

Study Of Serum Inorganic Phosphate Levels In Patients With Type Ii Diabetes Mellitus Admitted In Medical Icu And Wards In A Tertiary Care Centre

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Abstract

BACKGROUND AND OBJECTIVES:

1. To study serum inorganic phosphate concentration in patients with type II diabetes mellitus without comorbidities.
2. To study serum inorganic phosphate concentration in patients with type II diabetes mellitus with comorbidities.
3. To compare serum inorganic phosphate levels in these two groups.

METHODOLOGY:

120 patients with type 2 diabetes mellitus were included in the study over 1 month from chettinad hospital and research institute, kelambakkam, tamilnadu.

Blood samples were collected after a twelve-hour fasting period (Overnight fasting) under aseptic conditions, the obtained blood sample were centrifuged and plasma was separated. The plasma was analysed for the fasting and postprandial blood sugar, estimated by GOD-POD method¹⁰. Serum samples were separated from whole blood collected into tubes without anticoagulant, after clotting was complete, the tubes were then centrifuged for 10 minutes. Serum was removed and assayed for phosphorus. Patients will be considered diabetic according to the criteria defined by American Diabetes Association 2011 criteria.

RESULTS:

The present study was undertaken to determine the serum inorganic phosphate concentration in diagnosed cases of type 2 diabetes mellitus without comorbidities, type II diabetes mellitus with comorbidities like hypertension and ischemic heart disease and to compare between the two groups. Our study showed that serum inorganic phosphate concentration was reduced in 52% of the diagnosed cases of DM II without comorbidities and 21% of patients with DM II with comorbidities like HTN and IHD.

In the present study negative correlation was observed between serum inorganic phosphate levels and HbA1c, fasting and post prandial blood sugar levels in DM II patients with and without comorbidities. As long as glycaemic control was not attained decreased serum inorganic phosphate concentration may play a role in the progression of the disease and development of complications associated with diabetes mellitus.

CONCLUSION:

Serum phosphate levels were relatively more in patients with DM II with comorbidities like HTN and IHD than DM II without comorbidities.

INTRODUCTION:

Diabetes mellitus is a group of metabolic disorders in which the body does not produce enough insulin or respond normally to insulin or combination of both causing elevated blood glucose levels¹. There are two main types of diabetes mellitus, type I and type II diabetes mellitus. Among this type I is primarily due to autoimmune mediated destruction of pancreatic beta islet cells causing absolute insulin deficiency and type II is characterized mainly by insulin resistance or decreased insulin secretion or both.² Frequency of type II diabetes mellitus is more when compared to type I which accounts for more than 90% of diabetes cases globally.³ Currently there are thought to be 347 million cases of diabetes globally with type 2 diabetes accounting for more than 90% of occurrences.

Diabetes related complications place a major load on medical resources and lower overall quality of life. Complications of diabetes include acute complications⁴ like diabetic ketoacidosis, hypoglycaemia, lactic acidosis, non-ketotic hyperosmolar diabetic syndrome or coma. Chronic microvascular complications like Retinopathy (17.6%), Nephropathy (26.9%), Neuropathy (26.1%), Diabetic foot, Dermopathy and chronic macrovascular complications like Cerebrovascular, Cardiovascular (21.4%), Peripheral vascular disease (6.3%).

These complications of diabetes affect millions of people in India, manifest either in single or in combination. Energy synthesis, signal transduction, mineral metabolism and other metabolic activities are all controlled by the essential mineral phosphorus. Overt hyperphosphatemia is known to have negative consequences on bone and the parathyroid glands⁵. In investigation of both the general population and the population with chronic renal disease, greater serum phosphate concentrations have been found to be associated with cardiovascular events, vascular calcification, and even death⁶ over the past few years.

A paradoxical metabolic imbalance in trace elements such phosphorus, zinc, and magnesium is observed early in the development of diabetes. These alterations occur in cells and tissues where the entry of glucose is not under the control of insulin, especially in poorly controlled diabetic individuals who are more likely to experience long-term vascular problems. Because elevated blood glucose levels depolarize the brush border membrane for phosphate reabsorption which in turn cause a lack of intracellular phosphate and increase urinary excretion of phosphate which results in decreased blood phosphate levels. The normal serum phosphate levels are 2.5-4.5 gm/dl.

More glucose enters insulin-sensitive muscle and adipose tissues during hyperglycemic-hyperinsulinemic intervals. The phosphorylation of intracellular glucose results in a decrease in plasma inorganic phosphate which adversely affects glucose metabolism in tissues that are insulin-insensitive. Hypophosphatemia results in decreased intracellular adenosine triphosphate (ATP) which may lead to cell death.

Poor nutritional intake, decreased intestinal absorption, the movement of phosphate from extracellular fluid into the inside of the cell, and increased urine excretion all contribute to hypophosphatemia. The diabetic ketoacidosis patients, hyperalimentation, respiratory alkalosis, refeeding syndrome and medications including diuretics, steroids, antacids and intravenous dextrose can all cause severe hypophosphatemia. Both hypophosphatemia and hyperphosphatemia have deleterious effects on health. Hypophosphatemia leads to hemolysis, rhabdomyolysis and insulin resistance which in turn lead to acute and chronic complications of diabetes mellitus. Hyperphosphatemia will trap calcium to form calcium phosphate leading to seizures and hypocalcemic tetany.

MATERIALS AND METHODS:

The present study is a prospective study in which adult patients with type 2 diabetes mellitus qualified the inclusion and exclusion criteria were included. The study was conducted for a period of one month .before initiating the study ,the ethical committee approval and written informed consent were obtained from patients.

Inclusion criteria:

1. Diagnosed cases of type II diabetes mellitus without comorbidities that were admitted in medical ICU and wards in chettinad hospital and research institute .

2. Diagnosed cases of type II diabetes mellitus Patients with comorbidities (hypertension, ischemic heart disease)

Exclusion criteria:

1. Patients with diagnosed type I diabetes mellitus.
2. Patients who did not give consent to the study.
3. Pregnant women with type II diabetes mellitus.
4. Patients receiving phosphate supplementation.
5. Patients on drugs that alter serum phosphate level (diuretics, laxatives, bisphosphonates) or drugs modifying metabolism of phosphate.
6. Patients with hepatic disorders, chronic renal disease and patients with hypertension on diuretic therapy.

Detailed clinical history, clinical examination, and relevant laboratory investigations were done .Blood samples were collected after a twelve-hour fasting period (Overnight fasting) under aseptic. Conditions, the obtained blood sample were centrifuged and plasma was separated. The plasma was analysed for the fasting and postprandial blood sugar, estimated by GOD-POD method¹⁰. Serum samples were separated from whole blood collected into tubes without anticoagulant, after clotting was complete, the tubes were then centrifuged for 10 minutes. Serum was removed and assayed for phosphorus. Patients will be considered diabetic according to the criteria defined by American Diabetes Association 2011 criteria. Serum inorganic phosphate measurement: by molybdate U.V method. The normal range for serum phosphate is (2.5-4.5 mg/dl).Serum phosphate levels less than 2.5 mg/dl is hypophosphatemia and more than 4.5 mg/dl is hyperphosphatemia.

Statistical analysis: The range, mean, standard deviation (SD), frequencies (number of cases), and relative frequencies (percentages), when necessary, were used to explain the data. Comparison of quantitative variables between the study groups was done using Student t-test, for comparing categorical data Chi square (χ^2) test was used and fisher exact test was used when the expected frequency is less than a probability value (p value) of 0.05 which is considered statistically significant. The statistical software for Microsoft Windows SPSS 21version (SPSS Inc., Chicago, IL, USA) (Statistical Package for the Social Science) was used for all statistical calculations.

RESULTS:

The present study was a hospital-based study conducted in the Department of General Medicine at chettinad hospital and research institute Chennai to understand the role of serum inorganic phosphate levels in patients diagnosed with type II diabetes mellitus admitted in medical ICU and wards . A total of 120 patients were enrolled in the study out of which 54 comprise group I i.e., (Patients with DMII without commodities) and 66 in Group II (Patients with DMII with Comorbidities like HTN and IHD). Majority of cases 25.8% were between 51-60 years of age in group I and 30.3% in group II . There were 57 females and 63 males in the study.

Table 1. Comparison of group I and group II according to gender and age

		Group I	Group II	P-value
Gender	Male	28 (51.9%)	35 (53%)	0.898
	Female	26 (48.1%)	31 (47%)	
Age group	<40	10 (18.5%)	9 (13.6%)	0.745
	41-50	14 (25.9%)	16 (24.2%)	
	51-60	11 (20.4%)	20 (30.3%)	
	61-70	14 (25.9%)	14 (25.9%)	
	>70	5 (9.3%)	7 (10.6%)	

Table 2. Mean parameters of the study

	Group I	Group II	P-value
Age in years	54.35 ± 12.72	55.39 ± 12.13	0.648
DM II	8.42 ± 5.80	6.95 ± 3.99	0.220
Random Blood Sugar (mg/dl)	115.19 ± 21.78	129.09 ± 30.38	0.006
Fasting Blood Sugar (mg/dl)	140.85 ± 26.01	160.50 ± 32.98	0.001
Post Prandial Blood Sugar (mg/dl)	172.69 ± 31.27	213.38 ± 42.78	0.001
HBA1C (%)	8.43 ± 2.04	9.90 ± 3.08	0.003
Serum Phosphate (mg/dl)	2.92 ± 0.84	3.40 ± 0.68	0.001

In group I and group II serum phosphate levels had negative correlation with fasting and post prandial blood sugar levels. It was observed that in group I 55% had low serum phosphate levels and In group II 31% had low serum phosphate levels. Serum phosphate levels are more in patients with DMII with comorbidities when compared to DMII without comorbidities as majority of group II patients had less than 5 years duration of hypertension and they may be using anti hypertensives which prevents damage to kidney and increases renal threshold for phosphate reabsorption.

Table 3. Correlation of serum phosphate level among groups

Spearman's rho - Serum phosphate	Group I		Group II	
	R-value	P-value	R-value	P-value
Duration of DM II	-0.287	0.036	-0.265	0.031
HTN	.	.	-0.306	0.024
IHD	.	.	-0.426	0.036
Random Blood Sugar (mg/dl)	-0.251	0.068	-0.275	0.025
Fasting Blood Sugar (mg/dl)	-0.207	0.133	-0.264	0.032
Post Prandial Blood Sugar (mg/dl)	-0.216	0.117	-0.260	0.035
HBA1C (%)	-0.419	0.002	-0.537	<0.0001

Table 4. Correlation of serum phosphate level in group I and II

Co-relation of serum phosphate levels		Mean STD	Min-max	95% Confidence Interval for Mean		P-value
				Lower bond	Upper bond	
HbA1C	< 7.5	3.31 ± 0.69	2.30-4.80	3.00	3.61	0.012
	7.5-10.5	2.71 ± 0.92	1.30-4.80	2.32	3.11	
	>10.5	2.49 ± 0.63	1.40-3.00	2.01	2.97	
DM II + IHD		3.16 ± 0.38	2.60-3.80	2.92	3.40	0.388
DM II + HTN		3.45 ± 0.70	2.10-4.50	3.26	3.65	
DM II + HTN + IHD		3.50 ± 1.11	2.10-4.38	1.73	5.27	
DM + HTN	< 5	3.62 ± 0.71	2.80-5.60	3.38	3.86	0.020
	5-10.0	3.20 ± 0.60	2.10-4.50	2.89	3.51	
	> 10	2.10	2.10-2.10	.	.	

DM + IHD	< 2	3.16 ± 0.38	2.60-3.80	2.92	3.40	0.351
	> 2	3.50 ± 1.11	2.10-4.80	1.73	5.27	

In our study, the mean serum phosphate level in group I was 2.92 ± 0.84 mg/dl and in group II was 3.40 ± 0.68 mg/dl. There was statistically significant difference between these groups ($p=0.001$). In our study, mean serum inorganic phosphate levels in cases with HbA1c <7.5% was (3.31 ± 0.69 mg/dl) and in cases with HbA1c range 7.5-10.5 %, serum phosphate levels was (2.71 ± 0.92 mg/dl) and in cases with HbA1c range >10.5 %, serum phosphate levels was (2.49 ± 0.63 mg/dl.) which shows that there is decline in phosphorus levels with increase in hba1c.

DISCUSSION

The present study was conducted in the Department of General Medicine at chettinad Medical College & Hospital, Chennai to understand the role of serum inorganic phosphate levels in patients with type II diabetes mellitus admitted in medical ICU and wards. We compared serum inorganic phosphate levels in patients with type II diabetes mellitus without comorbidities and type II diabetes mellitus with comorbidities like ischemic heart disease and hypertension, other comorbidities are not taken into consideration as they alter serum inorganic phosphate levels.

Table 1: Age wise distribution of patients

A total of 120 patients were enrolled in the study, out of which 54 comprise Group I i.e., (Patients with DMII without comorbidities) and 66 comprise Group II i.e., (Patients with DMII with Comorbidities like HTN and IHD). Among 120 cases which were enrolled in the study, 19(15.8%) cases were in the age group of < 40 years, 30(25%) cases were in the age group 41 – 50 years, majority of cases 31(25.8%) were between 51-60 years of age, 28(23.3%) cases were between 61-70 years of age and 12(10%) cases were above 70 years of age, which was similar to study conducted by Rula Rashed et al. in which 21% of Patients were below the age of 45 years, (35%) between 45 and 60, and (44%) more than 60 years

Table 1 - Comparison of group I and group II according to age

In group I, equal number of cases were seen in the age group 41–50 years (14 of 54), 61 -70 years (14 of 54). In group II the majority of cases (20 of 66) were in the age group 51-60 years which accounts to 30.3% of total patients in group II. It was also found that in group II more patients were in the older age group when compared to group I. On comparison there was no significant difference between these groups.

Table : 1- Mean age of patients in group I and group II

The mean age of patients in group I was 54.35 ± 12.72 years and in group II was 55.39 ± 12.13 years which was similar to a study conducted by Raul KM et al.⁷² where patients' mean age was 52.96 ± 13.46 years, similar to study conducted by Rula Rashed et al. where mean age of patients was 55.15 ± 15.3 years.

Table 1 : Distribution of patients according to gender

In our study, Majority of patients were males [63 in 120 (52.5%)] and females were [57 in 120 (47.5%)] with male to female ratio 1.1:1. As per a study conducted by Rula Rashed et al. where (59.7%) of patients were females and (40.3%) of patients were males which was not consistent with findings in our study may be due random sampling.

In group I, 51.9% (28 of 54) were males, 48.1% (26 of 54) were females, in group II 53% (35 of 66) were males and 47% (31 of 66) were females. On comparison there was no significant difference between these groups.

Table 3 : -Comparison of serum phosphate levels between the groups

In our study, the mean serum phosphate level in group I (DMII without comorbidities) was 2.92 ± 0.84 mg/dl and in group II (DMII with comorbidities like HTN and IHD) was 3.40 ± 0.68 mg/dl. There was statistically significant

difference between these groups ($p=0.001$). Our results were consistent with a study conducted by Bora GK et al 2016⁸⁰ where the mean serum inorganic phosphate level in diabetic cases was found to be 2.68 ± 0.56 mg/dl.

Table 3 : -Comparison of serum phosphate levels among males and females in group I and group II

The mean serum phosphate level in males with type II diabetes was 3.16 ± 0.83 mg/dl and in females was 3.22 ± 0.75 mg/dl which had no statistically significant difference. In our study, mean serum phosphate levels in females was 3.22 ± 0.75 mg/dl and in males was 3.16 ± 0.831 mg/dl. In group I (DMII without co-morbidities), mean serum inorganic phosphorus levels in males was 2.77 ± 0.812 mg/dl and in females was 3.08 ± 0.861 mg/dl which had no statistically significant difference. Results of our study are consistent with a study conducted by Bora GK et al.,⁸⁰ it was observed that mean serum inorganic phosphate level in males with type II diabetes was 2.73 ± 0.58 mg/dl and in females with type II diabetes mellitus was 2.6 ± 0.54 mg/dl which was also not statistically significant as observed in our study.

In group II (DMII with co-morbidities like HTN and IHD), mean serum inorganic phosphate levels in males was 3.47 ± 0.717 mg/dl and females were 3.33 ± 0.636 mg/dl indicating that diabetic males with co-morbidities have more serum phosphate levels compared to females with co-morbidities which was statistically not significant with (p value= 0.429).

Table 2 : -correlation of HbA1c and serum phosphate levels

In our study, mean serum inorganic phosphate levels in cases with HbA1c $<7.5\%$ was 3.31 ± 0.69 mg/dl and in cases with HbA1c range $7.5-10.5\%$, serum phosphate levels was 2.71 ± 0.92 mg/dl and in cases with HbA1c range $>10.5\%$, serum phosphate levels was 2.49 ± 0.63 mg/dl which was consistent with a study conducted by Bora GK et al.⁸⁰ where cases with HbA1C range of $6.00- 7.50\%$ had highest concentration of serum inorganic phosphate i.e., 3.26 ± 0.45 mg/dl in contrast to the patients with HbA1C range of 10.51% and above had lowest concentration of serum inorganic phosphate i.e., 2.06 ± 0.15 mg/dl. So, the cases having higher values of HbA1C have lower values of serum inorganic phosphate concentration and vice versa.

In Present study it was observed that the level of serum inorganic phosphate showed a negative correlation with HbA1c. Our results were similar to a study conducted by Bora GK et al⁸⁰ where serum inorganic phosphate levels showed a negative correlation with HbA1c % that was statistically highly significant ($p<0.01$). The Pearson correlation coefficient “r” found to be -0.81 established the strong negative correlation between the two parameters.

Serum phosphate levels also had negative correlation with HbA1c levels in both group I ($p=0.002$) and group II ($p=0.000$) which were statistically significant and these findings are almost consistent with findings with a study conducted by Nagasaka S et al⁷² which showed that in NIDDM (DM II) patients at the time of admission, HbA1c was $11.1 \pm 0.3\%$ and the serum phosphate was 1.12 ± 0.03 mmol/l. The values of HbA1c and serum phosphate became $9.3 \pm 0.2\%$ and 1.21 ± 0.03 mmol/l respectively at the time of discharge from the hospital when glycemic control was markedly improved and the changes in the values were statistically significant ($p<0.01$), showing negative correlation between HbA1c and serum phosphate levels.

Table 2 : - correlation of serum phosphate level with FBS and PPBS in group I and group II

In group I (DMII without comorbidities) and group II (DMII with comorbidities like HTN and IHD), serum phosphate levels had negative correlation with post prandial blood sugar levels, our results are consistent with the study conducted by Revathi R et al⁸³. where post prandial blood sugar levels had negative correlation with serum phosphate levels.

In our study, serum phosphate levels showed negative correlation with fasting blood glucose levels in both group I ($P=0.133$) and group II ($P=0.032$). Results of our study are almost consistent with findings of Haglin et al., Park W et al.⁷⁵ which showed negative correlation between serum phosphate levels and fasting blood glucose levels.

Table 3 : -Comparison of serum phosphate levels in group I vs group II

In our study, it was observed that in group I, 55% (30 in 54) had low serum phosphate levels, 45% (24 in 54) had normal serum phosphate levels. Results of our study are almost consistent with a study conducted Revathi R et al.,⁸³ where 62% of diabetic individuals have low serum phosphate levels. In group II i.e., 31% (21 in 66) had low serum phosphate levels and 69% (45 in 66) had normal serum phosphate levels.

Table 3 : - Correlation of serum phosphate levels in group II

Patients with [DM II with HTN and IHD had high mean serum phosphate levels (3.5 ± 1.11 mg/dl)] compared to [DM II with HTN (3.45 ± 0.70 mg/dl)] and [DMII with IHD (3.16 ± 0.38 mg/dl)], this may be due to use of anti-hypertensive medications which reduces proteinuria, delays progression of damage to the kidney, increases renal threshold for phosphate reabsorption.⁸⁶ The majority of hypertensive patients (36 in 54) had less than 5 years history of hypertension and their blood pressure was well controlled.

Table 2,4 : - Correlation of serum phosphate levels with duration of HTN in patients with DMII

Mean serum phosphate levels in type II diabetic patients with less than 5 years history of hypertension was 3.62 ± 0.71 mg/dl, with 5-10 years history of hypertension was 3.2 ± 0.60 mg/dl and with more than 10 years history of hypertension was 2.1 mg/dl. Indicating that in type II diabetic patients as duration of hypertension increases serum phosphate levels decreases, our results are consistent with a study conducted by Wan Park et al.⁷⁵ where negative correlation was observed between mean serum phosphorus levels and hypertension with mean serum phosphorus 3.49 ± 0.44 mg/dl with mean estimated GFR was 77.46 ± 8.51 mL/(min 1.73 m²) indicating that our study population had normal GFR.

Table 2,4 : - Correlation of serum phosphate levels and IHD in patients with DMII

In our study, it was observed that the mean serum phosphate levels in type II diabetic patients with IHD was 3.16 ± 0.38 mg/dl, which was relatively more when compared to mean serum phosphate levels of DMII patients without comorbidities where mean serum phosphate level was 2.92 ± 0.84 mg/dl indicating that higher levels of phosphate are associated with IHD. This finding in our study is consistent with a study conducted by Jessica Kendrick et al .⁸⁴ where positive correlation was seen between serum phosphate levels and ischemic heart disease as hyperphosphatemia causes vascular calcification. It was observed that mean serum phosphate levels in DMII patients with history of IHD less than 2 years duration was 3.16 ± 0.38 mg/dl and mean serum phosphate levels in type II diabetic patients with history of IHD more than 2 years was 3.50 ± 1.11 mg/dl indicating that serum phosphate levels are more as the duration of IHD increases in DMII patients.

CONCLUSION

The present study was undertaken to determine the serum inorganic phosphate concentration in diagnosed cases of type 2 diabetes mellitus without comorbidities, type II diabetes mellitus with comorbidities like hypertension and ischemic heart disease and to compare between the two groups.

Our study showed that serum inorganic phosphate concentration was reduced in 52% of the diagnosed cases of DM II without comorbidities and 21% of patients with DM II with comorbidities like HTN and IHD.

In the present study negative correlation was observed between serum inorganic phosphate levels and HbA1c, fasting and post prandial blood sugar levels in DM II patients with and without comorbidities. As long as glycaemic control was not attained ,decreased serum inorganic phosphate concentration may play a role in the progression of the disease and development of complications associated with diabetes mellitus.

Serum phosphate levels were relatively more in patients with DM II with comorbidities like HTN and IHD than DM II without comorbidities.

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