Original Article

Association between Hyperphosphatemia and Inflammation in Patients with End-Stage Renal Diseases Undergoing Hemodialysis

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ABSTRACT

Background: One of the major complications of renal failure is hyperphosphatemia. It is revealed that hyperphosphatemia correlates with an increased risk of cardiovascular mortality in hemodialysis patients. But data about the direct correlation of hyperphosphatemia and inflammation is limited. We conducted this study to research the correlation between hyperphosphatemia and inflammation as an independent risk factor. Material and method: The kind of study was cross-sectional. Seventy hemodialysis patients from 2 hemodialysis centers who aged more than 18 years old enrolled in this study. To check the correlation between serum phosphorus and hs-CRP, Pearson correlation coefficients were used. An independent sample t-test was used to compare the mean value of groups in different breakpoints of phosphorus. Results: There was a direct correlation between phosphorus and hs-CRP (P= 0.034), especially when phosphorus increased to more than 5.5 mg/dl (P=0.032). Also, there was a direct correlation between phosphorus and Ca×P product (P= 0.018), especially when this product increased to more than 55 (P=0.006). Conclusion: Our data revealed that in hemodialysis patients, the plasma level of phosphorus directly correlates with inflammation especially when increased to more than 5.5 mg/dl. Therefore, hyperphosphatemia can be proposed as an independent risk factor of inflammation in hemodialysis patients.

Keywords: hyperphosphatemia, inflammation, uremia, hemodialysis patients

Introduction

Chronic kidney diseases and end-stage renal disease are of the major health problems worldwide with a high burden of financial issues for health services. Renal failure is accompanied by serious complications that most of them are life-threatening [1].

One of these side effects is hyperphosphatemia that is happened due to relative phosphorus overload secondary to decreased amount of renal excretion of phosphorus [2]. Many evidence revealed the important role played by hyperphosphatemia in a higher rate of cardiovascular and all-cause mortality in the uremic patient [2]. Uremic milieu per se is an inflammatory condition; several studies revealed that inflammatory markers are increased in uremic patients. Furthermore, inflammation and uremia are vigorous inducers of cardiovascular diseases that in a vicious cycle leading to increased mortality of uremic patients.

Therefore, it is very important to take into consideration, the potential factors that contribute to inflammation in chronic renal failure patients, independently.

Recent studies demonstrated that phosphorus acts as a toxin via several mechanisms [3]. Therefore, it can be proposed as a toxin that induces inflammation in chronic renal failure. The aim of the phosphorus level is determined in several guidelines worldwide, which supposed to be the best level that can inhibit the adverse effects of hyperphosphatemia in uremic patients.

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We designed this study to research the correlation between hyperphosphatemia and inflammatory markers and determine the breakpoint level of phosphorus that can induce inflammation significantly.

Material and Methods

Patient setting and data description

This study was a cross-sectional study. Eighty-eight hemodialysis patients attending the two major hemodialysis centers in Bushehr were evaluated. After obtaining informed consent, all patients who aged more than 18 years old, enrolled in this study. Individuals who had PTH more than 800 and platelet count more than 500000, active infections or active inflammatory disease, were under antibiotic or statin therapy, took NSAID or corticosteroids during recent one month, were a smoker and had morbid obesity were excluded (n=18). Demographic data were assessed from the questionnaire. Anthropometric and biochemistry measurements were taken at the entry of the study. Patients' blood samples were collected from the arterial line before starting dialysis and were centrifuged and frozen at -70 °C before measurement. Biochemical determination included the level of serum creatinine (Cr), Blood Urea Nitrogen (BUN), calcium (Ca), 25(OH) vitamin D, phosphorus (P), parathyroid hormone (PTH), and high sensitive CRP (hs-CRP).

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation. Variables were tested for normal distribution by the Kolmogorov-Smirnov test. Data were log-transformed to approximate normal distribution. Pearson correlation coefficients were appropriately used to test the correlation between serum phosphate, 25 (OH) vitamin D, intact PTH and calcium level with hs-CRP. A comparison between the mean value of groups in different cut-off points of phosphorus was performed with an independent sample t-test.

Results

As shown in Table 1, hs-CRP negatively correlated with albumin and vitamin D that was significant with albumin but significantly and positively correlated with phosphorus. Also, there was a significant correlation between hs-CRP and Ca×P product (P=0.018).

As shown in Table 2, when patients divided into two groups based on phosphorus level in different cut-off points, hs-CRP had a significant correlation in the cut-off level of 5.5, 6 and 6.5 mg/dl. When patients divided into two groups based on Ca×P product in different cut-off points, hs-CRP had a significant correlation in the cut-off level of 55 (Table 3).

Discussion

In this cross-sectional study, we found out that there is a direct correlation between phosphate level and some parameters of inflammation such as hs-CRP, independent of other confounding factors especially when phosphate level increased to more than 5.5 mg/dl. The product of calcium and phosphorus, especially when increase to more than 55, had a direct independent correlation with the plasma level of inflammatory markers.

Phosphate homeostasis is important for life and mammals to have a precise system to regulate it during evolution. Phosphate is the main component of nucleic acids adenosine triphosphate and phospholipids of the membrane and plays an important role in cytoplasmic cellular signaling [3]. The main organ for excretion of phosphate in the kidney. In patients who have decreased kidney function, phosphate balance is positive and hyperphosphatemia will occur. This complication is associated with an increased risk of cardiovascular risk and death [4, 5] especially in patients who undergo hemodialysis.

Numerous studies have reported the pivotal role of inflammation as an independent cardiovascular risk in CKD patients [6-9]. However, the impact of phosphorus as an independent risk factor for the induction of inflammation in end-stage renal failure patients is not documented.

Phosphorus loading can induce inflammation in aorta, heart, and kidneys in uremic rats that were accompanied by the high plasma level of TNF-α and TNF-α expression in vascular smooth muscle cells (VSMC) [2]. Additionally, phosphorus loading leads to increased generation of mitochondrial reactive oxygen species (ROS) that leads to in vitro and in vivo activation of NF-κB signaling and vascular calcification [10].

On the other hand, an inflow of phosphorus into intracellular space by PiT-1 is one of the proposed mechanisms of phosphorus-induced cellular inflammation [11]. Whenever phosphorus overload occurs, PiT-1 expression also will be increased to induce an influx of phosphorus and intracellular generation of ROS and H_2O_2 [12].

In-vitro studies on uremic rats also revealed that vascular smooth muscle cells ($VSMC_s$) exposed to phosphate overload, have increased expression of TNF-α and NOX4 (one of the NADPH oxidase family members) mRNA [2], that was in parallel with decreased expression of Klotho mRNA and increased expression of bone morphogenic protein-2 (BMP-2) (a marker of osteoblastic trans-differentiation). These findings imply an increased level of inflammation in phosphate overload milieu, in the uremic state.

Furthermore, high phosphate load can increase the level of the fetuin-mineral complex [13] that per se can be a direct cause of local and systemic inflammation in the uremic state with phosphorus overload.

All these data advocate the pivotal role of phosphorus as an independent risk factor for the induction of inflammation in uremic states that were compatible with the results of this study.

Our data revealed the breakpoint of 5.5 for phosphorus and 55 for Ca×P level as critical levels that inflammation tends to be increased. This level is compatible with the best level of phosphate and Ca×P level in guidelines for uremic patients.

As a conclusion and based on these data, we proposed that phosphate level per se, regardless of other inducers of inflammation in uremic patients who undergo hemodialysis, can induce inflammation in uremic patients.

Author contributions:

Mahmudpour M: Designing the study, writing the manuscript
Nasiri M: Obtaining the patient and blood samples collection, data analysis
Ghasemi K: Obtaining the patients

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Significance statement

Renal failure with serious life-threatening complications has a major impact on human health. One of these complications is hyperphosphatemia. On the other hand, the uremic state is accompanied by an inflammatory milieu that per se can increase mortality in end-stage renal disease patients. Therefore, detection of independent factors that induce inflammation in uremic patients, can be valuable. Data about the direct effect of hyperphosphatemia on inflammation in uremic patients are limited. So we investigated the independent effect of hyperphosphatemia on inflammation in hemodialysis patients.

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Table 1: hs -CRP level and it's correlations with Albumin, Vitamin D, PTH, Calcium, and Phosphorus.

variables	Albumin [mg/dl]	Vitamin D [ng/ml]	PTH [pg/ml]	Phosphorus [mg/ml]	Calcium [mg/dl]
Total (N=70)	3.86 ± 0.58	28.1 ± 15.86	257.49 ± 200.4	5.49 ± 1.61	8.61 ± 0.91
Hs-CRP Pearson correlation	-0.415	-0.025	-0.006	0.254	0.098
P-value	P (0.005)	P (0.836)	P (0.963)	P (0.034)	P (0.418)

Table 2: Comparison of hs-CRP concentration in different phosphorus cut off levels.

Phosphorus cut-off	Hs-CRP	P-value
≥4.5 (N=50)	1.82 ± 1.18	0.599
<4.5 (N=20)	1.65 ± 1.18	
≥5 (N=39)	1.94 ± 1.22	0.183
<5 (N=31)	1.56 ± 1.09	
≥5.5 (N=35)	2.07 ± 1.08	0.032
<5.5 (N=35)	1.47 ± 1.19	
≥6 (N=26)	2.27 ± 0.94	0.005
<6 (N=44)	1.47 ± 1.2	
≥6.5 (N=22)	2.22 ± 0.99	0.029
<6.5 (N=48)	1.57 ± 1.2	

Table 3: Comparison of hs-CRP concentration in different P×Ca cut-off levels.

P×Ca cut-off	Hs-RCP	P-value
≥50 (N=29)	2.05±1.33	0.1
<50 (N=41)	1.58±1.01	
≥55 (N=20)	2.38±0.97	0.006
<55 (N=50)	1.53±1.16	
≥60 (N=15)	2.23±1.03	0.091
<60 (N=55)	1.65±1.18	