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Incidence and aetiology of renal phosphate loss in patients with hypophosphatemia in the intensive care unit

Received: 2 March 2013
Accepted: 18 May 2013
Published online: 20 July 2013
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Abstract *Background:* Hypophosphatemia is a common finding in patients in the intensive care unit (ICU). Its cause is often poorly understood. *Purpose:* The aim of this study was to understand the incidence of renal phosphate loss in ICU-related hypophosphatemia, and to examine the role of phosphaturic hormones in its etiology. *Methods:* Plasma phosphate levels were measured on day 1, 3, 5 and 7 in 290 consecutive patients admitted to the ICU. Renal phosphate handling and phosphaturic hormones were studied in a subset of patients with phosphate levels <0.6 mmol/L. Renal phosphate loss was defined as a $\text{TmP/gfr} < 0.6$ mmol/L. *Main Results:* Hypophosphatemia developed in 24 % of all patients. This mainly occurred within the first 3 days of stay and in patients with

serum creatinine levels <150 $\mu\text{mol/L}$. Renal phosphate loss was present in 80 % of patients who developed hypophosphatemia, and was not related to serum levels of parathyroid hormone (PTH), PTH-related protein (PTH-rp), fibroblast growth factor 23 (FGF-23), or calcitonin. *Conclusion:* Hypophosphatemia in the ICU is commonly associated with renal phosphate loss. It mainly occurs within the first 3 days of admission, in particular in patients with preserved renal function. Renal phosphate loss is not explained by elevated PTH, PTH-rp, FGF-23 or calcitonin levels.

Keywords Hypophosphatemia · FGF-23 · ICU · Phosphaturia

Introduction

Hypophosphatemia occurs frequently in patients in the ICU, with a prevalence ranging from 10–80 % [1–4]. It is associated with increased ICU morbidity and mortality, but its significance as an independent risk factor of mortality is still under debate [5]. The highest prevalence is found after major surgery, multi-trauma, major burns or fulminant sepsis, a finding suggesting that severity of disease rather than the cause of critical illness is the major etiological factor. Severe hypophosphatemia, defined as a plasma level <0.3 mmol/L, can induce respiratory muscle failure, heart failure, arrhythmias, rhabdomyolysis,

neuropathy and thrombocytopenia. The clinical implications of moderate hypophosphatemia (plasma phosphate 0.3–0.6 mmol/L) are less clearly defined [4–7]. Mild hypophosphatemia (plasma phosphate 0.6–0.8 mmol/L) is generally believed to have no clinical consequences at all.

Serum phosphate levels are determined by intestinal absorption, phosphate exchange between intra- and extracellular compartments, bone turnover, and renal reabsorption. Quantitatively, renal reabsorption is the most important regulatory mechanism [8]. The daily filtered load is about 100–130 mmol, of which 80–90 % is reabsorbed in the proximal tubule. This reabsorption process is under the hormonal control of parathyroid

hormone (PTH), fibroblast growth factor 23 (FGF-23), calcitonin and PTH-related peptide (PTH-rp).

The pathophysiology of hypophosphatemia in patients receiving treatment in the ICU is often complex and poorly understood [19]. Decreased intake, intestinal loss, redistribution and renal loss of phosphate may all play a role [1, 4, 6]. In the present study we focused on renal phosphate loss and studied its incidence, as well as the endocrine aspects of its etiology. In theory, renal phosphate loss might occur as a result of increased activity of the phosphaturic hormones PTH, PTH-rp, calcitonin, or FGF-23. PTH-rP interacts with PTH and PTH-rP receptors in bone and kidney, and stimulates osteoclastic bone resorption, renal tubular absorption of calcium, and phosphaturia [10]. FGF-23 was discovered 13 years ago. It is a very potent phosphaturic hormone that is produced by osteocytes in response to phosphate excess [11]. To date, PTH is the only factor that has been studied in ICU-related phosphaturia. It does not appear to play an important role [2]. The impact of other phosphaturic hormones in ICU-related phosphaturia has not been described previously.

In the present study, we investigated the incidence of hypophosphatemia in ICU patients through examination of renal phosphate handling, phosphaturic hormones and bone turnover in patients who developed plasma phosphate levels <0.6 mmol/L, with the aim of increasing our understanding of the underlying pathophysiology and to create a rationale for the screening and treatment of ICU-related hypophosphatemia.

Patients and methods

Patients

This prospective cohort study was performed in a 15-bed ICU of a teaching hospital in the Netherlands. This ICU admits general medical and surgical patients, except acute neurosurgery and cardiothoracic surgery patients. All patients admitted to the ICU receive standard nutritional care, starting on day 1 and with a preference for enteral nutrition (EN). The daily phosphate load of standard nutritional care is 30–50 mmol/day. Patients developing glucose levels ≥ 9.0 mmol/L are treated with continuous intravenous insulin, with the aim of maintaining glucose levels between 4.5 and 8.9 mmol/L. Patients on total parenteral nutrition (TPN) were included in the study. Patients presenting with severe renal failure requiring renal replacement therapy were excluded.

Routine measurement of plasma phosphate at 6:00 a.m. on days 1, 3, 5 and 7 was introduced as standard policy in the ICU, starting in September 2011. Standard follow-up measurements were not performed in patients who were discharged to the general wards within this week.

Clinicians were free to do additional measurements on the days in between if they felt that this was indicated. Blood and urine sampling was performed according to the regulations of the hospital's ethics committee, which allow collection of blood for observational research on the condition that the amount is moderate and that vascular access is already present for routine care. Accordingly, additional blood sampling was done only in patients who had an intra-arterial or central venous line in situ. Other exclusion criteria were not employed. The first sample for measurement of serum phosphate (day 1) was taken at 6:00 a.m. of the first morning after admission. Hypophosphatemia was defined as a plasma phosphate level <0.6 mmol/L. Results of the ad hoc measurements ordered on days 2, 4 and 6 were included in the analysis. Patients with a plasma phosphate level <0.6 mmol/L were examined further on the same morning to assess renal phosphate handling and to study the endocrine aspects of its pathophysiology. This included an additional blood sample taken at 9:00 a.m. for measurement of serum creatinine, ionized calcium, phosphate, albumin, magnesium, glucose, pH, pCO₂, pO₂, bicarbonate, and base excess, PTH, PTH-rp, 25-hydroxyvitamin D (25-OHD), 1,25-dihydroxyvitamin D (1,25-OHD), fibroblast growth factor 23 (FGF-23), and calcitonin. Urine was collected for 2 h, from 8:00 to 10:00 a.m., to enable an assessment of the renal phosphate reabsorption threshold (TmP/gfr). After completion of this analysis, phosphate repletion was started at 12:00 a.m. in all patients with a plasma phosphate <0.6 mmol/L. Follow-up data of patients receiving phosphate repletion were not included in the analysis. Thus, all cases of hypophosphatemia represent de novo cases. Twenty-nine patients whose plasma phosphate levels had remained >0.8 mmol/L during the first 3 days of admission served as controls, with samples for hormone measurements taken on the third day of admission.

Assays

C-reactive protein (CRP) was measured with a latex-enhanced immunoturbidimetric method, reference interval for adults: <5 mg/L. Serum intact PTH (normal range: 1.3–6.8 pmol/L) was measured by solid-phase, two-site chemiluminescent immunoassay (Immulite 2500, Siemens, Los Angeles, CA, USA), with an intra- and interassay precision of <6 and <9 %, respectively. PTH-rp (normal range <0.3 pmol/L) was measured by a two-site immunoradiometric assay (IRMA, Beckman Coulter, Woerden, The Netherlands). Calcitonin (normal range <2 ng/L) was measured by a solid-phase, enzyme-labelled two-site chemiluminescent immunometric assay (Siemens, Breda, The Netherlands). Serum FGF-23 (normal range 5–210 kilo-Relative Units (kRU)/L) was measured by a two-site enzyme-linked immunosorbent assay with antibodies directed to the carboxy-terminal

(C-term) portion of FGF-23 (Immutopics, San Clemente, CA, USA). FGF-23 intra- and interassay coefficients of variation are 6 and 15 %, respectively. Serum 25-OHD (target range 50–150 nmol/L) and 1,25-OHD concentrations (reference range 48–161 pmol/L) were measured by radioimmunoassay (DiaSorin, Stillwater, Minnesota, USA). The detection limits of these assays are 10 nmol/L and 8 pmol/L, respectively, with intra- and interassay precisions of 8 and 10 % for 25-OHD, and 11 and 14 % for 1,25-OHD, respectively. Ionized calcium was measured by blood gas analyzer with ion-selective electrodes (OMNI Roche, Mannheim, Germany). The bone markers N-terminal propeptide of type 1 procollagen (PINP, marker for bone formation), and C-terminal telopeptide of type 1 collagen (ICTP, marker for bone resorption) were both measured by immunoradiometric assay (Orion Diagnostica, Espoo, Finland): PINP normal range 22.0–87.0 µg/L, intra- and interassay precision of 8.3 and 7.8 %; ICTP normal range 2.1–5.0 µg/L, intra- and interassay precision 6.4 and 7.3 %, respectively. All other laboratory parameters were measured by routine clinical chemistry assays (Roche Diagnostics, Almere, The Netherlands). The normal range for plasma phosphate in our laboratory is 0.87–1.45 mmol/L.

Calculations

The renal phosphate threshold TmP/gfr, the serum phosphate level above which the kidney excretes phosphate, was calculated according to the method of Bijvoet et al [12]. The TmP/gfr normal range is 0.80–1.35 mmol/L. In the present study, inappropriately high renal phosphate excretion was defined as a TmP/gfr < 0.6 mmol/L, to avoid overestimation of the incidence of renal phosphate loss in patients who had been selected based on a serum phosphate < 0.6 mmol/L.

Statistics

Data are shown as mean values ± standard error of the mean (sem). Data of patient groups were compared by unpaired *t* test, Mann–Whitney *U* test or Fisher's exact test, when appropriate. Relationships were examined by regression analysis. A *P* value < 0.05 was considered to be statistically significant.

Results

Patient characteristics

In total, 290 patients were included in the study. Their characteristics are summarized in Table 1. Two groups of

patients were compared: those who maintained phosphate levels > 0.6 mmol/L and those who developed phosphate levels < 0.6 mmol/L. APACHE (Acute Physiology and Chronic Health Evaluation) scores did not differ between these groups. Diagnosis on admission differed slightly among the groups.

Incidence of hypophosphatemia

During their first week of stay, 71 out of 290 patients (24 %) developed a plasma phosphate < 0.6 mmol/L, with levels ranging from 0.07 to 0.60 mmol/L (Fig. 1). Eighty-five percent developed hypophosphatemia within the first 3 days of admission (Fig. 2). Most patients had moderate hypophosphatemia at the time of detection. Only four (1.4 %) patients had severe hypophosphatemia, and all four cases were observed within the first 3 days on the ICU.

Phosphate levels and renal function

A total of 669 blood samples were taken during the one-week observation period. Serum creatinine and phosphate levels were correlated significantly in this data set ($R = 0.42$, $P < 0.001$, Fig. 3). Hypophosphatemia was observed in 70/611 (11 %) samples with serum creatinine levels < 150 µmol/L and in 1/58 (2 %) of blood samples with a serum creatinine > 150 µmol/L.

Etiology of hypophosphatemia

Twenty-two patients with hypophosphatemia (31 %) had to be excluded from further analysis: five patients due to incomplete urine collections, and 17 patients because

Table 1 Baseline characteristics of patients with serum phosphate levels remaining > 0.6 mmol/L and of those who developed phosphate levels < 0.6 mmol/L

	Serum phosphate level	
	> 0.6 mmol/L (<i>N</i> = 219)	< 0.6 mmol/L (<i>N</i> = 71)
Age (years)	67 ± 1	65 ± 1
Sex (male)	140	51
APACHE 2	19 ± 1	19 ± 1
APACHE 4	70 ± 3	70 ± 4
Admission reason		
Cardiac arrest	19 %	18 %
Resp insufficiency	27 %	31 %
Postoperative	28 %	16 %
Sepsis	11 %	15 %
Hemorrhage	6 %	1 %
Other	9 %	17 %

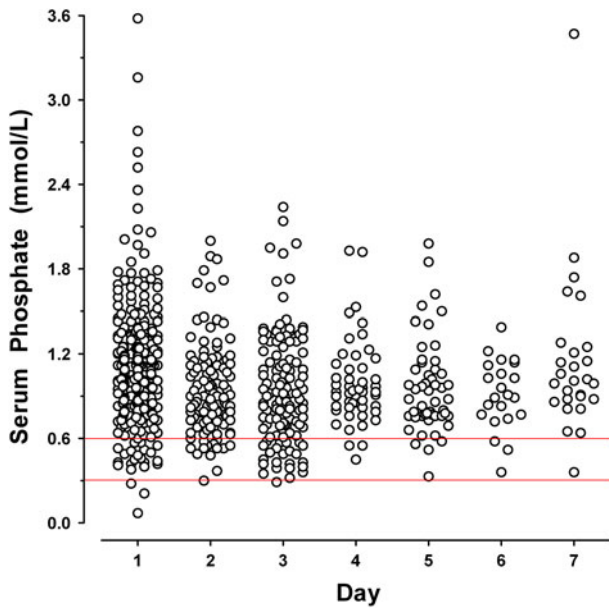


Fig. 1 Serum phosphate levels in patients in the ICU, not receiving phosphate supplementation

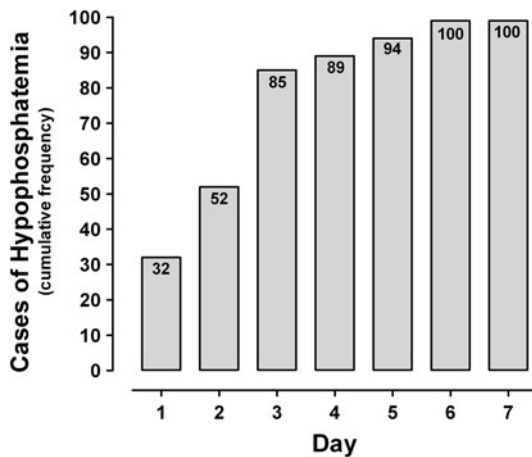


Fig. 2 Cumulative frequency of de novo cases of hypophosphatemia during the first week on the ICU ($N = 71$)

research guidelines did not permit additional blood sampling for the measurement of phosphaturic hormones in the absence of an intra-arterial or central venous line. APACHE scores and reasons of admission of the excluded patients were not different from those who were included for further analysis.

Thus, a complete set of laboratory data was available in 49 out of 71 patients with a plasma phosphate <0.6 mmol/L. The control group consisted of 29 consecutive patients who had maintained their plasma phosphate >0.8 mmol/L during the first 3 days of stay. This control group did not differ from the patients with hypophosphatemia with respect to age, APACHE score or

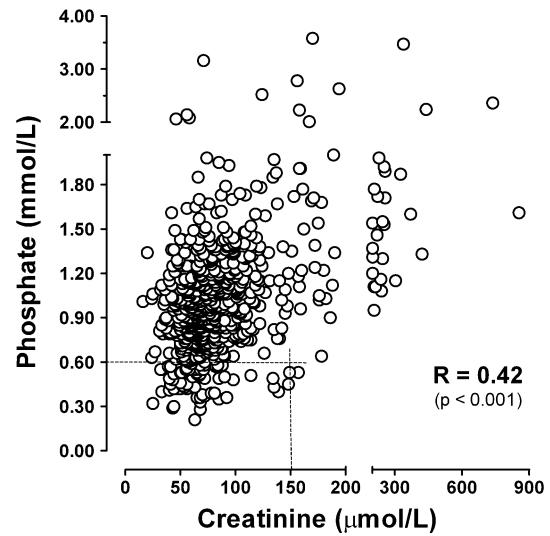


Fig. 3 Relationship between serum phosphate and creatinine levels in 669 samples obtained from 290 patients during their first week of stay in the ICU

diagnosis on admission (data not shown). Laboratory results of both groups are summarized in Table 2.

The group with hypophosphatemia showed a trend towards higher CRP levels (158 ± 17 vs. 106 ± 19 mg/L, $P = 0.05$), a lower serum creatinine (72 ± 5 vs. 111 ± 11 $\mu\text{mol/L}$, $P < 0.01$), a lower TmP/gfr (0.48 ± 0.05 mmol/L vs. 0.92 ± 0.04 mmol/L, $P < 0.01$), and a lower serum FGF-23 level (535 ± 114 vs. $1,926 \pm 902$, $P < 0.05$) than the control group. Thirty-nine out of 49 patients with hypophosphatemia (80 %) had excess renal phosphate loss, as indicated by a TmP/gfr <0.60 mmol/L. In the control group, TmP/gfr values <0.60 mmol/L were found in only 4/29 (14 %) patients. Plasma phosphate levels were positively correlated with serum creatinine levels (Fig. 3, $R = 0.42$, $P < 0.01$), and TmP/gfr (Fig. 4, $R = 0.56$, $P < 0.01$). Ten out of 49 patients (20 %) with serum phosphate levels <0.6 mmol/L had a TmP/gfr >0.60 mmol/L, indicative of a non-renal cause of hypophosphatemia (Fig. 4). Plasma phosphate or TmP/gfr were not correlated with CRP levels. There also was no correlation between FGF-23 and serum creatinine or between FGF-23 and TmP/gfr. Mean serum PTH, PTH-rp, and FGF-23 mildly exceeded the upper normal limit in both groups. Mean calcitonin levels remained within the normal range. Of all phosphaturic hormones tested, only FGF-23 was significantly different between the two groups. Patients with hypophosphatemia had the lowest FGF-23 levels, suggesting phosphate depletion. A backward stepwise multivariate regression analysis including TmP/gfr, serum creatinine, and all four phosphaturic factors revealed that serum phosphate levels were independently related to serum creatinine and TmP/gfr only. Together, these two factors explained 54.8 % of the variance in serum phosphate ($P < 0.001$).

Table 2 Laboratory results in patients with hypophosphatemia ($N = 49$) compared with a control group ($N = 29$) consisting of patients with phosphate levels >0.8 mmol/L at day 3 of admission to the ICU

	General reference range	Phosphate < 0.6 mmol/L ($N = 49$)	Phosphate > 0.8 mmol/L ($N = 29$)
CRP (mg/L)	0–9	158 \pm 17 ^c	106 \pm 19
Creatinine (μ mol/L)	70–105	72 \pm 5 ^a	111 \pm 11
Sodium (mmol/L)	133–143	143 \pm 1	142 \pm 1
Potassium (mmol/L)	3.6–4.8	3.9 \pm 0.1	4.1 \pm 0.1
Magnesium (mmol/L)	0.71–0.93	0.80 \pm 0.02	0.81 \pm 0.03
Ca ²⁺ (mmol/L)	1.10–1.32	1.14 \pm 0.01	1.16 \pm 0.01
Phosphate (mmol/L)	0.87–1.45	0.46 \pm 0.01 ^a	1.14 \pm 0.05
Ca ²⁺ \times PO ₄ (mmol ² /L ²)	<2.25	0.50 \pm 0.02	1.32 \pm 0.07
Albumin (g/L)	35–50	21 \pm 1	23 \pm 1
Glucose (mmol/L)	5–12	8.7 \pm 0.3	8.3 \pm 0.3
pH	7.35–7.45	7.38 \pm 0.01	7.36 \pm 0.01
pCO ₂ (kPa)	4.7–6.4	6.0 \pm 0.2	6.3 \pm 0.3
Base excess (mmol/L)	–2.0–3.0	0.3 \pm 0.6	–0.2 \pm 0.8
Urinary Ca excretion (mmol/L)	2.5–7.5	0.01 \pm 0.00	0.02 \pm 0.01
TmP/gfr (mmol/L)	0.70–1.40	0.48 \pm 0.05 ^a	0.92 \pm 0.04
25OHD (nmol/L)	50–150	31 \pm 3	28 \pm 2
1,25-OH vitamin D (pmol/L)	48–161	115 \pm 9 ^b	86 \pm 9
PINP (μ g/L)	22–87	34.1 \pm 3.0	34.5 \pm 4.5
ICTP (μ g/L)	2.1–5.6	14.5 \pm 1.5	14.3 \pm 1.8
PTH (pmol/L)	1.3–6.8	8.04 \pm 1.00	8.81 \pm 2.62
PTH-rP (pmol/L)	<0.05	0.09 \pm 0.03	0.11 \pm 0.04
FGF-23 (kRU/L)	5–210	535 \pm 114 ^b	1926 \pm 902
Calcitonin (ng/L)	<5	4.19 \pm 0.83	2.45 \pm 0.79

Comparison between groups: ^a $P < 0.01$ ^b $P < 0.05$ ^c $P = 0.05$

The TmP/gfr contributed 42.2 %, and serum creatinine 12.6 %. PTH, PTH-rp, FGF-23 and calcitonin had no significant impact.

Calcium and bone metabolism

Plasma ionized calcium levels were in the low–normal range in hypophosphatemic patients as well as in controls (Table 2). Both groups also had reduced serum 25-OHD levels and decreased urinary calcium excretion. In contrast, serum creatinine levels were lower and 1,25-OHD levels were significantly higher in the hypophosphatemic group ($P < 0.05$). Serum creatinine and 1,25-OHD were weakly correlated ($R = -0.27$, $P = 0.02$, Fig. 4). The serum levels of PINP (the bone turnover marker reflecting bone formation) were comparable and in the low–normal range in both groups. The levels of ICTP (the marker reflecting bone resorption) were elevated in both groups. No correlation was found between serum creatinine and ionized calcium. There also was no correlation between ionized calcium and PTH, PTH-rp levels, or ICTP levels.

Discussion

This study confirms that hypophosphatemia, defined as a plasma phosphate level <0.6 mmol/L, is a frequent finding in the first week of admission in a general ICU. It

occurred in 24 % of patients, and was mainly observed within the first 3 days. We propose to use the term early-onset hypophosphatemia (EOH) for this phenomenon. Hypophosphatemia developing in the first week of admission may have a different etiology than hypophosphatemia that develops during a prolonged stay in the ICU when malnutrition, vitamin D deficiency, or phosphate redistribution are predominant factors. We hypothesize that EOH may reflect a specific entity that is mainly characterized by increased renal phosphate loss, caused by factors yet unknown. Intact renal function appears to be a risk factor, because EOH was mainly observed in patients with serum creatinine levels <150 μ mol/L. Currently known phosphaturic hormones such as PTH, FGF-23, calcitonin or PTH-rp do not appear to play an important role in the etiology of EOH.

We found that most cases of EOH (80 %) were associated with increased renal phosphate loss. This confirms the findings of Srinivasagam et al., who were the first to note that 40 % of ICU patients on mechanical ventilation demonstrated excess renal phosphate loss on day 1 of admission that was unrelated to respiratory alkalosis or serum PTH levels [2]. The present study went further, evaluating renal phosphate excretion more extensively and examining its hormonal control. Although the mean serum levels of PTH, PTH-rp and FGF-23 were above the upper normal limit of healthy subjects, PTH and PTH-rp were elevated to a similar extent in the groups with and without hypophosphatemia. FGF-23 was higher in the control group with phosphate levels

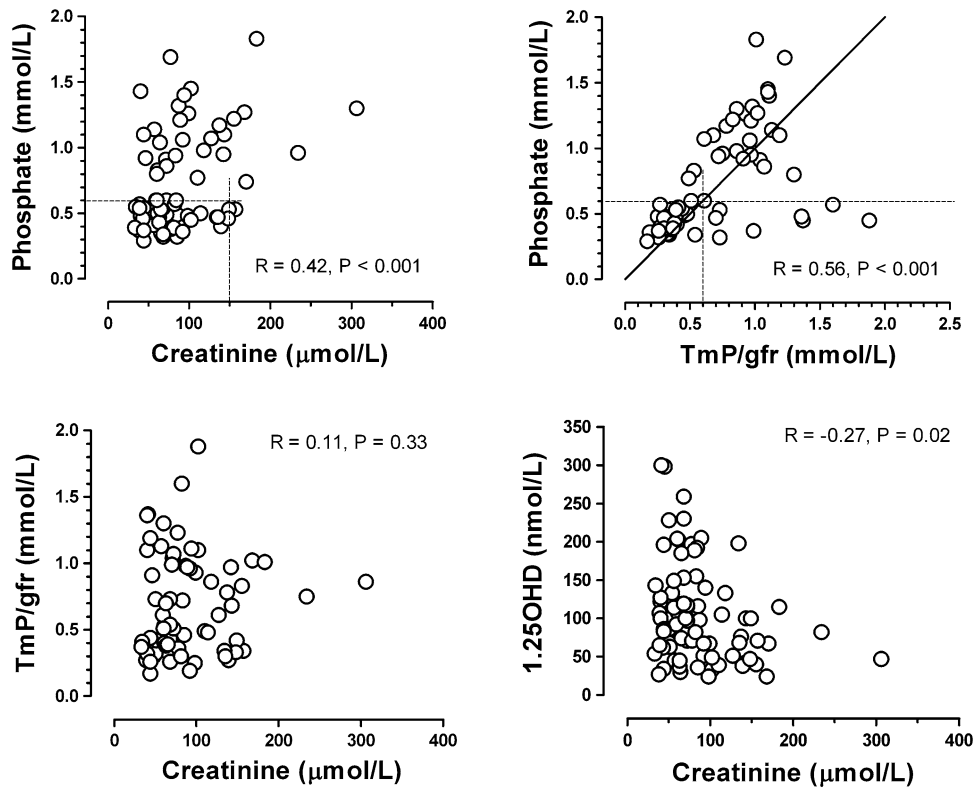


Fig. 4 Correlation between serum phosphate and creatinine, serum phosphate and TmP/gfr, and between 1,25-OH vitamin D and serum creatinine in a group of patients comprising 49 patients with hypophosphatemia and 29 controls with normophosphatemia.

Upper left figure: interrupted lines define the group of patients at risk of developing a serum phosphate <0.6 mmol/L, i.e. those with a serum creatinine <150 $\mu\text{mol/L}$. Upper right figure: solid line represents the line of unity

>0.8 mmol/L than in those who developed EOH. These findings, and the lack of correlation with renal phosphate threshold indicate that these four hormones do not play an important role in the development of renal phosphate in EOH. It suggests that there is a missing phosphaturic factor, dominating renal phosphate excretion in the acute phase of critical illness. TNF- α could be such a factor. Several studies in animals and humans have provided evidence of TNF- α 's phosphaturic effects [3, 13, 14]. Patients with macrophage activation syndrome have high TNF- α levels and demonstrate increased urinary phosphate excretion, and patients treated with recombinant TNF- α have been shown to develop phosphaturia [13, 14]. The importance of TNF- α in ICU-related phosphaturia has not yet been documented.

Renal phosphate loss may not be the only explanation of EOH. A non-renal cause for hypophosphatemia was suspected in 10 out of 49 hypophosphatemic patients (20 %) who had a renal phosphate threshold >0.60 mmol/L. Starting nutrition upon admission may have caused a phosphate shift to the intracellular compartment.

Disturbances in phosphate homeostasis are often linked to abnormalities in calcium and bone metabolism, and therefore this aspect was also evaluated in the present

study. Hypocalcemia is common in critically ill patients [15–18]. Elevated calcium levels in hepatocytes, adipocytes and lymphocytes of patients with sepsis suggest that hypocalcemia mainly results from an increased influx of calcium ions into the intracellular compartment [17, 19, 20]. Our findings are also compatible with a calcium influx. Serum Ca^{2+} levels were in the low-normal range, and were associated with extremely low urinary calcium concentrations, and mildly elevated PTH levels, indicating secondary hyperparathyroidism. The markedly elevated serum level of the bone resorption marker ICTP completes the picture. It indicates activated osteolysis to mobilize bone calcium (and phosphate) in order to maintain serum calcium levels within the normal range. The trigger and the clinical significance of this calcium shift in critical illness remain unknown, and the potential benefit of correcting calcium levels is controversial.

One of the limitations of this study is that it lacks quantitative data about phosphate redistribution, nutritional status, and gastrointestinal phosphate loss. In theory, these factors could all contribute to the development of hypophosphatemia in the ICU as well. The relative impact of these concomitant factors therefore remains unknown. Another limitation is the relatively

large number of hypophosphatemic patients that could not be analyzed completely because of lacking data. Although APACHE scores did not differ significantly from those with a complete dataset, a bias within the selection of patients with more severe illness is not completely excluded. This may have led to some overestimation of the incidence of excess renal phosphate loss.

In conclusion, we hypothesize that hypophosphatemia due to renal phosphate loss and hypocalcemia due to a shift into the intracellular compartment both appear to be basic responses in the acute phase of critical illness. The etiology of these changes remains unknown. The phosphaturic response is excessive in 80 % of patients

developing hypophosphatemia early in the course of admission to the ICU. This renal loss of phosphate loss should be taken into account when regimens are designed to treat hypophosphatemia. We have shown that the most commonly known phosphaturic factors such as PTH, PTH-rP, FGF-23, and calcitonin do not play a major role in the development of EOH. Future studies to evaluate the role of factors such as TNF- α are recommended to further elucidate the pathophysiology of renal phosphate loss in the acute phase of critical illness.

Conflicts of interest None.

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