Original Research Article

Estimating Serum Phosphate levels and correcting them may predict and/or check disease progression in acidosis: An ICU study

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Abstract

Phosphate is of vital importance in various critical metabolic processes as well as in formation of the structure of vital compounds. It is the primary intracellular anion which is involved in creation of high energy nucleotides involved in energy transfer. We analyzed its essential biochemical role in maintenance of acid-base balance, ventilation and oxygenation status and attempted to study the levels of phosphate and arterial blood gas measurements as well as find the correlation between the two. 100 adult patients of both sexes, admitted in the ICUs of Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), were taken and their serum inorganic phosphate and arterial blood gas measurements were taken. After collection and analysis of data it was seen that mean values of all four parameters showed insignificant gender-wise or age-wise variations. However, it was observed that in cases of acidosis, serum phosphate and pH were positively and significantly correlated ($p< 0.05$). This could be primarily attributed to the effect of acidosis on the sodium-phosphate cotransporters and NAD metabolism. Although mean levels of phosphate in alkalosis were also lower than in the normal group no correlation could be found between phosphate and pH in these cases. Thus, we postulate that any reduction of phosphate in ICU patients hints strongly at an underlying acid-base imbalance and if the patient is acidotic, the phosphate levels may be taken as indicators of the depth of acidosis almost as an adjunct to ABG. Thus, reductions observed on serial measurements of phosphate in such patients may indicate worsening acidosis and suitable interventions (including possible phosphate supplementation in addition to bicarbonate) tailored accordingly to improve the ventilation and acid base-status.

Keywords: Phosphate, acidosis, pH, bicarbonate.

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Introduction

An Intensive Care unit or ICU may be defined as a designated portion of the hospital that provides a one-on-one nursing care to patients requiring special attention[1], or special care to those at risk of a life-threatening deterioration, as happens in conditions such as myocardial infarction, respiratory failure, severe trauma and sepsis. The significance of biochemical tests in the ICU is evident in the high proportion of expenditure devoted to lab tests. With such intensive monitoring and continuous 24-hour biochemical evaluation, the ICU is a life-saving resource[2].Phosphate, used interchangeably with 'phosphorus' (although the former term is implied) is the major intracellular anion, and exists in the human body in chemical combination with lipids, sugars, and proteins apart from its existence as hydroxyapatite ($Ca_5(PO_4)_3(OH)$) in bones and teeth . Only 1% of the total body phosphate is in the extracellular space. This 1% is found in both organic and inorganic forms in the blood with a combined plasma concentration of around 12.18 mg/dl (3.9 mmol/ L). [3] Of this tiny amount, 70% is in the organic form as phospholipids [phosphate is the largest intracellular anion, and is largely found as organic moieties bound to lipids, sugars, and proteins]; 30% is inorganic.[4]. It is the inorganic component that is measured in the hospital laboratory . Around 85% of this is in the form of free inorganic phosphate ions HPO42- ,$H_2PO_4^-$,PO_4^{3-} ,with a 4:1 ratio of HPO42- to H2PO4- at the normal serum pH of around 7.40.[5] 10% of the inorganic phosphate in the blood is bound to protein and 5% complexed with calcium, magnesium, or sodium.[3] Thus, serum measurements of phosphate do not consistently reflect total body stores. [4]Phosphate, has primary and irreplaceable roles in mineral metabolism, immune regulation, maintenance of acid-base balance, determination of oxygen affinity for hemoglobin, clotting mechanisms and platelet aggregation.[3] It is involved in bone mineralization [for which extracellular phosphate is necessary],[6] serves as the building block of membranes, is a primary constituent of high energy nucleotides involved in energy transfer and also serves as a component of nucleic acids.[7] A myriad of phosphorylated intermediates, mostly proteins and lipids[8] and phosphate containing compounds participate in cellular signalling, by multiple mechanisms.[9,10]Alterations in serum phosphate levels in ICU patients, although mainly iatrogenic,[11] are common nonetheless and are contributory to the difficulties observed in recovery and weaning from mechanical ventilation, [12], [13] with several studies pointing to the role of phosphate level estimation in the determination of prognosis in some patient groups.[14],[15] Phosphate metabolism and handling in the

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body are thus subject to stress in critically ill patients.[16] Hypophosphatemia gets precipitated due to any or all of the combination of basic factors like inadequate intake, redistribution of phosphate into cells and loss of phosphate.[17]Generally serum levels fall below 1.5 mg/dl. It afflicts anywhere from a minimum of 2 % of all hospital admissions to as many as 34% [or higher) in ICU patients.[13,18] Levels in the blood are not completely representative of its quantity in the body. [19] Any of the following mechanisms can cause a reduced level of phosphate in the blood:

1.Uptake by cells or transcellular shift causing a 'redistribution': Certain conditions such as respiratory alkalosis, cause a shift in phosphates from the extracellular to the intracellular compartment. Respiratory alkalosis causes a decrease in carbon dioxide(CO_2) in the blood which results in diffusion of CO_2 from the cells to the plasma. This causes intracellular pH to rise, which in turn stimulates phosphofructokinase and consequently glycolysis. This increases the demands for phosphate in the cell and reduces that available in the blood. Phosphate uptake by myocytes is enhanced. [Phosphate is essentially 'sequestered' in the muscle). Overall, serum levels fall, but are stabilized by renal mechanisms increasing reabsorption of phosphate. In the refeeding hypophosphatemias, the increased insulin release and demand for high energy phosphates for pathways such as glycolysis, tricarboxylic acid cycle[TCA) and electron transport chain [ETC) and vital compounds like 2,3-DPG causes a transcellular shift and resultant shortage of phosphates in the blood. If the renal mechanism doesn't respond quickly enough, as happens in a few cases, more phosphates maybe lost and in some cases, total body phosphate stores may get depleted.

2.Reduced absorption :Malabsorption and certain medications, which tend to reduce availability of phosphate by binding to it, impede absorption at the level of the gut.

3.Increased excretion by the kidneys : In primary and secondary hyperparathyroidism, high PTH levels cause phosphate losses by the mechanisms discussed earlier. This is, however, of moderate severity , as compensation from bone stores and increased gut intake strive to maintain an optimum level. Acidosis, both metabolic as well as respiratory, cause renal loss of phosphate.Conversely, increased extrinsic intake of phosphorous, heightened absorption capacity, excess endogenous release from body /tumour cells and reduction in urinary excretion, are causes for hyperphosphatemia.[20]Arterial blood gas (ABG) measurements assess three primary parameters, viz. pH, pCO_2 and pO_2 of arterial blood [the latter two also referred to as paCO2 and paO2) and are utilized for gathering information concerning oxygenation, ventilation and acid-base status.[21] These parameters are maintained within a narrow range and are altered in various acute and chronic disease states.[22]The role of phosphate in alteration of the above three main parameters follows from the fact that phosphate imbalances crucially affect the formation or availability of various compounds such as 2,3-Diphosphoglycerate, which are directly associated with oxygenation of tissues and also theoretically with the availability of ATP, the lack of which can drastically alter ventilation status. Cardiac adenosine also is regulated by inorganic phosphate and has been found to regulate cardiac contractile force regulation in animal studies.Cardiomyopathy involves hypophosphatemia.[23] Contractile properties of the diaphragm respond to changes in phosphate levels as well.[24) Phosphate also has definitive influence on vascular calcification and endothelial dysfunction,[25] which has direct implications on the oxygenation status.[26]Investigations have come to occupy a large chunk of expenditure in critically ill patients, partly due to the routine nature of ordering by the clinician, who may request tests as per protocol, even when otherwise warranted.[27] Arterial blood gas sampling requires skill and although immensely vital to patient management, is relatively expensive and often requires several rounds of samplings in patients, especially those who are hemodynamically unstable. ABG measurements are the most repeatedly ordered laboratory tests in the ICU and iatrogenic anaemia is a real concern, with initiatives taken of late being largely ineffective.[28]Serum phosphate is a very affordable investigation, which can be economically added to the repertoire of routine tests ordered in the ICU and its role as an adjunct to ABG measurements maybe considered in an effort to curtail costs, by atleast marginally reducing the frequency of traumatic ABG arterial puncture and possibly garnering a biochemical insight into any imbalances observed .

Aims and objectives

The present study was conducted in the Department of Biochemistry in collaboration with Department of Anaesthesia, M.M Institute of Medical Sciences and Research, Mullana, Ambala. The aim and objectives of the present study were:

1.To estimate serum phosphate levels in ICU patients.

2.To estimate the arterial blood gas measurements ,namely, PaO_2 , $PaCO_2$ and pH.

3.To find the correlation between serum phosphate and ABG measurements, if any.

Materials and methods

Study area:The present study was undertaken in the Department of Biochemistry in collaboration with Department of Anaesthesia, M.M Institute of Medical Sciences and Research, Mullana, Ambala, Haryana.

Study design:Cross-sectional Study

Study period:From October 2015 to October 2017

Selection of patients :The present hospital based study was undertaken with a total of 100 subjects more than 18 years of age, irrespective of sex, from the various ICUs of M.M Institute of Medical Sciences and Research, Mullana, Ambala.

Study population :One hundred [100) subjects were taken in the study from the non-pediatric/neonatal ICU's. The patient selection was primarily from the respiratory intensive care unit [RICU), and also from the surgical intensive care unit [SICU) and the medical intensive care unit (MICU).A detailed history regarding the present or past illness was taken and the general physical examination, local examination and the systemic examination was done and duly noted as per the Proforma attached.

Inclusion criteria

1.Admitted in the adult ICUs.

2.Age > 18 years of either sex.

3.Either on nil per oral, enteral or parenteral feeding.

Exclusion criteria

1.Patients admitted only for temporary observation and not for active management.

2.Critically ill patients <18 years old.

3.Patients suffering from chronic renal failure, on renal replacement therapy and regular haemodialysis.

4.Administered phosphate agents prior to ICU entry.

Study tools and strategy

The study was carried out as per proforma attached. Samples, both venous as well as arterial, were taken from all the new admissions to the aforementioned ICU's, as soon as possible after/during stabilization of vitals of the patient.

Collection and processing of blood sample

2 ml of venous blood sample was collected from the antecubital vein of the subjects in a disposable syringe under aseptic conditions and transferred to a sterile, dry and acid washed vial for biochemical analysis. The blood was allowed to stand for 30 minutes. After clot formation, the supernatant was centrifuged to perform the necessary biochemical investigations.

For the arterial blood sample, a heparinized 1-2 ml syringe with 20 to 21 gauge needle was used, under all aseptic precautions, to pierce the radial artery for at least 1 ml of blood. The sample was processed immediately and transfered to the analyser without delay.

Biochemical investigations

1.Serum PO4 was estimated using ammonium molybdate method [end-point), using a kit supplied by Erba Mannheim [Germany), on semi-automatic analyser Pace-Plus.[29]

Principle- Inorganic phosphate combines with ammonium molybdate in the presence of strong acids to form phosphomolybdate. This compound thus formed, is measured at 340 nm and is directly proportional to the concentration of inorganic phosphate in the sample.

Assay procedure

Table 1:Assay procedure

Pipetted in to tubes marked	Blank	Standard	Test
Ammonium molybdate + sulphuric acid +surfactant	1000 µl	1000 µl	1000 µl
Distilled water	20 µl	---	---
Standard	---	20 µl	---
Test	---	---	20 µl

Calculation

Phosphate [mg/dl) = Absorbance of test / Absorbance of standard x concentration of standard

2.Arterial pH was estimated using Ion specific electrodes [ISE) on Stat Profile® pHOx® Blood Gas Analysers supplied by Nova Biomedical [US).[30]

pH is the negative log of hydrogen ion concentration.

pH is measured using a H + ion selective glass membrane. One side of the glass is in contact with a solution of constant pH, whereas the sample whose pH is to be measured is in contact with the other side of the glass. The change in potential thus developed is directly proportional to the pH difference of the two solutions. This potential change is measured against a reference electrode which has a constant potential. The potential difference thus measured, gives us the pH of sample.

3.Arterial PO_2, also called, PaO2 was measured using Ion specific electrodes [ISE) amperometrical methodology[21) on Stat Profile® pHOx® Blood Gas Analysers supplied by Nova Biomedical [US). PO2 and PaO2 have been used interchangeably although, technically, PaO2 is PO2 of arterial blood.

PO_2 is defined as the partial pressure of oxygen in the gas phase in equilibrium with the blood. PaO2 gives us an idea as to the availability of oxygen in inspired air.

PO_2 is measured amperometrically, by the generation of a current at the sensor surface. As O2 diffuses through a gas permeable membrane, the O2 molecules are reduced at the cathode, consuming 4 electrons for every molecule of oxygen reduced. The sensor measures this flow of e-'s or current which is directly proportional to the p O2 in the sample.

4.Arterial PCO2 , also called PaCO2 using Ion specific electrodes [ISE) Severinghouse methodology[21) on Stat Profile® pHOx® Blood Gas Analysers supplied by Nova Biomedical (US). PCO2 and PaCO2 have been used interchangeably although, technically, PaCO2 is PCO2 of arterial blood.

The pCO_2 is the partial pressure of carbon dioxide in the gas phase in equilibrium with the blood.

It is measured with a modified pH sensor. CO2 in the patient's sample makes contact with a gas permeable membrane which is mounted on a single combination measuring/reference electrode. CO2 diffuses across the membrane into a thin layer of electrolyte solution because of a difference in partial pressure. This solution then becomes equilibrated with the external gas pressure. CO2 in the solution reacts with H_2O producing carbonic acid resulting in a change in H+ ion activity as is evident by the below equation.

$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow H^+ + [HCO^{3-}]$

The electrolyte solution behind the membrane is in contact with a glass H+ ion selective sensor. The change in H+ ion activity in the electrolyte solution produces a potential which is measured against the internal filling solution. This change in potential is measured against that of the reference electrode half cell and is logarithmically related to the PCO2 of the unknown sample.

Normal values

1. Serum PO4- 2.5 - 4.5 mg/dl

2.Arterial pH - 7.35 - 7.45

3. Arterial PaO2- 83 - 108 mmHg or 11.04-14.36 kPa

4. Arterial PaCO2- 35 - 48 mmHg or 4.66-6.38 kPa [Male]

5.32 - 45 mmHg or 4.26-5.99 kPa [Female]

Statistical analysis

Data collected was entered into Microsoft Excel worksheet and statistically analysed by using SPSS [Statistical Package for Social Sciences) version 20. Proportions were expressed as percentage & chi square test was applied to know association between various variables. For quantitative data mean, standard deviation & t-test was calculated. P value < 0.05 will be considered as statistically significant at 95% confidence interval.

Ethical consideration: Informed and written consent [in the language they best understand) was taken from each subject/guardian before collecting data and blood sample. Only those individuals, who volunteered to participate in the study, were included and the data has been kept confidential. The study did not impose any burden on the subjects and the Institute, therefore the study was ethically justified. The proposed study was also undertaken after approval by the Institutional Ethical Committee.

Results & discussion

The present study was undertaken in the Department of Biochemistry in collaboration with Department of Anaesthesia, M.M Institute of Medical Sciences and Research, Mullana, Ambala, Haryana. The present hospital based study was carried out on 100 subjects more than 18 years of age, of both genders, from the various ICUs of M.M Institute of Medical Sciences and Research, Mullana, Ambala.The subjects were taken from the non-pediatric/ neonatal ICU's. The patient selection was primarily from the respiratory intensive care unit [RICU), although cases fulfilling below criteria were also taken from the surgical intensive care unit [SICU) and the medical intensive care unit [MICU).

61 males and 39 females were taken in the study.

Table 2: Age distribution of study subjects

Age group [years)	N	%
Upto 25	10	10.0%
26-40	24	24.0%
41-55	20	20.0%
56-70	35	35.0%
>70	11	11.0%
Total	100	100.0%

Table 3: Mean and standard deviation [SD] of pH, pCO_2, $pO_2$and phosphate levels according to age groups

Age group [years]	pH	pCO_2	pO_2	Phosphate
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Upto 25	7.42 ± 0.06	38.33 ± 6.74	81.10 ± 34.29	3.53 ± 0.6
26-40	7.42 ± 0.06	37.14 ± 9.81	76.50 ± 41.96	3.28 ± 0.88
41-55	7.42 ± 0.07	38.82 ± 9.78	91.45 ± 32.95	3.28 ± 0.78
56-70	7.41 ± 0.09	38.12 ± 9.31	74.37 ± 33.63	2.84 ± 0.71
>70	7.41 ± 0.07	34.59 ± 9.25	83.82 ± 39.87	2.62 ± 0.29
P value	0.374	0.944	0.901	0.644

There was no significant variation in all the 4 parameters as a function of age. Although patients aged 70 years and above had generally slightly lower levels.

Table 4: Mean and standard deviation [SD] of Phosphate, pH, pCO2 and pO2 levels according to gender

	Males[n=61]		Females[n=39]		t value	p value
	Mean	SD	Mean	SD		
Phosphate	3.15	0.83	2.97	0.66	1.126	0.263
pH	7.41	0.07	7.42	0.08	-0.617	0.539
pC02	38.33	8.73	36.61	9.93	0.908	0.366
p02	78.92	37.71	81.72	34.32	-0.375	0.709

Table 5: Distribution of study subjects according to level of pH

pH	N	%
Decreased [<7.35)	18	18.0%
Normal [7.35-7.45)	50	50.0%
Increased [>7.45)	32	32.0%

50 % patients were having pH in the normal range(7.35-7.45), 18% were acidotic(<7.35) and 32% were alkalotic (>7.45).The mean values of phosphate were lower (2.93 ± 0.74) and (2.60 ± 0.64) in conditions of acidosis as well as in conditions of alkalosis, respectively, as compared to the normal pH group which was highly significant.[p <0.001). Post-hoc associations were also found to be very significant when comparing the phosphate levels of the alkalotic group with that of the group having normal pH (p <0.001). When comparing the acidotic group with the normal pH group, association was significant (p <0.05).

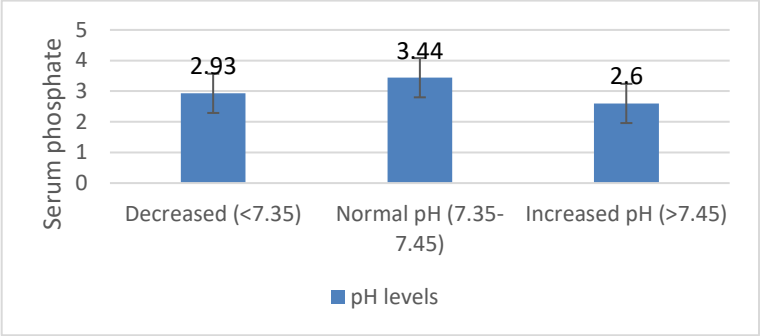

Fig 1:Association of Phosphate and pH levels

Table 6: Association of Phosphate and pH levels

pH	Phosphorous		F value	p value
	Mean	SD		
Decreased [<7.35)	2.93	0.74	15.458	<0.001
Normal [7.35-7.45)	3.44	0.68		
Increased [>7.45)	2.60	0.64		
Post- hoc comparison of association of phosphate and pH among above groups				p value
Increased pH vs. Normal pH				<0.001
Decreased pH vs. Normal pH				0.020
Increased pH vs. Decreased pH				0.235

The mean values of phosphate were lower [2.93 ± 0.74) and [2.60 ± 0.64) in conditions of acidosis as well as in conditions of alkalosis, respectively, as compared to the normal pH group, which was highly significant (**Figure 17**).Post hoc analysis revealed that the association

between phosphate levels in patients suffering from alkalosis and the phosphate levels in patients having a normal pH range was highly significant (<0.001). It also revealed that the association between phosphate levels in patients suffering from acidosis and the phosphate levels in patients having a normal pH range was significant at <0.05 level. There was no significant association of phosphate levels between the group of patients with alkalosis and the patients with acidosis .

Table 7: Correlation of pH and phosphate levels in subjects with different pH level

pH levels	Values	
Decreased [<7.35)	Pearson Correlation coefficient [r)	0.561
	p value	0.015
	N	18
Normal [7.35-7.45)	Pearson Correlation coefficient [r)	-0.240
	p value	0.094
	N	50
Increased [>7.45)	Pearson Correlation coefficient [r)	0.044
	p value	0.811
	N	32

On dividing the patient data into 3 groups based on pH, only one interesting associations was uncovered. In acidotic patients, with pH less than 7.35, the pH and serum phosphate were found to be significantly
associated [$p < 0.05$).Pearson correlation could not show any other significant associations.
Thus, any reduction in pH from the normal range was found to have a significant lowering effect on that of the serum phosphate levels. Although mean levels of phosphate in the alkalotic group were lower than that in the normal group, the Pearson correlation between the two was insignificant.Thus, phosphate and pH in the acidotic range showed a significant positive correlation.
In 1924, Haldane et al established that metabolic acidosis caused reduction in phosphate levels due to phosphaturia. The phosphaturia of acidosis was later confirmed by Bolger and Peters in 1925 and Guest and Rapaport in 1939. Knochel in 1971 stated that acidosis caused a decomposition of inorganic phosphates intracellularly, which moved to plasma and consequently to the urine. [31]Some studies have suggested that reduction in pH of the lumen may increase concentration of a 'less permeant' species of phosphate which may not be as efficiently absorbed .Kinetic analysis in a study by Levine et al showed that acidosis decreased the maximum velocity [Vmax) of phosphate uptake. Levine et al suspected a 'dissipation of the Na+ gradient' [which is necessary for maintaining the electronegativity inside the Brush Bordered-Membrane [BBM) cells of the Proximal Convoluted Tubule) as a viable reason for NPT-II transporter failure but could not prove it.
A novel angle was given to explaining the cause of phosphaturia by linking it to the nicotinamide adenine dinucleotide [NAD) concentration of the cytosol of the PCT cells. Scholars suggested that many processes causing phosphate wasting such as increased Parathyroid hormone[PTH), cAMP and fasting/starvation are associated with gluconeogenesis which is associated with increased NAD. Similarly, low phosphate intake stimuli results in increased reabsorption in the PCT along with a suppression of gluconeogenesis. In vitro studies have shown that NAD inhibits phosphate uptake in BBM samples. Even when nicotinamide is given in-vivo, the resultant increase in NAD strongly inhibits phosphate uptake in the BBM and causes brisk phosphaturia. Thus there may be a theoretical possibility that changes in phosphate reabsorption in metabolic acidosis may have links to enhanced gluconeogenesis.[32) Acidosis stimulates a rate limiting enzyme of gluconeogenesis, thus also depleting NADH , while increasing levels of NAD which has a role in inhibition of phosphate uptake in the BBM, thus precipitating loss of the mineral in urine.
Hypophosphatemia causes low levels of ATP and high levels of AMP. This results in stimulation of AMP deaminase and 5' nucleotidase, thus eventually resulting in increased degradation of the nucleotides to uric acid. The excess uric acid produced is hampered from excretion at the level of the kidneys by the excess lactic acid which was itself primarily due to the effects of hypophosphatemia.[33) The high uric acid levels accumulate in the blood and they themselves inhibit phosphate reabsorption in the kidneys, which thus reduces the already strained phosphate stores in the body.[34) Thus, a vicious cycle is created.
The positive correlation of phosphate and pH as seen in our study was explained decisively from the findings of Ambuhl et al in 1998, whereby they hinted at the downregulation of the BBM NPT-II [a or c) transporters and NPT-II mRNA, stimulated by acidosis of atleast 12 hours duration. Another plausible mechanism as discussed before, is of the influence of other transporters as well. Since [metabolic) acidosis causes an increase in BBM Na+/H+ antiport activity, the increased dissipation of the Na+ gradient could cause decreased efficiency of the NPT-II transporters, thus causing increased phosphate wasting in urine. A prolonged acidosis of more than 7-10 days caused reductions in NPT-II mRNA significantly. Early alterations are due to post-translational and post-transcriptional modifications. Two ways there would be reduced availability of the NPT-II transporters is by either reduced trafficking to the apical BBM, or increased internalization and lysis.[35)The phosphaturia in acidosis is independent of PTH activity or even dietary phosphate intake.Also, mean levels of phosphate were significantly lower in alkalotic patients although no significant association could be established between phosphate and pH in the patients with a pH above 7.45. The low mean levels of phosphate could be attributed to the effect of alkalosis on stimulating glycolyis and increasing the demand for extracellular phosphate for the synthesis and phosphorylation of various metabolites in glycolytic and related pathways. This fact was stressed by Hans Krebs in 1959 when he maintained that the extracellular phosphate is the primary reservoir for catering to the intracellular requirements. Robin in 1961, Mostellar et al in 1964, Knochel et al in 1977 and Storm et al in 1984 all attested to the reduced phosphate found in alkalosis. [31, 36,37]
Correcting these low levels of phosphate, while not possibly correcting underlying pathologies in some cases, could hypothetically play a role in maintaining sufficient levels for proper tissue oxygenation/ventilation by its actions on the synthesis of vital compounds such as ATP and 2,3-Diphosphoglycerate. Consequently, tissue hypoxia might be avoided.[38) It has also been seen that cardiac contractility resumes normal function on correction of hypophosphatemia[39] . This is probably due to the role of phosphate in replenishing ATP stores in myocytes.[40]Palmese etal, had observed 4 cases of patients in their ICU's with metabolic acidosis (caused by lactic acid accumulation) associated with hypophos-phatemia. They figured that low phosphate levels depleted ATP

intracellularly and concomitantly erythrocyte 2,3 diphosphoglycerate(DPG) were reduced. The resultant increased affinity for O_2 and reduced release to tissues could have precipitated /accentuated lactic acidosis. However, they also noted cases of non-lactic acid metabolic acidosis along with hypophosphatemia. In these cases, bicarbonate administration was found to help only if it was preceded by phosphate supplementation to normalize low phosphate levels. Unless phosphate levels were corrected, there was wasting of bicarbonate in the urine.[41]In 2016, a Turkish study by Erikilinc et al, with an aim to evaluate the interdependence between the serum phosphate level and pulmonary functions post-surgery, found that there was significant correlation between the two, and that the major intracellular anion had been unjustly ignored and neglected as a diagnostic tool for the analysis of pulmonary functions.

Summary and conclusion

The study including 100 adult patients of both sexes was conducted in the various ICU's of MMIMSR and involved the departments of Biochemistry and Anaesthesia. Serum phosphate levels and arterial blood gas measurements [pH, pO2 and pCO2) were taken in an attempt to study levels as well as establish relevant correlations between the two. After collection and analysis of data it was seen that mean values of all four parameters showed insignificant gender-wise or age-wise variations. However, it was observed that in cases of acidosis, serum phosphate and pH were positively and significantly correlated [$p< 0.05$). This was primarily attributed to the effect of acidosis on reducing both the availability of the sodium-phosphate transporter in the renal tubules as well as its increased internalization and the reduction in the mRNA coding for the transporters. The latter mechanism would have a complete effect only after 7 days.Acidosis also increases levels of NAD which inhibit phosphate reuptake in the BBM as well.Although mean levels of phosphate in alkalosis were also lower than in the normal group no correlation could be found between phosphate and pH in these cases. Thus, we postulate that any reduction of phosphate in ICU patients hints strongly at an underlying acid-base imbalance and if the patient is acidotic, the phosphate levels may be taken as indicators of the depth of acidosis. Reductions in serial measurements of phosphate in such patients may indicate worsening acidosis and suitable interventions [including phosphate supplementation before bicarbonate administration) may be tailored accordingly to improve the ventilation and acid base-status.

Limitations of study

Due to the exigencies prevalent in ICU's, where primary focus is on stabilizing patients, rather than taking samples, some minor delays for drawing venous samples/ABG were inevitable, thus not all patients could be sampled immediately upon entering in ICU and sampling was accordingly delayed. However, delays, in no case exceeded 5 minutes, and an average sample retrieval time of 2 minutes [+/- 45 seconds) from entering ICU to sampling was uniformly achieved.The analysis was performed on Stat Profile® pHOx® Blood Gas Analysers, which were located inside the ICUs.

Sample size was restricted to 100 so as to be proportionate to patient flow and also to take into account subjects fulfilling inclusion/exclusion criteria. Further studies with larger sample size are recommended.

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