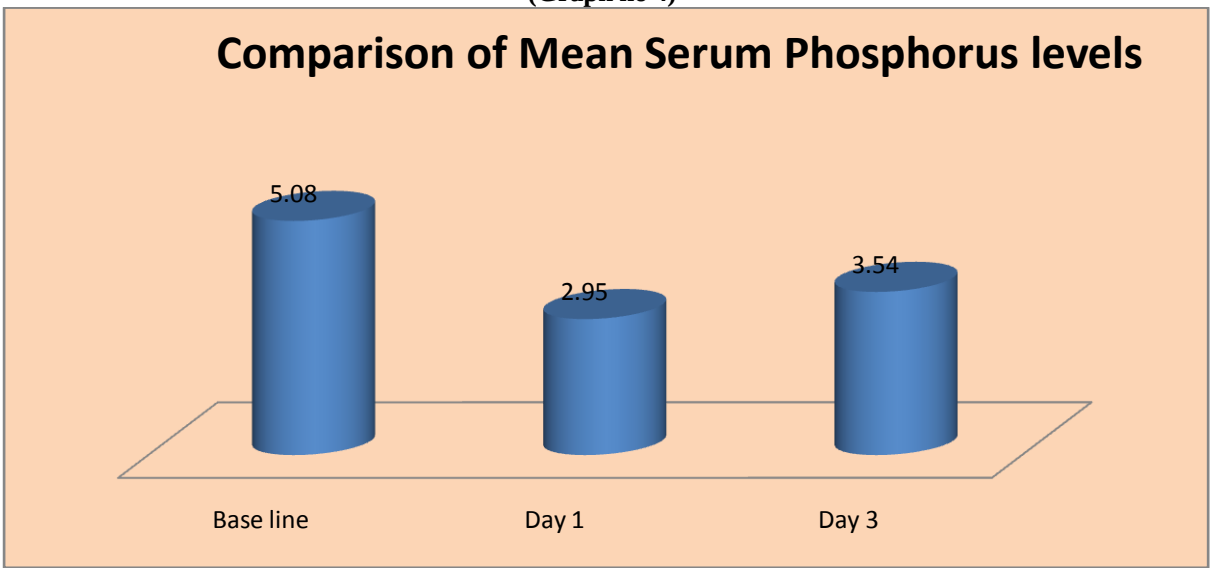
As shown in Graph no.3, At baseline out of the 110 studied patients 42 (38.18%) patients had normal serum phosphorous levels, 11 (10%) patients had hypophosphatemia (serum phosphorous levels of less than 2.5mg/dl) and 57 (51.82%) patients had hyperphosphatemia (serum phosphorous levels of more than 4.5mg/dl). On day 1, 41 (37.27%) patients had normal serum phosphorous levels, 52 (47.17%) patients had hypophosphatemia and 17 (15.46%) patients had hyperphosphatemia. On day 3, 75 (68.18%) patients had normal serum phosphorous levels, 19 (17.7%) patients had hypophosphatemia and 16 (14.56%) patients had hyperphosphatemia. When chi sqare test was applied to these results we found statistically significant result.(p=o.ooo)

(Graph no 3)



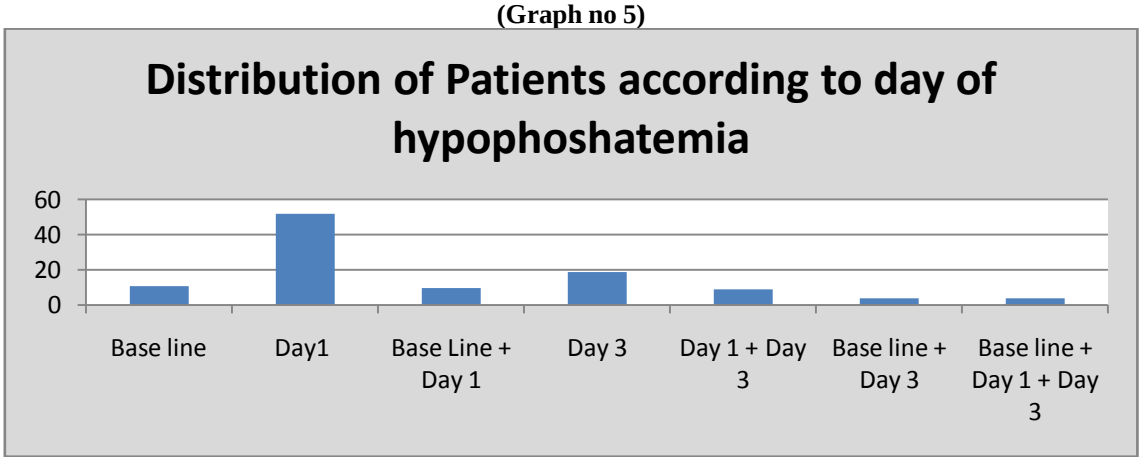
As shown in graph no.4, the mean phosphorous level on admission was 5.08 ± 2.15mg/dl , On day 1, 2.95± 1.32mg/dl and On day 3, 3.54 ± 0.99mg/dl. During the entire study the minimum phosphate level found was 1 mg/dl and maximum was 12 mg/dl.

(Graph no 4)

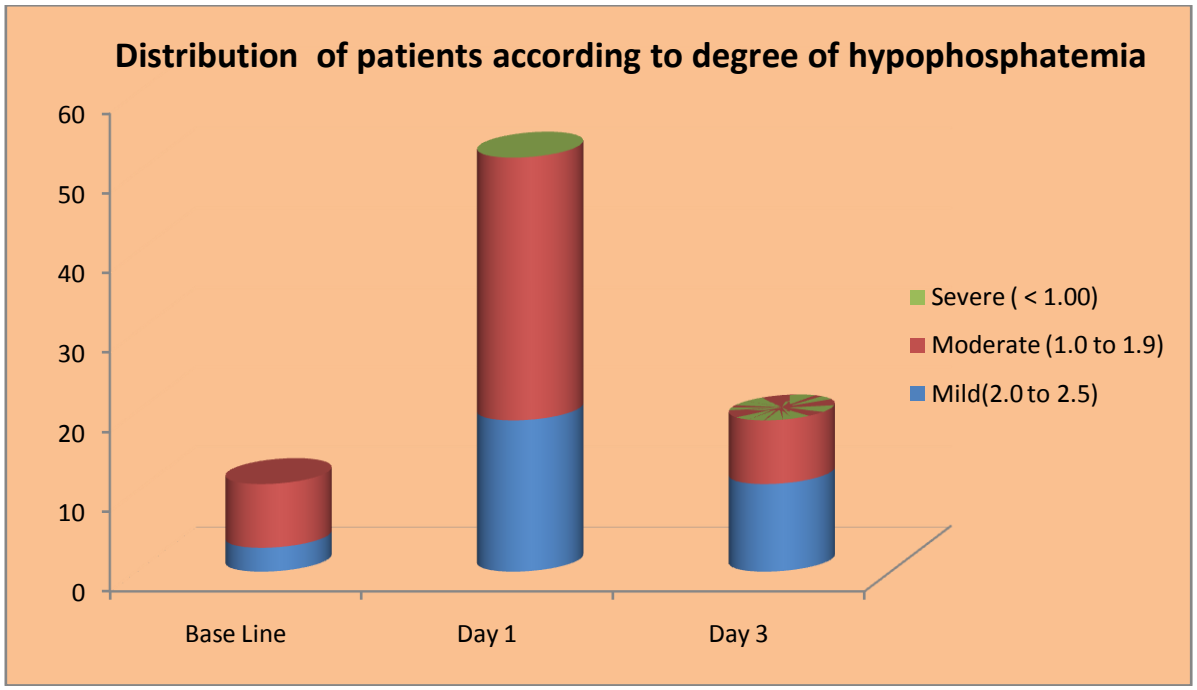


As shown in graph no.5 total 52 patients had hypophosphatemia on day 1.Out of these 52 patients,10 patients had hypophosphatemia at baseline also. So new 42 patients developed hypophosphatemia on day 1.Out of total 19 hypophosphatemics on day 3, 9 patients also had hypophosphatemia on day 1 also .4 patients had persistent hypophosphatemia i.e. at baseline , at day 1 and on day 3.

(Graph no 5)

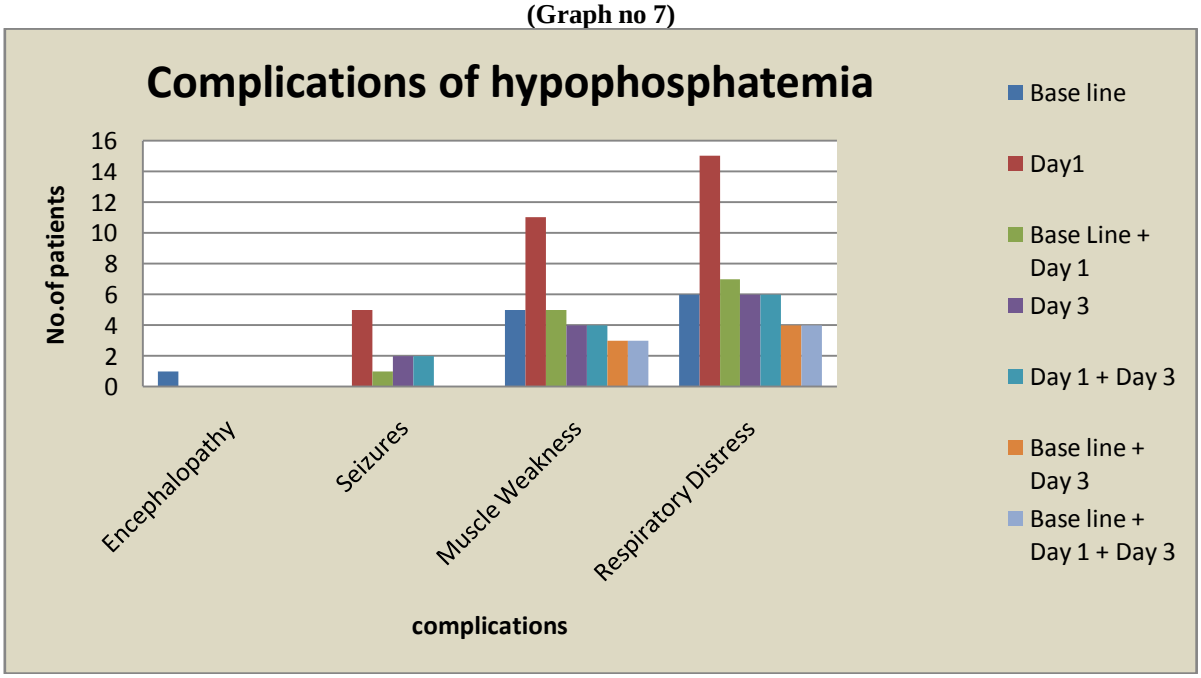


As shown in Graph no.6 when assessed on the scale of degree of hypophosphatemia, none of the study patient had severe hypophosphatemia(<1.00). On day 1, where maximum(52) hypophosphatemic patients were there ,19(36.53%) had mild hypophosphatemia (1 to 1.9)and 33(63.46%) had moderate hypophosphatemia(2 to 2.5).
(Graph no 6)



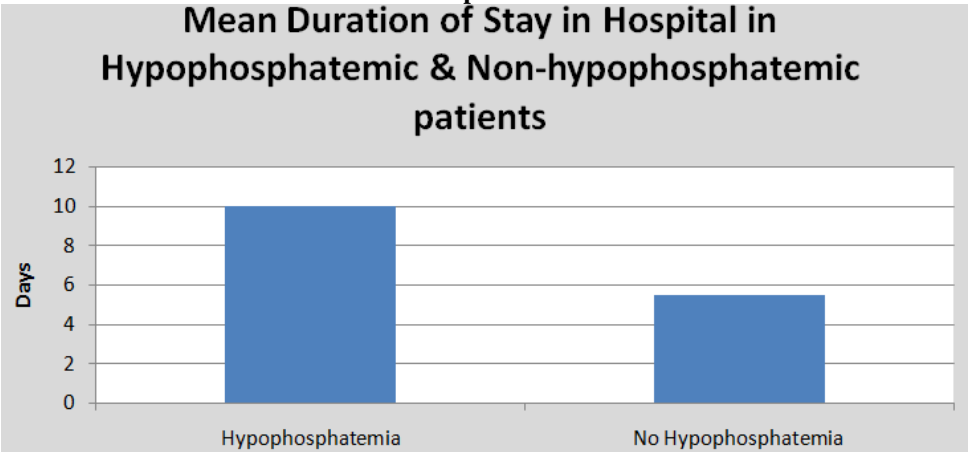
As shown in graph no.7, when patients with hypophosphatemia were assessed for complications of hypophosphatemia, respiratory distress was the most common complication. Muscle weakness was the 2nd most common symptom followed by seizures. Of the 4 patients with persistent hypophosphatemia (i.e., baseline +day 1+day3 hypophosphatemia) all 4 had respiratory distress and 3 had muscle weakness that none of the symptom was specific to any particular day on which hypophosphatemia developed. Maximum number of patients (57%) had no symptoms.

(Graph no 7)



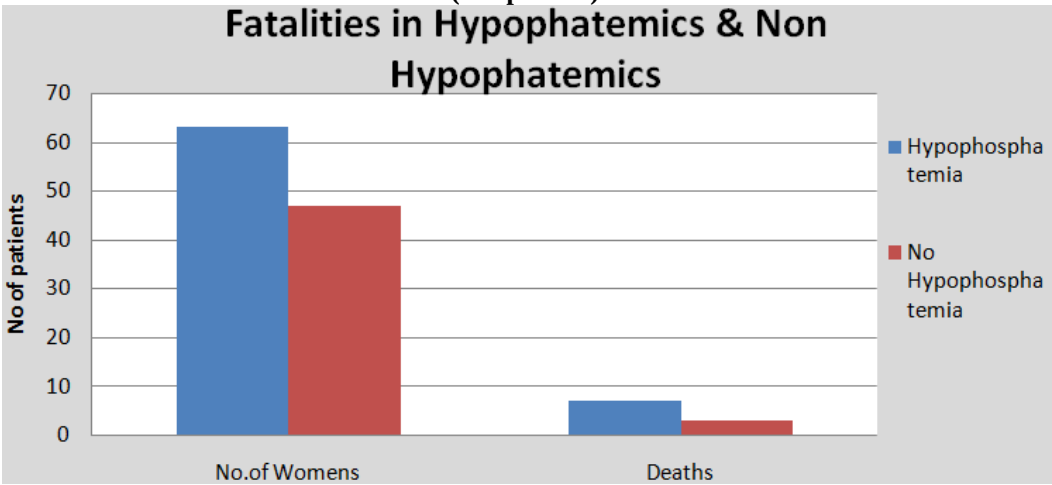
As shown in Graph no 8, when 63 patients who had hypophosphatemia at least once were compared with 47 patients who never had hypophosphatemia (euphosphatemics and hyperphosphatemics),it was found that mean duration of stay in hypophosphatemic patients was 10 days compared to 5.45 days in patients who never had hypophosphatemia. When Z test was applied we found statistically significant (P=0.0000) correlation between length of hospital stay and occurrence of hypophosphatemia.

Graph no 8



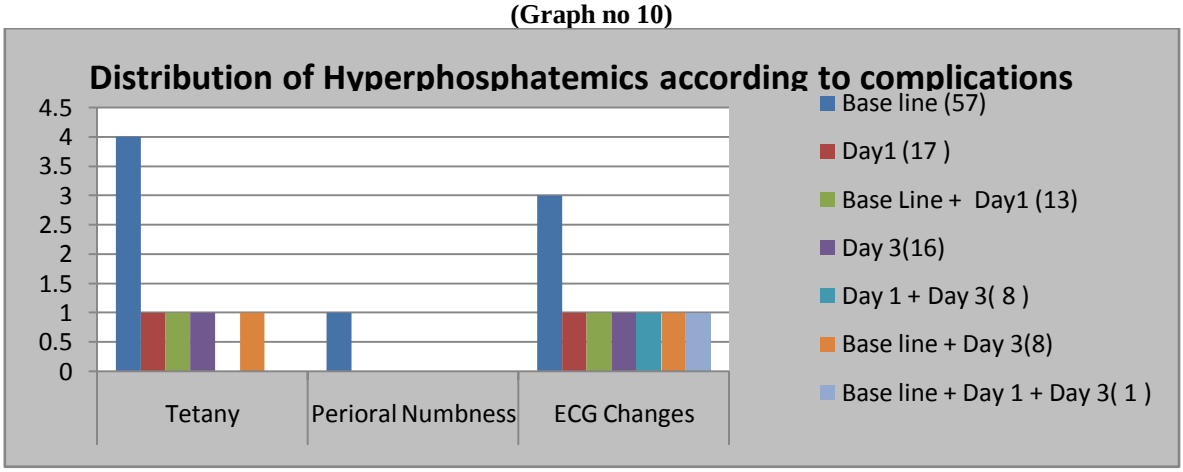
As shown in Graph no.9,when mortality was compared between hypophosphatemics and non-hypophosphatemics,we found that in hypophosphatemic group 7 patients died and in non hypophosphatemic group 3 patients died.

(Graph no 9)



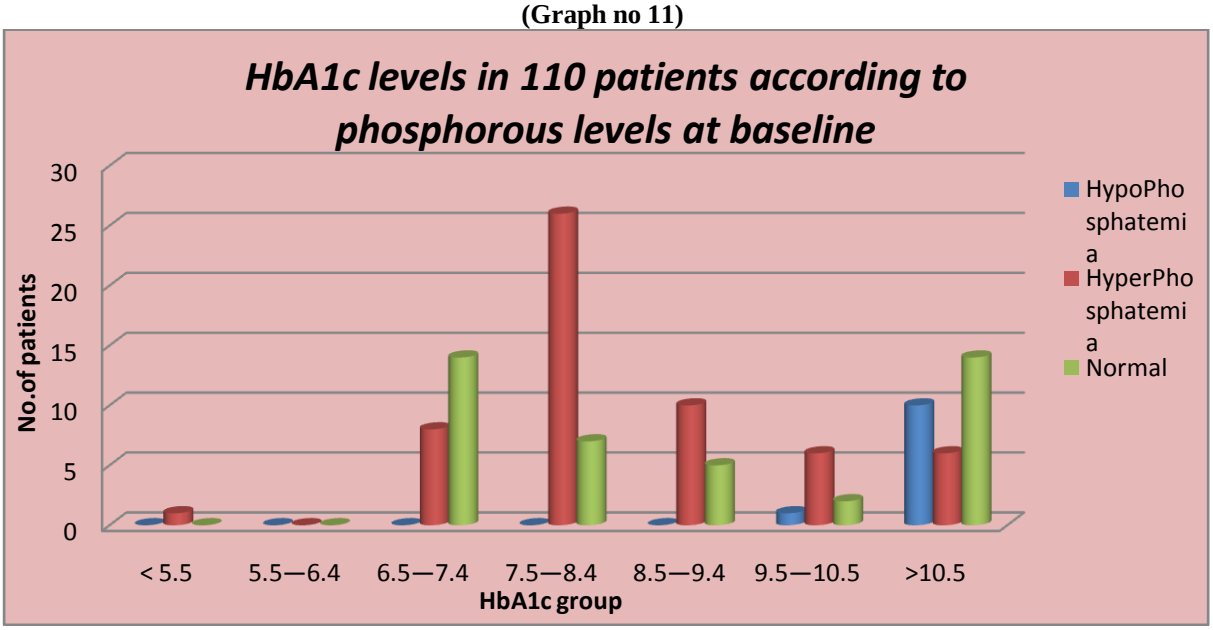
As shown in Graph no.10 when complications of hyperphosphatemia were analyzed, 4 patients with baseline hyperphosphatemia had tetany, 3 had cardiac manifestation in the form of prolonged corrected QT interval and 1 patient had perioral numbness. On day 1 and day 3 only 1 patient each had complaints of tetany and ECG changes. So maximum number of patients with hyperphosphatemia were asymptomatic.

(Graph no 10)



As depicted in Graph no. 11, When baseline phosphorous levels were analyzed according to HbA1C levels, of the 11 hypophosphatemic patients 10 had HbA1C levels more than 10.5. Of the 57 hyperphoshatemic patients only 6 had HbA1C levels more than 10.5. Of the 42 normo-phosphatemic patients 14 had HbA1C levels more than 10.5. When Chi-square test was applied to these readings, it showed statistical significance. This means high HbA1C levels indicating poor glycemic control had statistically significant(p=0.0000)negative correlation with low phosphorous levels.

(Graph no 11)



When phosphorous levels were correlated with blood sugar level at baseline, negative correlation was found. However this negative correlation was statistically non-significant .

Relation Between	r-value	p-value
Phosphorus vs HbA1c	**-0.267**	**P=0.005 s**
Phosphorus vs BSL	**-0.010**	**P=0.965 NS**

IV. Discussion

Out of the 110 patients we studied, 58 (52.73%) were males and 52 (47.27%) were females. CDC data showed slight female preponderance in cases of diabetic ketoacidosis.. Dharma Rao et al[10], in their study of adult diabetic ketoacidotic shows male prepondereance(63.4%)

In our study maximum number of patients of ketosis were found in the age group of 51-60 years(30.91%) The mean age of patients was 52.96 ± 13.46 years. CDC data revealed more occurrence of diabetic ketoacidosis episodes among young diabetics. This happened most probably because only adult patients (i.e. more than 18 years of age) were included in the present study. So, patients less than 18 years of age having more prevalence of type 1 diabetes who are more prone for episodes of diabetic ketoacidosis were not taken into account. Dharma Rao et al[10], , found that maximum numbers of patients in the age group of 41-50 years, (45.3%). The mean age in Dharma Rao study was 43.1 years. The age group distribution results in present study were more in line with Dharma Rao study.

Rao et al[10] Chih-Husn-Chu et al[11]in showed infection as the major precipitating event in ketosis. Second most cause is treatment omission(28%).Our study result regarding cause of diabetic ketoacidosis was also comparable with this study.

According to National Health Survey Data[12], two third of all diabetic patients hospitalized for diabetic ketoacidosis have type 1 diabetes mellitus and the remainder one third have type 2 diabetes mellitus. Present study results regarding type of diabetes were opposite to National Health Survey data. This contradiction in the results occurred because in the present study only adult patients included So large number of young patients having type 1 diabetes mellitus who frequently have episodes of diabetic ketoacidosis were not considered in this study. In our study (17.27%) had type 1 diabetes mellitus and 91 (82.73%) patients had type 2 diabetes

mellitus. our Results similar to Chih-Husn-Chu et al[11] study and Dharma Rao et al[10] who had included adult patients. .

Riley et al[13], in their study of diabetic ketoacidosis patients found that hypophosphatemia usually occurs after 24 hours of treatment of diabetic ketoacidosis and may last for a week. In the present study results also maximum number of hypophosphatemics were found after 24 hours of initiation of treatment, but in our study as soon as hypophosphatemia was detected sodium phosphate twice/thrice a day and diet rich in phosphorous was administered .This may be the reason why 68.18% patients had normal phosphorus levels on day 3 and did not continue to have persistent hypophosphatemia.

Shen T and Braude found that 62.5% patients were hyperphosphatemic on presentation and phosphate levels fell in all patients and out of these 90% of patients developed hypophosphatemia. In our study we found tha t51.82% patients having hyperphosphatemia on presentation, 47.17% patients developed hypophosphatemia on day 1 and overall 57% had hypophosphatemia at least once. . Miller DW et al[14] study that hypophosphatemia occurred with insulin therapy in patients with diabetic ketoacidosis after 12 to 24hrs and this hypophosphatemia lasted for 36 to 48hrs. our study also has comparable results with 47.17% of patients having hypophosphatemia on day 1, 68.8% of patients having normal phosphorous levels on day3 and only 17.2% patients having hypophosphatemia even on day 3.

. Y Kanter et al[15] studied levels of 2, 3 DPG, nucleotide phosphate, organic and inorganic phosphate levels during early phases of diabetic ketoacidosis. They observed that steady drop in serum in inorganic phosphate was found during 1st 24hrs of insulin treatment and was profound at 24hrs. Present study findings, were similar to these findings, having maximum number of hypophosphatemics on day 1.

Alexander Bindels et al[16], stated that serum phosphate levels do not accurately reflect total body phosphorous stores, hence the degree of hypophosphatemia does not always correlate to the presence of symptoms. Although most patients with hypophosphatemia do not develop symptoms but fatal complications can occur. Respiratory muscle dysfunction, resulting in respiratory distress and weaning problems is most common. Muscle weakness in severe form leading to rhabdomyolysis is second most common symptom. Other symptoms include myocardial dysfunction, arrhythmias, neurological problems including encephalopathy, seizures. In present study most of the hypophospahtemic patients were asymptomatic. Respiratory distress was the most common manifestation followed by muscle weakness. Professor James P. Knochel[17] in his article on 'Hypophosphatemia' stated that acute hypophosphatemia can manifest in 8 ways; Rhabdomyolysis, CNS manifestations including encephalopathy, seizures, Respiratory distress are the commonest manifestations. Other manifestations include myocardial dysfunctions, osteomalacia, leukocyte dysfunction and platelet dysfunction. The underlying cause for these abnormalities is decreased levels of both 2,3-DPG and ATP.

mean duration of stay in hypophosphatemic patients was 10 days compared to 5.45 days in patients who never had hypophosphatemia in our study. There is a negative correlation between length of hospital stay and hypophosphatemia which is statistically significant. In one prospective study[18], duration of hospitalization was studied among 62 patients. Duration of hospitalization was 12.1± 7.1 among hypophosphatemic patients versus 8.2 ±4.6 days among controls.

M Brunelli et al[19], in their article 'Hypophosphatemia: clinical consequences and management' found that in-hospital mortality was more in cases of hypophosphatemia than controls. . In a retrospective study conducted by Schibe JR and study conducted by Mattu A on 651critically ill patients, Measured mortality was higher in hypophosphatemic group. In our study also mortality was more in hypophosphatemic group but it was statistically non significant. This finding was observed may be because in our study patient who had hypophosphatemia were given treatment with sodium phosphate.

Few no of patients had complications of hyperphosphatemia four had tetany, 3 had cardiac manifestation in the form of prolonged corrected QT interval and 1 patient had perioral numbness and maximum number of patients with hyperphosphatemia were asymptomatic. This finding was comparable with the Markowitz et al[20], Berner YNet al[21,] Anderson JJ et al[22] study who stated that most patients with hyperphosphatemia are asymptomatic. Occassionally, patients report hypocalcemic symptoms such as cramps, tetany, perioral numbness.

We found in our study high HbA1C levels indicating poor glycemic contol have statistically significant correlationship with low phosphorous levels. . Nagasaka et al [24], in their study on Non-Insulin dependent Diabetes Mellitus found that when glycemic control improved, serum phosphorous increased. UKPDS group[24] found that normalization of blood glucose level leads to a subsequent increase in plasma inorganic phosphorus levels. Dietzel et al[25], in their study found that the maximal capacity of renal tubular reabsorption of phosphate /L of filtrate (Tm PO4/GFR) was significantly suppressed in diabetic patients when compared to healthy controls despite lower fasting inorganic phosphorus levels in diabetics. So, increased urinary phosphorous excretion leading to hypophosphatemia correlates with blood glucose concentration.

V. Conclusion

1) The present study is a prospective observational study of 110 adult patients of diabetic ketoacidosis.
2) In this study we observed that maximum number of cases were found between the ages 51 to 60 years and median age of patients in our study was 52.96 years. There were 58 male and 52 female patients in our study. Male:Female ratio was ratio was 1.115: 1 indicating slight male preponderance.
3) Infection was the most common precipitating factor accounting for 55% cases of DKA followed by treatment omission(26%).
4) 82% had type 2 DM and 18% had type 1 DM.
5) The mean phosphorus level at baseline was 5.08±2.15 mg/dl which decrease to 2.95±1.32 mg/dl on day 1.
6) Hyperphosphatemia was observed in 52% patients at baseline.
7) Hypophosphatemia was observed in 48% of patients on day 1.
8) Overall out of 110 patients 63 patients (57%) had hypophosphatemia at least once.
9) Among hypophosphatemic patients, all of them had either mild or moderate hypophosphatemia.No body had severe hypophosphatemia.
10) Among 63 hypophosphatemics 36 patients (57%) were asymptomatic.
11) Among symptomatic hypophosphotemics respiratory distress was the most common symptom.

The mean length of stay among hypophosphatemics (10 days) was significantly higher than euphosphatemics or hyperphosphatemics (5.45 days).

12) Number of fatalities recorded among hypophosphatemics was 7 and among euphosphatemics and hyperphosphatemics was 3.This difference was statistically non-significant.
13) There was statistically significant negative correlation between HBA1C levels and serum phosphorus levels at baseline.

Hence we conclude that phosphorus the neglected aspect of diabetic ketoacidosis needs due consideration. Significant negative correlation was observed between HBA1C levels and serum phosphorus levels. Significant long length of hospitalization was observed in diabetic ketoacidosis patients having low phosphorus levels. Mortality rate was found high in hypophosphatemic group however this observation was found to be statistically insignificant. All patients having symptomatic hypophosphatemia in the form of unexplained respiratory distress and difficulty in weaning off from ventilator need appropriate attention for medical management of hypophosphatemia.

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