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DIABETES MELLITUS;
HYPOPHOSPHATEMIA IN PATIENTS

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ABSTRACT… Objectives: To determine the frequency of hypophosphatemia in patients with diabetes mellitus. **Study Design:** Cross sectional study. **Period:** Six months. **Setting:** Liaquat University Hospital Hyderabad. **Patients and methods:** All the patients of ≥35 years of age, either gender with known cases of diabetes mellitus type 2 for one year duration were recruited, enrolled and evaluate for serum phosphate level. The data was analyzed in SPSS 16 and the frequency and percentage was calculated. **Results:** During six months study period, total one hundred patients with type 2 diabetes mellitus were studied for serum phosphate level. The mean age ±SD for overall population was 53.85±7.63 whereas it was 54.53±6.87 and 55.93±6.94 in male and female populations respectively while the mean ±SD for serum phosphate in male and female population was 1.52±0.74 and 1.90±0.93 respectively. The hypophosphatemia was observed in 67% patients of which 37(55%) were males and 30(45%) were females (p=0.03) statistically significant. The HBA1c was raise in 72% patients of which 52 cases had hypophosphatemia (p=0.05) statistically significant. **Conclusion:** One hundred diabetic patients were studied and 67% shown significantly decreases serum phosphate level in context to age and gender while raised HBA1c, shown inversely proportional relationship with HBA1c respectively.

Key words: Phosphate, Hypophosphatemia, Phosphorous, Diabetes mellitus, HBA1C

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INTRODUCTION

Diabetes mellitus is an ice berg disease, a growing public health issue and the most common endocrinal disorder in the word.[1] Hyperglycemia due either due to absolute insulin deficiency, or a reduction in the biologic effectiveness of insulin or both cause secondary patho-physiologic alterations in multiple organ systems of body and high mortality and morbidity worldwide by DM is one of the public health burden especially in developing countries.[2] Global prevalence of diabetes mellitus is increasing from 4.0% to 5.4% while the number of people with diabetes is rises from 150 to 220 million in 2010 and 300 million by the year 2025.[3] The countries with the increase number of people with diabetes mellitus are and will be by the year 2025, India, Pakistan, China, Bangladesh, Nepal and the US.[4]

A paradoxical metabolic disturbance in inorganic phosphate occurs from the early onset of diabetes and may result in reduction of high energy phosphates and tissue hypoxia. These are cellular / tissue level changes and the patients of which blood sugar is not controlled by insulin or hypoglycemic agents, and subjects with uncontrolled diabetes has long-term vascular or neuropathic complications are more prone to acquire phosphate deficiency.[5,6] The highest oxygen consumption leads to lowest content of inorganic phosphate, and maintaining oxygen level is associated with higher concentration of inorganic phosphate.[7,8] Since a reduction of high energy phosphates and tissue hypoxia may be major factors in the development of diabetic complications, the effects of phosphate on the metabolism, RBC and kidney tubular cell function, as well as local and systemic consequences of hypophosphatemia in diabetic populations had

been reviewed but the Asian literature is still scarce.

Therefore, by considering such need, the present study was conducted at tertiary care teaching hospital to determine the alterations in serum phosphorus levels in diabetic population as adjudged by HbA1c because early screening and treatment can save the patients to acquire various life threatening complications associated the phosphate imbalance.

PATIENTS AND METHODS

This cross sectional descriptive study of six months was conducted in the department of medicine at Liaquat University Hospital Hyderabad / Jamshoro. All the patients of ≥35 years of age, either gender with known cases of diabetes mellitus type 2 for one year duration were recruited, enrolled and entered in the study while the patients with prolong nasogastric feeding, hyperparathyroidism, hypoparathyroidism, osteomalacia, Fanconi syndrome and chronic renal failure, alcoholics, malignancy, pregnancy and already on calcium and phosphate supplements were excluded from the study. The informed consent was taken from the every patient to participate in the study while the data was collected by structured proforma. The detail history was taken and relevant clinical examination was performed. All routine investigations were evaluated and the patients were managed accordingly while for specific investigations after all aseptic measures the 3cc blood sample was collected and sent to laboratory for analysis of blood glucose level (fasting), serum phosphate and HBA1c level. The normal range for phosphorous is 2.5-4.5 mg/dL, the level below the reference range was considered as low / deficient. The data was entered, saved and analyzed in SPSS 16. The frequency and percentage (%) was calculated while the mean ± SD was calculated for numerical variables. The stratification was done for age, gender, phosphate and diabetes mellitus, the chi-square test was applied on categorical variables and independent sample t-test was applied to compare the mean at 95% confidence interval and the level of significance was p-value ≤0.05.

RESULTS

During six months study period, total one hundred patients with type 2 diabetes mellitus were studied for serum phosphate level. The mean age ±SD for overall population was 53.85±7.63 whereas it was 54.53±6.87 and 55.93±6.94 in male and female populations respectively. The stratification of age, gender and hemoglobin A1C and serum phosphate is shown in Table I-VI while the mean ± SD of serum phosphate and HBA1C is shown in Table VII-VIII respectively.

		GENDER		Total	P-value
		Male	Female		
AGE	35-39	10	12	22	0.01*
		20.8%	23.1%	22.0%	
	40-49	25	14	39	
		52.1%	26.9%	39.0%	
	50-59	7	21	28	
		14.6%	40.4%	28.0%	
	60 +	6	5	11	
		12.5%	9.6%	11.0%	
Total		48	52	100	
		100.0%	100.0%	100.0%	

Table-I. The age and gender distribution
**Statistically significant*

		HYPOPHOSPHATEMIA		Total	P-value
		Yes	No		
AGE	35-39	11	11	22	0.02*
		16.4%	33.3%	22.0%	
	40-49	33	6	39	
		49.3%	18.2%	39.0%	
	50-59	16	12	28	
		23.9%	36.4%	28.0%	
	60 +	7	4	11	
		10.4%	12.1%	11.0%	
Total		67	33	100	
		100.0%	100.0%	100.0%	

Table-II. The age and hypophosphatemia
**Statistically significant*

		HEMOGLOBIN A1C		Total	P-value
		Raised	Normal		
AGE	35-39	19	3	22	0.03*
		26.4%	10.7%	22.0%	
	40-49	31	8	39	
		43.1%	28.6%	39.0%	
	50-59	15	13	28	
		20.8%	46.4%	28.0%	
	60 +	7	4	11	
		9.7%	14.3%	11.0%	
Total		72	28	100	
		100.0%	100.0%	100.0%	

Table-III. The age and hemoglobin A1C
**Statistically significant*

		HYPOPHOSPHATEMIA		Total	P-value
		Yes	No		
GENDER	Male	37	11	48	0.03*
		55.2%	33.3%	48.0%	
	Female	30	22	52	
		44.8%	66.7%	52.0%	
Total		67	33	100	
		100.0%	100.0%	100.0%	

Table-IV. The gender and hypophosphatemia
**Statistically significant*

		HEMOGLOBIN A1C		Total	P-value
		Raised	Normal		
GENDER	Male	38	10	48	0.12*
		52.8%	35.7%	48.0%	
	Female	34	18	52	
		47.2%	64.3%	52.0%	
Total		72	28	100	
		100.0%	100.0%	100.0%	

Table-V. The gender and hemoglobin A1C
**Statistically significant*

		HEMOGLOBIN A1C		Total	P-value
		Raised	Normal		
HYPOPHOSPHATEMIA	Yes	52	15	67	0.05*
		72.2%	53.6%	67.0%	
	No	20	13	33	
		27.8%	46.4%	33.0%	
Total		72	28	100	
		100.0%	100.0%	100.0%	

Table-VI. The hypophosphatemia and hemoglobin A1C
**Statistically significant*

HBA1C	N=100	Mean ±SD of Phosphate	P-value
Raised	72	1.67±0.85	0.05*
Normal	28	1.85±0.90	
GENDER	**N=100**	**Mean ±SD of Phosphate**	**P-value**
Male	48	1.52±0.74	0.03*
Female	52	1.90±0.93	

Table-VII. The stratification of hba1c and mean ±sd of serum phosphate
**Statistically significant*

HYPOPHOSPHATEMIA	N=100	Mean ±SD of HBA1C	P-value
Yes	67	7.49±1.15	0.04*
No	33	7.43±1.45	
GENDER	**N=100**	**Mean ±SD of HBA1C**	**P-value**
Male	48	7.83±1.10	0.03*
Female	52	7.13±1.29	

Table-VIII. The stratification of hypophosphatemia and mean ±sd of hba1c
**Statistically significant*

DISCUSSION

Diabetes mellitus is the chronic metabolic disease with high rate of morbidity and mortality characterized by impaired glucose metabolism and other energy yielding fuels as well as development of vascular and neuropathic complications in advance disease.[9]

In present study the mean FBS and RBS values of the overall population was 160.75 ± 6.85 mg/dl and 260.76 ± 13.72 mg/dl respectively. Glycosylated hemoglobin (HbA1c), a cumulative marker of blood sugar concentrations over the previous 3 months, has become a powerful clinical parameter for diabetes management and is predictive of further complications of diabetes.[10,11] The use of the HbA1c level can play a main role in OPD and hospitalized patients with random blood glucose as it does not require fasting sample, less blood draws, not affected by recent food intake or recent change in blood glucose levels. There is a positive relation between blood sugar and glycated HbA1c and will allow the diabetic patients with their physician to manage appropriate day to day blood sugar targets based on HbA1c goals. Glycated hemoglobin (HbA1c) is used with increasing frequency to monitor and manage long term blood sugar control in diabetes mellitus and its reading gives an accurate index of the average concentration of blood sugar during the previous two to three months.[12]

In our study the mean HbA1c for male and female population was 7.83±1.10 and 7.13±1.29 (P=0.03). Several studies observed a positive correlation between HbA1c and the duration of diabetes and a prediction for risk for diabetes complications.[13,14] Phosphorus is widely distributed compound in the body and is present in both organic and inorganic form but only serum inorganic phosphorus is measured.[15] Inorganic phosphorus in the form of hydroxy apatite (in bone) plays major role in structural support of the body and also provides phosphate for extra cellular and intracellular body fluids.[16] Intracellular phosphate is a component of nucleotide derivatives such as NADP, ATP, GTP etc, is involved in nucleic acid structure formation and also in regulation of intermediary proteins, CHO and fats metabolism, cell growth and gene transcription and also has a major role in body buffer system.[17] In healthy individual, the infusion of glucose orally or intravenously is associated with decrease in plasma phosphate.[18] Schneeberg NG had observed the average fall in serum inorganic phosphorus in most subjects with diabetes mellitus.[19] The studies had shown that insulin also enhances the reduction in plasma phosphate in both diabetic and healthy persons.[20] In severe uncontrolled diabetes mellitus, raised sugar results in low phosphate levels due to intracellular phosphorylation of glucose. It has been also observed that depletion of phosphate in uncontrolled diabetes mellitus is due to increase loss in urine results in diabetic osteopenia.[21] Former studies had found decreased in phosphate concentration in uncontrolled diabetic subjects and the level stabilize when blood sugar is controlled.[22,23] Gartner et al 86 studied juvenile onset of diabetic patients and observed that as serum glucose decreased from 221mg/dl to 95.5 mg/dl and serum phosphate rise from 4.09 - 5.01 mg/dl.[24] Ditzel J et al was found that maximal capacity of renal tubular reabsorption of phosphate were significantly low in diabetic population, also observed that phosphate excretion was 3 times higher in diabetic population when compared to normal individual.[5] Raskin P, et al shown decrease in blood glucose from 17.1mmol/L - 5.2mmol/L leads to increase in splasma phosphate level from 1.12 - 1.26 mmols/L.[25]

Therefore normalization of blood sugar level to maintained capacity of the renal tubules to reabsorb inorganic phosphorus and gradually increase in serum inorganic phosphorus levels is an appropriate step in the management. The blood glucose control will also positively influence and help in preventing long term complications of diabetes mellitus as proved by former studies.[26,27] Severe hypophosphatemia clinically presented as dizziness, dysartria, irritability, confusion and coma along with decrease in 2,3- DPG.[28] As a result, increased glycated hemoglobin is formed with increase oxygen affinity to meet the tissue

oxygen demand.[29] In uncontrolled diabetes mellitus, raised glycated hemoglobin is associated with decreased phosphate concentration that may further decrease with insulin therapy or glucose infusion.

Thus, the diabetic population with poor glycemic control (raised HbA1c level) there is decrease in serum phosphorus level. Furthermore, insulin therapy also causes phosphate to shift intracellular which may further leads to decrease in phosphate level resulting in hypophosphatemic symptoms. Therefore diabetic subjects on insulin therapy should not only monitor for potassium but serum phosphorous level as well.

CONCLUSION

In diabetes mellitus due to uncontrolled blood sugar there is a significant decrease in serum phosphorus levels. One hundred diabetic patients were studied and 67% shown significantly decreases serum phosphate level in context to age and gender while inversely proportional relationship with raised HBA1C respectively.

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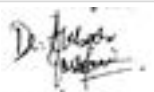
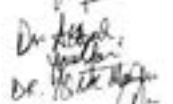
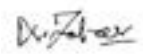
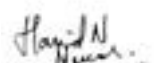
1	Dr. Akbar Hussain Yousfani	Contribution to conception and design, Acquisition of data, Analysis and interpretation of data	
2	Dr. Iqbal Ahmed Memon	Drafting the article and shares its expert research opinion and experience in finalizing the manuscript	
3	Dr. Tariq Zaffar Shaikh	Contributed in conception and interpretation of data and give his expert view for manuscript designing	
4	Dr. Zaheer Ahmed	Analysis and interpretation of data contributed in conception and shares its expert research opinion	
5	Dr. Hamid Nawaz Ali Memon	Drafting interpreting and analyzing the data	
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