J Med Biochem 2012; 31 (3) DOI: 10.2478/v10011-012-0002-5

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 31: 239–245, 2012

Original paper
Originalni naučni rad

HYPERPHOSPHATEMIA – THE RISK FACTOR FOR ADVERSE OUTCOME IN MAINTENANCE HEMODIALYSIS PATIENTS

HIPERFOSFATEMIJA – FAKTOR RIZIKA ZA RAZVOJ NEPOVOLJNOG ISHODA KOD BOLESNIKA KOJI SE LEČE REDOVNIM HEMODIJALIZAMA

Dejan Petrović[1], Radmila Obrenović[2], Jasna Trbojević-Stanković[3], Nada Majkić-Singh[2], Biljana Stojimirović[4]

[1]Clinic for Urology and Nephrology, Clinical Center »Kragujevac«, Kragujevac
[2]Institute of Medical Biochemistry, Clinical Center of Serbia, University of Belgrade
[3]Department of Hemodialysis, Clinical Hospital Center »Dragiša Mišović«, Belgrade
[4]Institute for Urology and Nephrology, Clinic of Nephrology, Clinical Center of Serbia, Belgrade, Serbia

Summary: Hyperphosphatemia is a potent stimulator of vascular and valvular calcifications in hemodialysis patients. To determine the prevalence of hyperphosphatemia and assess its effect on the outcome of hemodialysis patients, a total of 115 chronic hemodialysis patients were studied. Laboratory parameters were determined at baseline, and after 12 and 24 months of follow-up. Valvular calcification was assessed with echocardiography. Laboratory parameters were statistically analyzed with ANOVA. Survival analysis was performed with the Kaplan-Meier test and Log-Rank test. Hyperphosphatemia was present in 31.30% of the patients, high calcium-phosphate (Ca x P) product in 36.52% and valvular calcifications in 48.70%. Patients with serum phosphate >2.10 mmol/L and Ca x P product >5.65 $mmol^2/L^2$ at baseline were at high risk for all-cause and cardiovascular mortality. Hyperphosphatemia is a risk factor for adverse outcome in patients on regular hemodialysis.

Keywords: hemodialysis, hyperphosphatemia, cardiovascular mortality

Kratak sadržaj: Hiperfosfatemija ima značajnu ulogu u kalcifikaciji srčanih valvula i koronarnih arterija bolesnika na hemodijalizi. Radi utvrđivanja prevalencije hiperfosfatemije i ispitivanja njenog uticaja na ishod bolesnika koji se leče redovnim hemodijalizama, ispitano je 115 bolesnika koji se leče redovnim hemodijalizama duže od 6 meseci. Laboratorijsko ispitivanje je sprovedeno na početku, posle 12 i 24 meseci praćenja bolesnika. Kalcifikacija srčanih valvula je procenjivana ehokardiografskom metodom. Za statističku analizu podataka korišćeni su jednofaktorska parametarska analiza varijanse – ANOVA i analiza preživljavanja (Kaplan-Meier test, Log-Rank test). Hiperfosfatemiju ima 31,30% bolesnika, povećan proizvod solubiliteta 36,52% bolesnika, a kalcifikaciju srčanih valvula 48,70% bolesnika. Bolesnici kod kojih je na početku ispitivanja koncentracija fosfata u serumu >2,10 mmol/L i proizvod solubiliteta >5,65 $mmol^2/L^2$ imaju visok rizik za razvoj opšteg i kardiovaskularnog mortaliteta. Hiperfosfatemija je faktor rizika za razvoj nepovoljnog ishoda kod bolesnika koji se leče redovnim hemodijalizama.

Ključne reči: hemodijaliza, hiperfosfatemija, kardiovaskularni mortalitet

Introduction

Phosphate is a predominantly intracellular anion, either complexed or bound to proteins or lipids. It is essential for most cellular processes. Several transport proteins enable the intracellular uptake of phosphate. Type 1 and Type 2 sodium phosphate cotransporters are expressed in the kidneys, bones and intestines. Type 3 transporters were initially identified as viral transport proteins, but they may also

Address for correspondence:
Dejan Petrović MD, PhD
Clinic for Urology and Nephrology
Center for Nephrology and Dialysis
Clinical Center »Kragujevac«, Zmaj Jovina 30,
34000 Kragujevac
Phone: ++381 34 370–302, Fax: ++381 34 370–302
e-mail: aca96@eunet.rs

participate in the regulation of renal and intestinal transepithelial transport (1, 2). The kidney is a key player in the phosphate balance. Hyperphosphatemia can occur as a result of: excessive phosphate intake in the setting of impaired renal phosphate excretion (renal failure, milk-alkali syndrome); vitamin D intoxication (excessive gastrointestinal absorption and increased renal reabsorption); decreased excretion (mostly due to acute or chronic renal failure) or shift from intracellular to extracellular space (rhabdomyolysis, tumor lysis, insulin deficiency, acute acidosis) (3).

Hyperphosphatemia, even of a quite severe degree, is largely a clinically asymptomatic condition, and morbidity is mostly associated with the underlying condition. The short-term complications of hyperphosphatemia include acute hypocalcemia with possible tetany and, more rarely, acute deposition of calcium/phosphate complexes into joints, subcutaneous tissue or other soft tissue areas (4). The long-term complications of chronic, uncontrolled hyperphosphatemia can be devastating, and can develop progressive extensive soft tissue calcifications (4, 5). Organs most commonly affected include the vascular system, heart, skin, bones, joints, tendons, ligaments and eyes (4, 5). Capillary and small arteriole deposition of calcium is generally the pathology detected in classic calciphylaxis. Intimal calcifications cause vascular lumen stenosis, resulting in impaired blood supply and leading to necrotic skin lesions, hemorrhagic subcutaneous lesions and myocardial ischemia (6).

In patients with renal failure the most significant long-term complication of chronic uncontrolled hyperphosphatemia and elevated calcium-phosphate product is the development of vascular calcifications, either in the subintimal (atherosclerotic plaques) or submedial vascular space (7). Plaque rupture may even cause acute coronary syndrome (7).

Submedial calcifications may be a consequence of the dedifferentiation of smooth muscle cells in the media into cells with a more osteoblastic phenotype, allowing for mineralization of the blood vessel. Furthermore, the loss of normal inhibitors of soft tissue calcification, such as matrix GLA protein or osteoprotegerin, may play a role in the pathogenesis. Recent data suggest that phosphate uptake through Pit-1 sodium-dependent phosphate cotransporter is essential for smooth muscle cell calcification in response to elevated phosphate (8). The hemodynamic consequences of medial calcification are increased arterial stiffness, left ventricular pressure overload and the development of left ventricular hypertrophy (8). Valvular calcification eventually leads to aortal and mitral stenosis (9). Calcium deposited into the heart tissue itself can disrupt the cardiac conduction system, producing significant arrhythmias (10).

Hyperphosphatemia and high calcium-phosphorus (Ca × P) product are key contributors to the vascular and valvular calcification and cardiovascular mortality of hemodialysis (HD) patients (8–11).

The aims of this study were to assess the prevalence of hyperphosphatemia, high Ca x P product and aortic and mitral valve calcification in HD patients, as well as to assess the influence of hyperphosphatemia and high Ca × P product on the outcome of patients on regular HD.

Patients and Methods

Patients

This prospective study included 115 patients (71 men and 44 women, average age 53.30±12.17) on maintenance HD at the Dialysis Department, Clinic of Urology and Nephrology, Clinical Center »Kragujevac« in Kragujevac, Serbia. Only the patients without clinical symptoms or electrocardiographic signs of coronary syndrome, and without symptoms or signs of congestive heart failure up to three months prior to the enrollment in the study were included. All patients had been on regular HD for at least 6 months. All were hemodynamically stable and had less than 200 mL residual diuresis. The study was conducted according to the Helsinki Declaration and all patients gave their informed consent for participation. The follow-up period was two years.

Methods

Blood samples for laboratory analyses were drawn after 12 hours of overnight fasting, before the dialysis session and heparin administration. Laboratory parameters were determined at baseline, after 12 and 24 months.

Serum urea was determined with the complete enzymatic method (*urease-glutamate-dehydrogenase*; reference range 3.5–7.5 mmol/L).

Hemoglobin concentration was measured by colorimetry. The standard range was 110–180 g/L.

Hematocrit (Hct) was determined automatically with a COULTER® A^C machine and from the formula: Hct (%) = (RBC × MCV)/10, where RBC – red blood cells and MCV – mean cell volume. Normal range was 0.35–0.60.

Serum albumin level was measured by the photometric colour test with bromcresol green. The normal range was 38–46 g/L, and levels <36 g/L suggested malnutrition.

Serum calcium and phosphorus concentrations were determined as the mean value from two consequtive monthly measurements taken prior to laboratory, and echocardiographic evaluation by photometric color test and photometric UV test, respectively. The reference range was 2.20–2.65 mmol/L for calcium and 0.80–1.60 mmol/L for phosphorus.

Serum iPTH was determined by radioimmunoassay (IRMA). Normal iPTH concentration is 11.8–64.5 pg/mL for healthy individuals. The target range for HD patients is 200–300 pg/mL.

Arterial blood pressure (BP) was calculated as the average value of twelve monthly measurements, taken prior to the laboratory and echocardiographic investigations.

The echocardiographic study was performed 15 to 20 hours after the dialysis session, in order to avoid end-diastolic left ventricle diameter alterations induced by the interdialytic volume gain. All studies were performed on a SHIMADZU-2200 ultrasound machine, with a 2.5 MHz transducer probe, by a single experienced physician.

Hemodialysis adequacy was assessed with Kt/Vsp index, calculated based on the Daugridas second-generation formula:

$$Kt/Vsp = -\ln(C_2/C_1 - 0.008 \times T) + (4 - 3.5 \times C_2/C_1) \times UF/W,$$

where C_1 stands for predialysis serum urea, C_2 – postdialysis serum urea (mmol/L), T – treatment time (h), UF – ultrafiltration (L) and W – body weight after dialysis (kg). According to K/DOQI guidelines the delivered Kt/V should be ≥1.2.

Statistical analysis

The demographic data and laboratory parameters were analyzed with the one-factorial ANOVA, Kruskall-Wallis test, Student t-test and Mann-Whitney U test. Survival analysis was performed with the Kaplan-Meier test and Log Rank test. P values of less than 0.05 were considered significant, and values less than 0.01 were considered highly significant.

Results

Table I provides the demographic and clinical parameters of patients during the follow-up period. Average time on dialysis and average Kt/Vsp at the beginning of the study were 4.51±4.01 years and 1.17±0.23 respectively.

Almost one third of the patients (31.30%) had increased serum phosphate, and 36.52% had high calcium × phosphate (Ca × P) product. High serum iPTH, denoting the presence of secondary hyperparathyroidism, was present in 20% of the patients.

Standard laboratory parameters of anemia, calcium and phosphorus metabolism and protein status are shown in *Table II*. A highly significant increase in hematocrit levels ($p<0.01$) was noted after 12 months

Table I Demographic and clinical data in the study group during the two-year follow-up period.

VARIABLE		Baseline (I)	12 months (II)	24 months (III)
		Mean ± SD	Mean ± SD	Mean ± SD
Number of patients (N)		115	100	86
Sex (M/F)		71/44	63/37	57/29
Age (years)		53.30±12.17	54.27±11.31	54.00±11.48
Body-mass index – BMI (kg/m^2)		22.60±3.18	22.73±3.24	22.72±3.21
Time on dialysis (years)		4.51±4.01*	5.30±4.07	5.46±4.24**
Systolic arterial pressure – SAP (mmHg)		138.13±20.95	136.90±19.58	137.33±19.73
Diastolic arterial pressure – DAP (mmHg)		84.09±12.89	83.15±12.34	84.24±12.24
Mean arterial pressure – MAP (mmHg)		102.10±15.07	101.07±14.24	101.94±14.37
Ultrafiltration – UF (kg)		2.63±0.84	2.63±0.80	2.64±0.77
Interdialysis weight gain – IDWG (%)		4.15±1.54	4.10±1.51	4.12±1.51
Dialysis adequacy – Kt/Vsp index		1.17±0.23	1.21±0.26	1.23±0.22
Underlying renal disease	*Diabetic nephropathy*	12 (10.44%)	11 (11.00%)	7 (8.14%)
	Chronic pyelonephritis	19 (16.52%)	14 (14.00%)	12 (13.95%)
	Hypertensive nephropathy	21 (18.26%)	19 (19.00%)	17 (19.77%)
	Chronic nephropathy	7 (6.09%)	6 (6.00%)	5 (5.81%)
	Chronic glomerulonephritis	35 (30.43%)	31 (31.00%)	28 (32.56%)
	Obstructive nephropathy	4 (3.48%)	3 (3.00%)	3 (3.49%)
	Polycystic renal disease	15 (13.04%)	14 (14.00%)	12 (13.95%)
	Endemic nephropathy	2 (1.74%)	2 (2.00%)	2 (2.33%)

*PI,II < 0.05, **PI,III < 0.05

Table II Biochemical parameters in the study group during the two-year follow-up period.

VARIABLE	Baseline (I)	12 months (II)	24 months (III)
	Mean ± SD	Mean ± SD	Mean ± SD
Hemoglobin – Hb (g/L)	89.67 ± 14.10*	93.65 ± 15.06	95.07 ± 15.41
Hematocrit – Hct (%)	26.66 ± 4.23**	31.80 ± 8.77***	32.39 ± 9.25
Total proteins (g/L)	73.69 ± 6.17**	66.92 ± 4.99***	68.23 ± 5.18
Serum albumin (g/L)	40.55 ± 4.62**	38.59 ± 3.34***	37.47 ± 3.71
Serum calcium – Ca^{2+} (mmol/L)	2.35 ± 0.25	2.38 ± 0.25	2.37 ± 0.25
Serum phosphate – PO_4^{3-} (mmol/L)	1.76 ± 0.55	1.68 ± 0.54	1.67 ± 0.54
Solubility product – Ca × P ($mmol^2/L^2$)	4.15 ± 1.37	3.98 ± 1.29	3.94 ± 1.28
Parathormone – iPTH (pg/mL)	310.17 ± 347.89	299.47 ± 347.38	270.19 ± 321.82

*PI,III < 0.05, **PI,III < 0.01, ***PI,II < 0.01

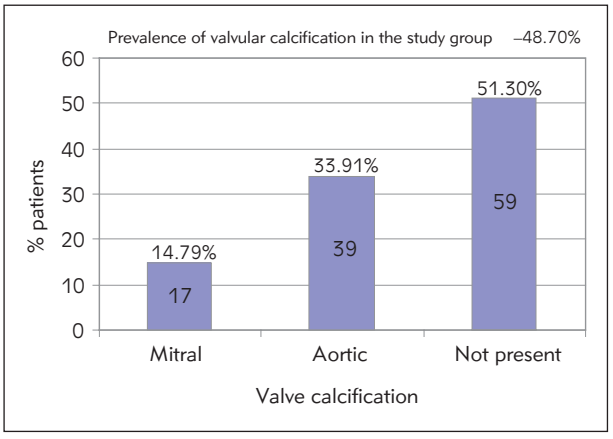

Figure 1 Echocardiographic assessment of valvular calcification at the beginning of the study.

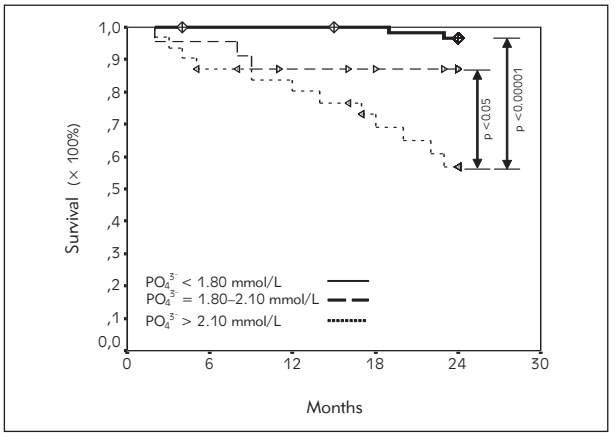

Figure 3 The influence of serum phosphate on survival of hemodialysis patients during the two-year follow-up period (cardiovascular mortality).

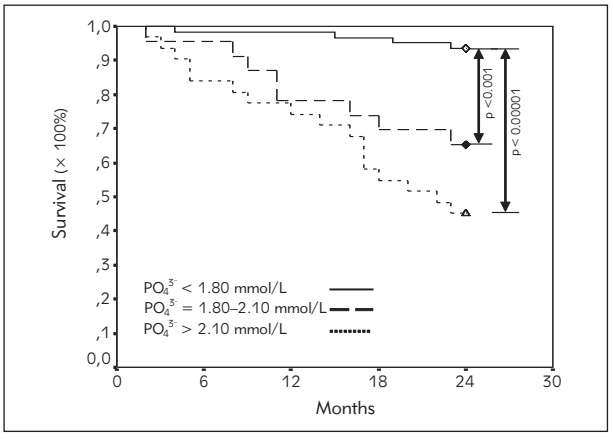

Figure 2 The influence of serum phosphate on survival of hemodialysis patients during the two-year follow-up period (all-cause mortality).

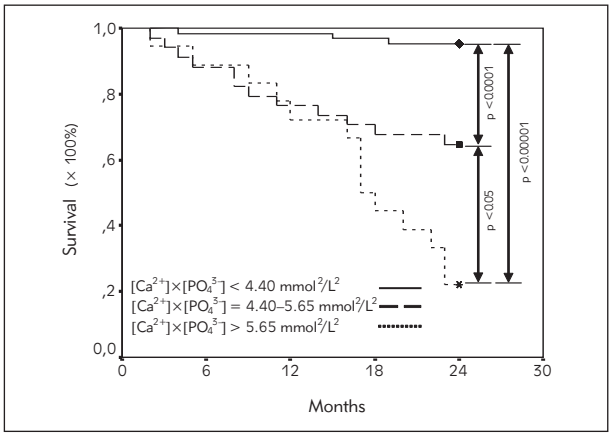

Figure 4 The influence of calcium–phosphate product on survival of hemodialysis patients during the two-year follow-up period (all-cause mortality).

of follow-up. After two years of follow-up the patients had significantly higher hemoglobin ($p<0.05$) and hematocrit ($p<0.01$) levels than at the beginning of the study. Total protein and serum albumin levels significantly decreased during the follow-up period ($p<0.01$). Serum calcium, phosphate and iPTH levels, as well as Ca × P product, did not change significantly during the follow-up period ($p>0.05$).

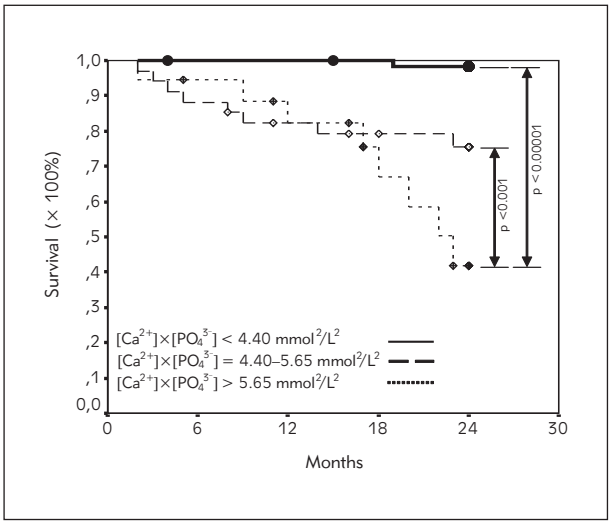

Figure 5 The influence of calcium–phosphate product on survival of hemodialysis patients during the two-year follow-up period (cardiovascular mortality).

Aortic and mitral valve calcifications were found in almost half of the patients (48.70%), as shown in *Figure 1*.

Patients with a serum phosphate level between 1.80 and 2.10 mmol/L or >2.10 mmol/L had significantly higher all-cause mortality risk ($p<0.01$) than the patients with serum phosphate levels <1.80 mmol/L (*Figure 2*). Cardiovascular mortality risk was significantly higher ($p<0.01$) in patients with serum phosphate between 1.80 and 2.10 mmol/L or >2.10 mmol/L than in patients with serum phosphate <1.80 mmol/L (*Figure 3*).

Patients with Ca x P product >5.65 $mmol^2/L^2$ at baseline had significantly higher risk of all-cause mortality than patients with Ca × P <4.40 $mmol^2/L^2$ or between 4.40 and 5.65 $mmol^2/L^2$. Furthermore, patients with baseline Ca × P product 4.40–5.65 $mmol^2/L^2$ had significantly higher all-cause mortality risk than those with solubility product <4.40 $mmol^2/L^2$ (*Figure 4*).

Patients with baseline Ca × P product >5.65 $mmol^2/L^2$ had significantly higher cardiovascular mortality risk than those with solubility product <4.40 $mmol^2/l^2$ or 4.40–5.65 $mmol^2/L^2$ (*Figure 5*).

Discussion

Cardiovascular disease represents the leading cause of mortality in HD patients (12–15). Several risk factors, such as anemia, hypertension, volume overload, shunt blood flow, oxidative stress, microinflammation, hypoalbuminemia, hyperhomocysteinemia and hyperphosphatemia have been identified as cardiovascular risk factors in the HD population (16–20).

High phosphate may contribute to several mechanisms that initiate and/or promote the progression of vascular calcification: promoting osteochondrogenic conversion of vascular cells, inhibiting osteoclastic differentiation, promoting apoptosis as well as raising the Ca × P product, thereby thermodynamically favoring crystal formation. It is still undetermined whether elevated phosphate contributes to the loss of anticalcific molecules, such as decreased fetuin levels in ESRD patients, circulating nucleational complexes or matrix degradation (21).

The prevalence of hyperphosphatemia, high Ca × P product and high iPTH in this chronic dialysis population was 31.30%, 36.52% and 20%, respectively. Secondary hyperparathyroidism, hyperphosphatemia and high Ca × P product are independently related to the calcification of heart valves and coronary artery and increased cardiovascular mortality of HD patients (21–27). The presence of valvular and cardiovascular calcification is an important predictor of cardiovascular morbidity and mortality in these patients (21–27). Aortic valve calcification was reported to be present in 28–55% of HD patients, while mitral valve calcification was observed in 24% of HD patients (28). In our study population calcified aortic valve was found in 33.91% of the patients, and calcified mitral valve was present in 14.79% of the patients. Aortic valve calcification causes aortic stenosis, left ventricle pressure overload and left ventricle concentric hypertrophy. Mitral valve calcification induces left atrial dilatation, atrial fibrillation and absolute arrhythmia (29–31). Hemodialysis patients with a serum phosphate concentration >2.10 mmol/L (>6.5 mg/dL) and Ca × P product >5.65 $mmol^2/L^2$ (>72 mg^2/dL^2) are at highest risk for sudden cardiac death (32). Our study shows that HD patients with serum phosphate >2.10 mmol/L and Ca × P product >5.65 $mmol^2/L^2$ have significantly higher risk for all-cause and cardiovascular mortality than those with serum phosphate <1.80 mmol/L and Ca × P product <4.40 $mmol^2/L^2$. This finding is in agreement with the previously reported data (31–33). Serum phosphate >1.6 mmol/L (>5.0 mg/dL) and iPTH ≥ 600 pg/mL are associated with a higher mortality rate in patients on maintenance HD (33, 34).

In patients with chronic kidney disease (CKD) phosphate is regarded as a 'uremic toxin'. Statistical association between serum phosphate and all-cause mortality in patients on dialysis has transformed the phosphate molecule from a subject of little interest 10 years ago to the 'dialysis enemy number 1' today (35). Until recently, PTH and vitamin D were the only recognized regulators of phosphate metabolism. In the last decade, several novel regulators of mineral homeostasis have been discovered: phosphate regulating gene, fibroblast growth factor 23 (FGF23), and the family of stanniocalcins (STC1 and STC2) (36).

Even with the increasing knowledge on phosphate metabolism and its role in renal failure patients, interventional measures are still limited. Restricted phosphate intake, non-calcium based phosphate binders, new vitamin D metabolites and calcimimetics contribute to better control of secondary hyperparathyroidism, prevent coronary calcification and decrease the morbidity and mortality rate in patients on regular HD (37–43).

In conclusion, hyperphosphatemia and high Ca × P product are risk factors for adverse outcome in patients on maintenance HD. Regular monitoring and maintaining of serum calcium, phosphorus and Ca × P product within the target range contribute to lowering the cardiovascular morbidity and mortality and improving the quality of life of HD patients.

Acknowledgments. Authors would like to express their deepest gratitude to the Serbian Ministry of Education and Science for their Grant No 175036, which was used as one of the sources to financially support the study.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

References

1. Prie D, Urena P, Friedlander G. Latest findings in phosphate homeostasis. Kidney Int 2009; 75(9): 882–9.
2. Murer H, Hernando N, Forster I, Biber J. Proximal tubular phosphate reabsorption: molecular mechanisms. Physiol Rev 2000; 80(4): 1373–409.
3. Prie D, Beck L, Urena P, Friedlander G. Recent findings in phosphate homeostasis. Curr Opin Nephrol Hypertens 2005; 14(4): 318–24.
4. Levin NW, Hoenich NA. Consequences of hyperphosphatemia and elevated levels of the calcium-phosphorus product in dialysis patients. Curr Opin Nephrol Hypertens 2001; 10(5): 563–8.
5. Block GA, Port FK. Calcium Phosphate Metabolism and Cardiovascular Disease in Patients with Chronic Kidney Disease. Semin Dial 2003; 16(2): 140–7.
6. Block GA. Control of serum phosphorus: implications for coronary artery calcification and calcific uremic arteriolopathy (calciphylaxis). Curr Opin Nephrol Hypertens 2001; 10(6): 741–7.
7. Cannata-Andia JB, Carrera F. The Pathophysiology of Secondary Hyperparathyroidism and the Consequences of Uncontrolled Mineral Metabolism in Chronic Kidney Disease: The Role of COSMOS. Nephrol Dial Transplant 2008; 1(Suppl 1): 29–35.
8. Toussaint ND, Kerr PG. Vascular calcification and arterial stiffness in chronic kidney disease: Implications and management. Nephrology 2007; 12(5): 500–9.
9. London GM, Pannier B, Marchais SJ, Guerin AP. Calcification of the Aortic Valve in the Dialyzed Patient. J Am Soc Nephrol 2000; 11(4): 778–83.
10. Petrović D, Stojimirović B. Secondary hyperparathyroidism – risk factor for development of cardiovascular complications. Med Pregl 2010; 63(9–10): 674–80. (in Serbian)
11. Petrović D, Obrenović R, Stojimirović B. Risk factors for aortic valve calcification in patients on regular hemodialysis. Int J Artif Organs 2009; 32(3): 173–9.
12. Parfrey PS. Cardiac disease in dialysis patients: diagnosis, burden of disease, prognosis, risk factors and management. Nephrol Dial Transplant 2000; 15(Suppl 5): 5868.
13. Petrović D, Stojimirović B. Cardiovascular morbidity and mortality in hemodialysis patients – epidemiological analysis. Vojnosanit Pregl 2008; 65(12): 893–900. (in Serbian)
14. Petrović D, Obrenović R, Trbojević-Stanković J, Majkić-Singh N, Stojimirović B. Cardiovascular mortality in hemodialysis patients: clinical and epidemiological analysis. Journal of Medical Biochemistry 2011; 30(4): 302–8.
15. Ležajić V. Serum and urinary biomarkers determination and their significance in diagnosis of kidney disease. Journal of Medical Biochemistry 2010; 29: 288–297.
16. Zoccali C, Mallamaci F, Tripepi G. Traditional and emerging cardiovascular risk factors in end-stage renal disease. Kidney Int 2003; 63(85): 105–10.
17. Zoccali C, Mallamaci F, Tripepi G. Novel Cardiovascular Risk Factors in End-Stage Renal Disease. J Am Soc Nephrol 2004; 15(Suppl 1): 77–80.
18. Zoccali C. Traditional and emerging cardiovascular and renal risk factors: An epidemiological perspective. Kidney Int 2006; 70(1): 26–33.
19. Rigatto C, Parfrey PS. Uraemic Cardiomyopathy: an Overload Cardiomyopathy. J Clin Basic Cardiol 2001; 4(2): 93–5.
20. Đerić M, Čabarkapa VS. Cardiovascular biomarkers in chronic kidney disease. Journal of Medical Biochemistry 2010; 29(4): 298–303.
21. Giachelli CM. The emerging role of phosphate in vascular calcification. Kidney Int 2009; 75(9): 890–7.
22. Chertow GM, Burke SK, Raggi P, for the Treat to Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002; 62(1): 245–52.
23. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, Raggi P. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 2005; 68(4): 1815–24.

24. Ribeiro S, Ramos A, Brandao A, Guerra A, Resina C, Vila-Lobos A, et al. Cardiac valve calcification in haemodialysis patients: role of calcium-phosphate metabolism. Nephrol Dial Transplant 1998; 13(8): 2037–40.

25. Qunibi WY. Consequences of hyperphosphatemia in patients with end-stage renal disease (ESRD). Kidney Int 2004; 66(Suppl 90): 8–12.

26. Hörl WH. The clinical consequences of secondary hyperparathyroidism: focus on clinical outcomes. Nephrol Dial Transplant 2004; 19(Suppl 5): 2–8.

27. Goodman WG. The Consequences of Uncontrolled Secondary Hyperparathyroidism and Its Treatment in Chronic Kidney Disease. Semin Dial 2004; 17(3): 209–16.

28. Ventura JE, Tavella N, Romero C, Petraglia A, Baez A, Munoz L. Aortic valve calcification is an independent factor of left ventricular hypertrophy in patients on maintenance haemodialysis. Nephrol Dial Transplant 2002; 17(10): 1795–801.

29. Rufino M, Garcia S, Jimenez A, Alvarez A, Miquel R, Delgado P, et al. Heart valve calcification and calcium × phosphorus product in hemodialysis patients: Analysis of optimum values for its prevention. Kidney Int 2003; 63(Suppl 85): 115–18.

30. Zebe H. Atrial fibrilation in dialysis patients. Nephrol Dial Transplant 2000; 15(6): 765–8.

31. Aronow WS. Acute and Chronic Management of Atrial Fibrilation in Patients With Late-Stage CKD. Am J Kidney Dis 2009; 53(4): 701–10.

32. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of Elevated Serum PO_4, Ca × PO_4 Product, and Parathyroid Hormone with Cardiac Mortality Risk in Chronic Hemodialysis Patients. J Am Soc Nephrol 2001; 12(12): 2131–8.

33. Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality Effect of Coronary Calcification and Phosphate Binder Choice in Incident Hemodialysis Patients. Kidney Int 2007; 71(5): 438–41.

34. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis. J Am Soc Nephrol 2004; 15(8): 2208–18. (27)

35. De Broe ME. Phosphate: despite advances in research, the benefits to patients remain limited. Kidney Int 2009; 75(9): 880–1.

36. Wolf M. Forging Forward with 10 Burning Questions on FGF in Kidney Disease. J Am Soc Nephrol 2010; 21(9): 1427–35.

37. Hutchison AJ. Oral phosphate binders. Kidney Int 2009; 75(9): 906–14.

38. Chertow GM, Blumenthal S, Turner S, Roppolo M, Stern L, Chi EM, et al. Cinacalcet Hydrochloride (Sensipar) in Hemodialysis Patients on Active Vitamin D Derivatives with Controlled PTH and Elevated Calcium × Phosphate. Clin J Am Soc Nephrol 2006; 1(2): 305–12.

39. Chertow GM, Pupim LB, Block GA, Correa-Rotter R, Drueke TB, Floege J, et al. Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): Rationale and Design Overview. Clin J Am Soc Nephrol 2007; 2(5): 898–905.

40. Messa P, Macario F, Yaqoob M, Bouman K, Braun J, Von Albertini B, et al. The OPTIMA Study: Assessing a New Cinacalcet (Sensipar/Mimpara) Treatment Algorithm for Secondary Hyperparathyroidism. Clin J Am Soc Nephrol 2008; 3(1): 36–45.

41. Bushinsky DA, Messa P. Efficacy of Early Treatment with Calcimimetics in Combination with Reduced Doses of Vitamin D Sterols in Dialysis Patients. NDT Plus 2008; 1(Suppl 1): 18–23.

42. Eddington H, Klara PA. The association of chronic kidney disease-mineral bone disorder and cardiovascular risk. J Ren Car 2010; 36(Suppl 1): 61–7.

43. Kanabay M, Afsar B, Goldsmith D, Covic A. Sudden Death in Hemodialysis: An Update. Blood Purif 2010; 30(2): 135–45.

Received: December 21, 2011

Accepted: January 23, 2012