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Mini Review

Phosphorus and Cardiovascular System

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Abstract

Several factors play an important role in the pathogenesis of cardiovascular disease (CVD) in chronic kidney disease (CKD) patients. Among these the phosphatemia play a crucial role. In CKD patients the phosphatemia (P) levels increase as a consequence of decreased renal elimination.The dramatical effect of phosphatemia on cardiovascular system is mediated by P stimulation on the synthesis of Fibroblast Growth Factor-23 (FGF-23). FGF-23 in turn stimulates the angiotensin converting enzyme (ACE) and accordingly the renin-angiotensin-aldosterone system (RAAS). The RAAS stimulation exceeds the positive reno-protective effect of Ramipril especially at the tissue level. Moreover P reduces the nitric oxide (NO) production, directly or by FGF-23, and in this way P reduces the ACE inhibitor effects.

In this paper we review the main effects of mineral metabolism disturbances on CVD particularly focusing on P effects.

Keywords: Phosphatemia; Cardiovascular System; Chronic Kidney Disease

Introduction

Chronic Kidney Disease (CKD) is a relevant public health problem in industrialized countries.

American epidemiological data published in the study NANHES IV show that a 13% of population has a CKD in each stage of disease [1].

In Europe we observe prevalence data smaller than the US (e.g.11, 6% in Holland and 9% in Spain) [1].

In Italy we have conflicting data: the two most representative studies, Gubbio and INCIPE, show a CKD prevalence of 6% and 12, 7% respectively.

In the clinical perspective, the CKD patients have a higher risk for death and cardiovascular disease (CVD) than general population. The CVD risk increases directly with the CKD progression [2].

CVD Risk Factor and CKD: the role of Phosphorus

Several factors play a role in CVD pathogenesis in CKD patients. Stevinkel has evaluated all traditional risk factors (age, gender, dyslipidemia, blood hypertension, diabetes and smoking), known from the Framingham study, and has added endothelial dysfunction and inflammatory markers including the presence of secondary hyperparathyroidism (SHPT) that is a common condition in CKD cohort [3] (Figure 1).

It's well known that reducing the glomerular filtration rate (GFR) we observe mineral disorders.

Between these the phosphatemia play a crucial role. In CKD patients the phosphatemia (P) levels increase as a consequence of decreased renal elimination [3].

The first clinical data was gathered in end stage renal disease (ESRD) patients and showed an association between death and phosphatemia. In this particular setting the mortality risk is high also for normal/low phosphorus levels as consequence of chronic malnutrition and inflammation [4].

In CKD stage 3 and 4 also a "normal" level of phosphorus (<4, 5 mg/dl) is associated with higher CV events [5].

The PIRP study and a secondary analysis of the REIN study underline the role of the phosphorus (P) in the progression of CKD and increasing the mortality for all causes and for CV causes [6,7].

The PIRP study showed that phosphorus level >4.2 mg/dl increases the mortality rate for all causes, while the REIN study described that the protective effect of Ramipril is reduced when P levels grow up 3.45 mg/dl [6,7]. An increase of phosphorus equal to 1 mg/dl was associated with a 85% risk of developing ESRD.

The reason of this dramatical effect is that P stimulates the synthesis of Fibroblast Growth Factor-23 (FGF-23). FGF-23 in turn stimulates the angiotensin converting enzyme (ACE) and accordingly the renin-angiotensin-aldosterone system (RAAS).

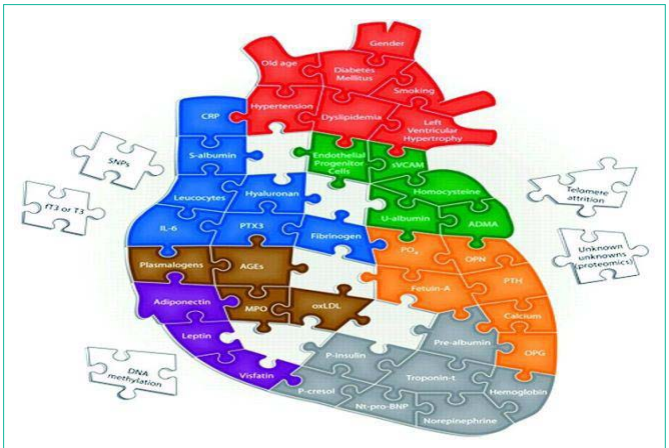

Figure 1: Traditional and non-traditional CV risk factors (modified by Stevinkel P et al. *CJASN 2008; 3: 505-521).*

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The RAAS stimulation exceeds the positive reno-protective effect of Ramipril especially at the tissue level. Moreover P reduces the nitric oxide (NO) production, directly or by FGF-23, and in this way P reduces the ACE inhibitor effects [7].

It's very interesting that P levels are associated with a higher CVD risk also in the general population without kidney or heart disease. In the Framingham study we can observe that CVD incidence increases proportionally with increasing levels of P.

Why the phosphatemia is crucial for the CVD pathogenesis?

First and foremost, phosphorus exerts a direct damage to the endothelium; increases the FGF-23 blood levels and speeds up decisively the processes leading to vascular and valve calcifications.

In the last few years, the researchers described the strict relation between P and FGF-23 that is one of the most important actors to promote the left ventricular hypertrophy (LVH) in CKD patients.

The FGF-23 increases the urinary elimination of P when this exceed in the blood. In the same time the FGF-23 reduces the renal activation of calcitriol to avoid the gut absorption of P.

With the reduction of calcitriol we observe an activation of RAAS system and consequently a higher risk to develop blood hypertension and LVH (also for a direct action on myocardial cells by FGF-23) [8]. The results of MESA study confirm the above description [8].

The PREPARE study underlined that high levels of phosphatemia (and PTH) are an independent risk factor for non- dippers blood hypertension (this condition increases the CVD risk).

Hyperphosphatemia and cardiovascular calcification

The phosphatemia is an inducer factor of bone transformation of the endothelial cells. The endothelial cells become osteocytes [9]. In CKD patients the calcification process involves both the intima (as like in atherogenesis) and the media tunica (Moenckeberg calcification) of vessels. This transformation leads an important impact in the cardiovascular function. The more important risk is thromboembolic event due to instability of calcified plaque.

Moreover, we can observe a high stiffness of arterial vessel due to loss of elasticity and therefore an increasing of systolic pressure (more than diastolic pressure) and pulse wave velocity. In the mean time we observe a coronaric perfusion and reserve reduction and a LVH worsening that will lead to develop a myocardial fibrosis. Particularly dangerous are the presence of calcification at the level of the coronary arteries (evaluated by CAC score). These are responsible of high incidence of ischemic heart attack in CKD patients. Hemodialysis patients with coronaric calcification have a higher CV risk than patient not in dialysis but with coronaric disease [10].

The prevalence for coronaric calcification in ESRD cohort was estimated from 40 to 100% depending on different studies, while the prevalence of valve calcification fluctuates from 30 to more than 50% [11].

In the hemodialysis patients the progression of calcification seems be faster and, therefore, the incidence of CV events is higher [12]. Block and al have published the RIND study in which they confirmed the strict association between coronaric calcification and higher CV risk [13].

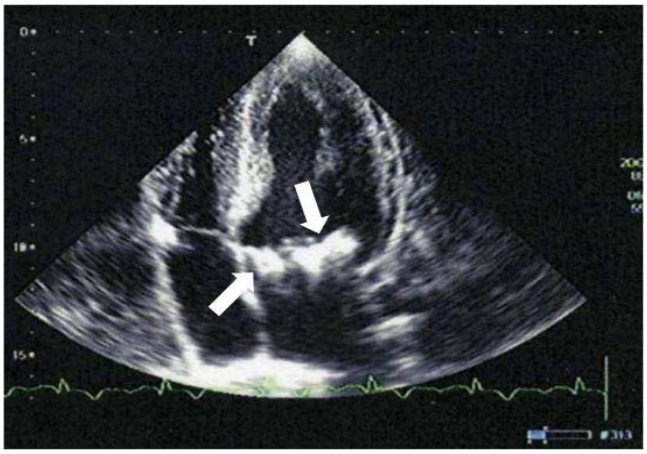

Figure 2: Extensive calcifications (annulus and anterior flap of mitral valve) in stage 5 CKD patient.

The coronaric calcifications are present also in patients without renal disease and without CV symptoms. The CARDIA (Coronary Artery Risk Development in Young Adults) study showed in a young cohort of people (age >18 and <30 ys) with normal renal function (eGFR = 116 ml/min/1.73 m^2) the direct correlation between P levels and CV traditional risk (age, gender, race, BMI, CVD family history, low levels of HDL cholesterol). Furthermore, the study showed a correlation between P and coronaric calcification (not confirmed by multivariate analysis) [14].

The MESA study has described that in patients with mean eGFR equal to 60 ml/min/1.73m^2 the high P levels, albeit within the normal range, are associated with higher prevalence of valve calcification, in particular mitral valve calcification [15]. The mitral calcification involves primarily the annulus and subsequently the flaps, especially in Stage 2-3 CKD patients. In ESRD patients with severe SHPT we can observe frequently extensive calcification and an involvement of sub-valvular apparatus, too (Figure 2). This condition was defined with a Wilkins Score equal to 4 (Figure 3).

The aortic calcifications are strictly related with P and with FGF-23 and PTH levels [16].

Score	Mobility	Subvalvar thickening	Thickening	Calcification
1	Highly mobile valve with only leaflet tips restricted.	Minimal thickening just below the mitral leaflets.	Leaflets near normal in thickness (4-5 mm).	A single area of increased echo brightness.
2	Leaflet mid and base portions have normal mobility.	Thickening of cordal structures extending up to one third of the chordal length.	Mid-leaflets normal, considerable thickening of margins (5-8 mm).	Scattered area of brightness.
3	Valves continues to move forward in diastole, mainly from the base.	Thickening extending to the distal third of the cords.	Thickening extending through the entire leaflet (5-8 mm).	Brightness extending into the mid-portions of the leaflets.
4	No or minimal forward movement of the leaflets in diastole.	Extensive thickening and shortening of all cordal structures extending down to the papillary muscles.	Considerable thickening of all leaflet tissue (> 8-10 mm).	Extensive brightness throughout much of the leaflet tissue.

Figure 3: Wilkins Score to evaluate the extension and severity of mitral valve calcifications.

Conclusion

As described above, the P level is an important CV risk factor in CKD patients, but also in general population. The P was defined as a "silent killer" because it can damage the cardiovascular system also while it's in the normal range. The central role of phosphatemia to develop the vascular and valve calcifications is well demonstrated. Therefore we have to consider the P a crucial therapeutic target in CKD cohort, but also in the general population.

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