ASSOSIATION BETWEEN PARAMETERS OF MINERAL BONE METABOLISM AND SURVIVAL IN PATIENTS UNDERGOING CHRONIC HEMODIALYSIS

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Beside the traditional risk factors which have an effect on cardiovascular diseases, hemodialysis patients are exposed to metabolic factors, such as malnutrition, micro-inflammation and oxidative stress, along with mineral bone disorder.

The aim of this study was to determine a three-year survival in patients undergoing chronic hemodialysis and to analyse correlation with parameters of mineral bone metabolism.

During the three-year follow-up 186 patients were included, of which 115 men (61.83%) and 71 women, with a mean age 61.47±12.42. The exact date and the direct cause of death were recorded and mineral bone metabolism parameters were analysed.

Out of 67 dead patients, 33 (49.25%) died from cardiovascular cause. Out of the total number of deaths in our study, only 11.9% of patients had a target PTH values. Patients with PTH>600 pg/ml are exposed to an increased risk from the overall mortality (RR=0.48, 95% CI (0.24-0.95), p=0.04), but also from cardiovascular mortality (RR=0.34, 95% CI (0.12-0.93), p=0.034) compared to patients with normal serum PTH. These patients have a statistically significant higher serum phosphorus in comparison with patients with normal PTH levels (1.72±0.42 vs. 1.39±0.36, p=0.032). Phosphorus above 2.10 mmol/L increases the relative risk for the overall mortality rate by 60% (RR=0.59, 95% CI (0.35-0.89), p=0.049). In our study, 2-fold higher risk of all-cause mortality (RR=2.00, 95% CI (0.92-4.36), p=0.048), and even 3-fold higher risk of cardiovascular mortality (RR=3.03, 95% CI (0.71-1.29), p=0.039) were found in patients with CaxP levels above 4.50 mmol^2/L^2.

Three-year mortality rate of patients undergoing hemodialysis was 36.02%, while half of the patients died from cardiovascular disease. Patients with hyperparathyroidism and elevated calcium phosphorus product are at the highest risk, both for all-cause and cardiovascular mortality. Patients with hyperphosphatemia are at higher risk for all-cause mortality. *Acta Medica Medianae 2015;54(4):37-45.*

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Introduction

Ten percent of the population worldwide is affected by chronic kidney disease (CKD) (1). The number of patients in the terminal stage of CKD has been constantly increasing, and accordingly the number of patients on regular hemodialysis program. Annual growth rate in patients on dialysis is about 5-8%, therefore, these patients represent a major medical and socio-economic problem in the world (2).

A large number of complications as well as renal replacement techniques can lead to a significant reduction quality of life in patients on hemodialysis. Five-year survival in these patients is approximately 40% (3). The risk of developing cardiovascular disease (CVD) is 10 to 20 times higher compared to the general population (4).

Besides the traditional risk factors which have an effect on cardiovascular diseases, hemodialysis patients are also exposed to metabolic factors, such as malnutrition, microinflammation and oxidative stress, along with mineral bone disorder (5-8).

Changes in the metabolism of calcium, phosphorus, parathyroid hormone (PTH) and vi-

tamin D are common consequences in chronic kidney disease mineral bone disorder (CKD-MBD). Vascular calcification within the CKD-MBD represents a significant predictor of mortality in these patients (9).

Intima calcification of the coronar arteries leads to the artery lumen narrowing and blood flow reduction with ischemic myocardium, while the rupture of atherosclerotic plaque leads to the development of acute coronary syndrome. Calcification of the media results in arteriy elasticity reduction and subsequent left ventricle hypertrophy (LVH) (10). Valvular calcifications give rise to mitral and aortic stenosis. Secondary hipreparatireoidizam, hyperphosphatemia, and high values of calcium phosphorus products in patients undergoing hemodialysis, have a crucial role in the development of valvular calcification. However, hyperphosphataemia within adynamic bone disease may have a significant contribution to the development of valvular calcification (11). Calciphilaxis represents a specific type of vascular calcifications in dialysis patients, characterized by diffuse media calcification and proliferation of small and medium-sized arteries and arterioles (12). The result is calcium phosphorus product increasing, followed by hypercoagulability, skin ulceration and peripheral gangrene.

Coronary artery calcification have a high prevalence in patients on hemodialysis. Electron beam computed tomography (EBCT) and multi slice computed tomography (MSCT) are used for the assessment of calcium in the coronary arteries. Patients with coronary artery calcification score ≥400 have a lower survival rate compared to the patients without coronary artery calcification (13).

Early detection of risk factors and timely application of appropriate therapy significantly reduces cardiovascular morbidity and increases survival and quality of life in patients on hemodialysis.

Aim

The aim of this study was to determine a three-year survival in patients undergoing chronic hemodialysis and to analize correlation with parameters of mineral bone metabolism.

Patients and Methods

Prospective observational study was conducted at the Clinic of Nephrology, Clinical Center Niš. The principles of evidence-based medicine were respected. The study included 186 patients, 115 men (61.83%) and 71 women, mean age 61.47±12.42 years, with terminal renal failure undergoing hemodialysis treatment for more than three months. The excluding criteria were: patients with changed treatment modality, transplanted patients, patients with renal function recovery, these who left the dialysis center and patients undergoing hemodialysis treatment less

than 3 months. We have monitored patients for 36 months. At baseline, data were collected from medical records while blood samples were taken before the initiation of dialysis sessions.

During the follow-up the exact date and the direct cause of death were recorded, according to which all patients were divided into two groups. Cardiovascular mortality included deaths attributed to sudden cardiac death, ischemic heart disease, heart rhythm disorders, cerebrovascular disease and heart failure. All-cause mortality included deaths attributed to sepsis, gastrointestinal bleeding, malignancy and liver cirrhosis. The following parameters were evaluated: sex and age structure, hemodialysis vintage, haematological and biochemical parameters.

Routine laboratory analyses were performed on the Automatic biochemistry analyzer Erba XL-600 (Erba diagnostics Mannheim, GmbH, Germany). Number of leukocytes, erythrocytes, platelets and hemoglobin were analyzed on haematology analyzer Nihon Koden (Japan). C-reactive protein serum levels were determined using immuno-turbidimetric method, on Olympus AU-600 automated analyzer (Olympus Diagnostic, GmbH, Germany). Determination of intact PTH was performed by immuno-radiometric analysis (IRMA) on LKB gamma counter.

Dialysis adequacy was evaluated by Kt/V index, calculated according to the following formula: $Kt/Vsp = -\ln(C2/C1 - 0008xT) + (4 - 3.5xC2/C1)xUF/W$, where: C1-the predialysis urea value (mmol/L), C2-postdialysis urea value (mmol/L), T-hemodialysis duration (h), UF-interdialysis yield (L), W-body weight after hemodialysis sesion (kg). Serum calcium was corrected for serum levels of albumin with the following formula: corrected calcium (CaALB)=total calcium+((40-albumin concentration)x0.02).

Based on the PTH values patients were subgrouped: first group <150 pg/ml, second group 151-300 pg/ml, third group 301-600 pg/ml and fourth group>601 pg/ml of PTH.

Statistical analysis was performed using the statistical package SPSS software version 16.0 (SPSS Chicago, IL, USA). A value for $p<0.05$ was considered statistically significant. We compared clinical and biochemical data using the t-test for normally distributed data (expressed as mean ±SD) and Mann-Whitney U test for data that were not normally distributed. One way analysis of variances (ANOVA) with Boniferroni post hoc test and Kruskal-Wallis test for not normally distributed data was used for comparison three and more groups. Relative risk (RR) was determined.

Results

Addition 1.

Table 1 shows demographic and laboratory characteristics of survived patients, and patients who died from all-cause and cardiovascular causes. Survived patients were significantly younger

Table 1. Demographic and laboratory characteristics of hemodialysis patients

	Surviving patients	All-cause Mortality	Cardiovascular mortality
Number of patients (%)	119 (63.98)	67 (36.02)	33 (17.74)
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	$\bar{x} \pm SD$
Age (*years*)	59.43±12.45	65.10±11.59 [A]	66.64±9.87 [C]
HD vintage (*months*)	62.49±62.93	62.96±70.28	55.03±52.35
Calcium (*mmol/L*)	2.34±0.24	2.34±0.21	2.36±0.23
Ca×P product ($mmol^2/L^2$)	3.59±1.16	3.82±1.22	3.83±1.17
Phosphorus (*mmolL*)	1.53±0.47	1.64±0.52	1.64±0.53
Corected calcium (*mmol/L*)	2.41±0.24	2.45±0.20	2.44±0.22
PTH (*pg/mL*)	388.59±1385.68	305.23±348.26	289.18±298.66
Alkaline phosphatase (*IU/L*)	91.93±72.32	93.43±62.35	90.64±46.52
Albumin (*g/L*)	36.66±2.59	34.75±4.04 [B]	35.60±3.71
CRP (*mg/l*)	9.91±18.65	13.10±15.98 [A]	13.04±16.14
Kt/V	1.33±0.28	1.25±0.25	1.31±0.22

[A] $p < 0.05$ Surviving patients compared to all-cause mortality
[B] $p < 0.001$ Surviving patients compared to all-cause mortality
[C] $p < 0.05$ Surviving patients compared to cardiovascular mortality

±11.59 vs. 59.43±12.45, p=0.003) and also from cardiovascular cause (66.64±9.87 vs. 59.43± 12.45, p=0.003). Albumin concentration was significantly higher (34.75±4.04 vs. 36.66±2.59, p=0.001) while the concentration of CRP was significantly lower among survived patients (13.10 ±15.98 vs. 18.65±9.91, p=0.050) compa-red to the patients who died from all-cause. There were no statistically significant differences in para-meters of bone mineral metabolism among stu-died groups.

Addition 2.

In the three-year follow-up period, of the total number of deaths (67; 36.02%), 33 patients (49.25%) died from cardiovascular diseases (Table 2).

Table 2. Mortality rate of patients

	All-cause mortality (%)	Cardiovascular mortality (% of deaths patients)
1-year mortality rate	15.05	50.00
2-year mortality rate	28.49	49.06
3-year mortality rate	36.02	49.25

Addition 3.

There was no statistically significant dif-ference in the number all-cause deaths, neither of KVS mortality. Parameters of mineral and bone metabolism show statistically significant differen-ces compared to the PTH group.

Addition 4.

The Figure 1.shows the Kaplan-Meier sur-vival curves in relation to the values of PTH. Patients with values of PTH>601 pg/ml had the shortest survival for all cause mortality but with-out statistical significance in relation to the other groups of PTH (Log Rank (Mantel-Cox)=6.008; p=0.111) (Figure 1.A, Table 4.A). Similar situa-tion is found for cardiovascular mortality (log rank (Mantel-Cox)=61.432; p=0.698) (Figure 1.B, Ta-ble 4.B).

Addition 5.

Our results have shown that the risk of cardiovascular mortality was higher for 34% (RR=0.34, 95% CI(0.12-0.93), p=0.034) and 48% of all-cause mortality (RR=0.48,95% CI (0.24-0.95), p=0.04) with PTH levels above 600 pg/ml compared to the referent group (151-300 pg/ml) (Figure 2.B). Patients with values of P>2.10 mmol/L have a higher risk of 59% of overall mortality (RR=0.59, 95% CI (0.35-0.89), p=0.049) (Figure 2.C). Calcium phosphorus product over 4.50 $mmol^2/L^2$ provides 2-fold higher risk of all-cause mortality (RR=2.00, 95% CI (0.92-4.36), p=0.048) (Figure 2.A), and more than 3–fold risk of cardiovascular mortality (RR=3.03, 95% CI (0.71-1.29), p=0.049) (Figure 2.H).

Discussion

Mineral bone metabolism disorder occurs in the early stages of CKD and constantly increases with kidney failure. Changes in vitamin D and PTH concentrations with consequent disbalance in the metabolism of calcium and phosphorus are main disturbances which are evident. This disorder

Addition 3.

Table 3. Mortality and parameters of bone and mineral metabolism according to
parathyroid hormone levels

PTH (*pg/mL*)	<150	151-300	301-600	>601	p value	post hock[*]
Number of patients (%)	91 (48.9)	33 (17.7)	38 (20.4)	24 (12.9)	<0.001	
	n (%)	n (%)	n (%)	n (%)		
All-cause mortality	34 (50.7)	8 (11.9)	13 (19.4)	12 (17.9)	0.246	
Cardiovascular mortality	16 (48.5)	4 (12.1)	8 (24.2)	5 (15.2)	0.770	
	$\bar{x}$±SD	$\bar{x}$±SD	$\bar{x}$±SD	$\bar{x}$±SD		
Calcium (*mmol/L*)	2.39±0.24	2.24±0.21	2.24±0.22	2.43±0.17	<0.001	A, B, E, F
Corrected calcium (*mmol/L*)	2.78±0.22	2.32±0.22	2.32±0.23	2.52±0.33	<0.001	A, B, E, F
Phosphorus (*mmolL*)	1.68±0.55	1.39±0.42	1.54±0.43	1.73±0.36	0.043	A, B, E
Ca×P product (*mmol²/L²*)	3.84±1.34	3.12±0.93	3.43±0.97	4.18±0.79	0.002	A, E
Alkaline phosphatase (*IU/L*)	64.08±21.11	87.64±55.83	112.54±44.40	175.00±133.21	<0.001	B, C, E, F

[*]A (I vs. II), B (I vs. III), C (I vs. IV), D (II vs. III), E (II vs. IV), F (III vs. IV).
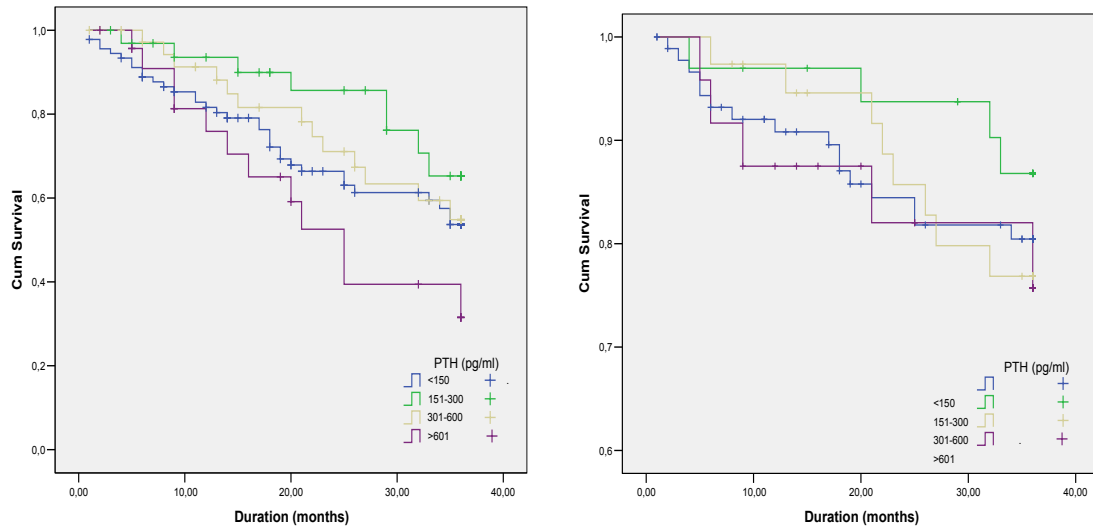
Addition 4.

Figure 1. Kaplan-Meier curves for all-cause mortality according to PTH levels (A), Kaplan-Meier curve for
cardiovascular mortality according to PTH levels (B)

Table 4. Three-year survival compared to the values of PTH – all cause mortality (A), cardiovascular mortality (B)

PTH (*pg/ml*)	$\bar{x}$±SG	95% CI	p
<150	27.02±1.33	24.40-29.63	
51-300	31.61±1.57	28.53-34.69	0.111
301-600	29.99±1.75	25.57-32.42	
>601	23.68±2.71	18.38-28.99	

A

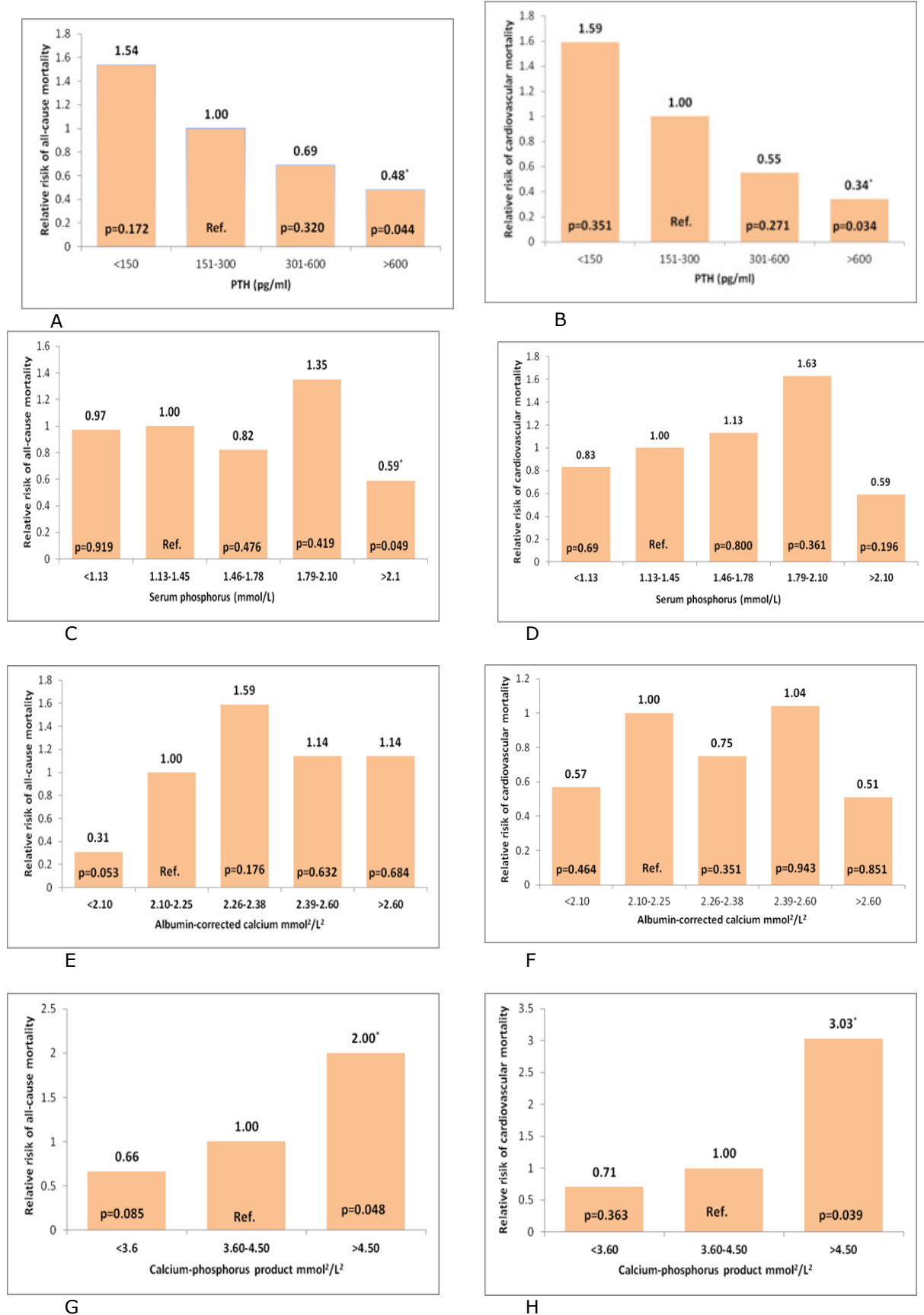| PTH (*pg/ml*)	$\bar{x}$±SG	95% CI	p
<150	31.79±1.03	29.78-33.81	
151-300	34.27±1.08	32.17-36.37	0.698
301-600	32.65±1.19	30.32-34.96	
>601	31.51±2.32	26.96-36.07	

B

Addition 5.

Figure 2. Association between all-cause mortality and cardiovascular mortality with categorical measures of the mineral metabolism indicators: PTH (A and B), phosphorus (C and D), albumin-corrected calcium (E and F) and calcium phosphorus product (G and H)

leads to a long-term consequences that include changes in bones (renal osteodystrophy), immune and hematopoietic systems, as well as in vessel (calcification) and the entire cardiovascular system structure and function (14, 15). In our study of 186 patients, in the three-year follow-up period, 36.02% of the patients died. Out of the total number of deaths, 49.25% died from some cardiovascular cause (Table 2.). In a previous study (16) that included 225 patients on hemodialysis, the overall mortality rate was 37.0%, while specific mortality rate from cardiovascular disease was 63.8%. Other studies demonstrated smilar survival in population of hemodialysis patients (17, 18). The demographic characteristics of our patients were similar to other studies. Men were more frequent, with 61.83%, compared to the COSMOS study 59.7%, ARO study 7.9% and DOPPS study (19-21). The mean age of our patients was 61.47±12.42 years, similar as in other studies (19-23). Thus, our data support the hypothesis that this population is characterized by high mortality rate, especially from cardiovascular diseases as a main cause of death.

Parathyroid hormone, uremic cardiotoxin, has a significant role in the pathogenesis of cardiovascular disease. Out of the total number of deaths in our study, only 11.9% of patients had a target PTH values (Table 3.). Left ventricular hypertrophy (LVH) has been reported in over 80% of patients on dialysis (24, 25). High prevalence of hypertension, anemia, hypoalbuminemia and arteriovenous fistula have an independent effects in hemodialysis patients, but at the same time acts synergistically in the development of LVH (26). Previous studies have demonstrated significant correlation between left ventricular mass and the serum PTH level (27). In this regard, some experimental models studied the effects of PTH on cardiomyocytes, endothelial cells, and vascular smooth muscle cells. It was found that parathyroid hormone-related peptide (PTH-rP), a peptide hormone structurally related to PTH, is expressed in various tissues including the heart. Stimulation of PTH receptors act as a paracrine or endocrine modulator in cardiovascular organs. PTH and PTH-rP activates protein kinase C in adult cardiomyocytes, with a consequent increasing in protein synthesis, increasing the mass of the protein, and reexpression of fetal proteins (28). Clinical studies justifying the application of this hypothesis to cardiomyocytes *in vivo*. Namely, after parathyroidectomy, in patients with extremely high serum PTH levels and accelerated left ventricular mass, a marked reduction of both mentioned pa-rameters occured (29).

Our results have shown that patients with PTH>600 pg/ml are exposed to an increased risk from the overall mortality (RR=0.48, p=0.04), but also from cardiovascular mortality (RR=0.34, p=0.034) compared to patients with normal serum PTH (Figure 2.A and B). These patients have a statistically significant higher serum phosphorus in comparison with patients with normal PTH levels

(1.72±0.42 vs. 1.39±0.36, p=0.032) (Table 3). The analysis of the Kaplan-Meier survival curves of these in relation to the values of PTH has shown that patients with PTH values >601 pg/ml, had the shortest survival both for general as well as for cardiovascular mortality, but without statistically significance different than the other groups PTH (Figure 1.A and B, Table 4.A and B).

Hyperphosphatemia has a notable role in initiating the process of calcification inside the media of coronary arteries. The accumulation of phosphorus in the area of smooth-muscle cells enables vascular osteogenic cells transformation. Increased activity of the Na^+/PO_4^{3-} cotransporter (especially NPC-type III sodium – dependent phosphate uptake system) leads to the increased phosphorus concentration in smooth-muscle cell arteries. Core Binding Factor α-1 (CBF α-1), a transcription factor, is stimulated further to induce differentiation into cells similar to osteoblasts, and so begins the process of left ventricular remodeling, which greatly contribute to hypertension and anemia (30,31). In our study, P>2.10 mmol/L increases the relative risk for the overall mortality rate by 60% (RR=0.59, p=0.049) (Figure 2.C).

Arterial lesions in patients with terminal renal failure are much different from the formed atherosclerotic plaques lesions in the general population. A typical atherosclerotic plaque has the appearance of atheromatous or fibro-atheromatous plaque with prominent lipid accumulation while dialysis patients have calcified plaque (32). Table 3. shows that albumin-corrected calcium values were significantely elevated in the group of patients with PTH>600 pg/ml (2.25±0.33 vs. 2.32±0.22, P<0.001) as well as in the group with PTH<150 pg/ml (2.78±0.22 vs. 2.32±0.22, p=0.001) compared with normal PTH level. This speaks in favor that adynamic bone disease, with increased levels of calcium and phosphorus, represents a significant risk factor for mortality, regardless of the low value of PTH. In the group of patients with PTH<150 pg/ml was the highest percentage of deaths, both from the overall and cardiovascular mortality, but with no statistically significant differences (Table 3.).

Numerous studies have emphasised the connection between increased values of Ca×P product and reduced survival in patients with CKD. The study of Ganesh et al. (33) have found a linear relationship between Ca×P product and sudden cardiac death. Similarly, Block et al. (34) have shown that the increase in Ca×P product was associated with a higher risk of the overall mortality and all-cause hospitalization, while Young et al. showed correlation with both general and cardiovascular mortality (35), in patients on hemodialysis. However, in predialysis patients the product of Ca×P remain an independent predictor for cardiovascular morbidity, but also shows association with hypertension, dyslipidemia, micro-inflammation, hyperhomocysteinemia, LVH and oxidative stress (36). In our study, 2-fold higher risk of all-cause mortality (RR=2.00, p= 0.048)

and even 3-fold higher risk of cardio-vascular mor-tality (RR=3.03, p=0.039) was found in pa-tients with Ca×P levels above 4.50 mmol^2/L^2 (Figure 2.G and H). Ca×P product was statistically higher in patients with hyperparathyroidism (4.18 ±0.79 vs. 3.12±0.93, p<0.001) and in patients with low values of serum PTH (3.84±1.34 vs. 3.12±0.93, p=0.011) (Table 3).

Despite significant progress in dialysis pro-cedure improving and more accessible medical therapy, the mortality rate in dialysis patients re-mains unacceptably high. Management of pati-ents undergoing hemodialysis is a complex pro-sess, hence it requires a higher number of multi-center studies the primary goal of which should be a better understanding of pathophysiological me-chanisms of cardiovascular events.

Conclusion

A three-year mortality rate of patients undergoing hemodialysis was 36.02%, while half of the patients died from cardiovascular disease. Patients with hyperparathyroidism and elevated calcium phosphorus product are at the highest risk, both for all-cause and cardiovascular mortality. Patients with hyperphosphatemia are at higher risk for all-cause mortality.

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POVEZANOST PARAMETARA MINERALNO-KOŠTANOG METABOLIZMA I PREŽIVLJAVANJA BOLESNIKA NA HRONIČNOM PROGRAMU HEMODIJALIZE

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Pored tradicionalnih faktora rizika koji utiču na etiopatogenezu kardiovaskularnih bolesti, bolesnici na hemodijalizi su izloženi i metaboličkim faktorima, gde pored malnutricije, mikroinflamacije i oksidativnog stresa, značajnu ulogu ima i poremećaj mineralno-koštanog metabolizma.

Cilj rada bilo je trogodišnje praćenje preživljavanja i analiza povezanosti parametara mineralno-koštanog metabolizma sa preživljavanjem bolesnika na hroničnom programu hemodijalize.

Tokom 36 meseci praćeno je 186 bolesnika, 115 muškaraca i 71 žena, prosečne starosti 61,47±12,42 godine. Beležen je datum smrti, neposredni uzrok smrti i analizirani parametri mineralno-koštanog metabolizma.

Preminulo je 67 bolesnika, kod 33 bolesnika (49.25%) neposredni uzrok smrti bio je kardiovaskularni događaj. Od ukupnog broja umrlih, samo njih 11,9% imalo je ciljne vrednosti PTH-a. Bolesnici sa vrednostima PTH>600 pg/ml su u povećanom riziku za opšti mortalitet (RR=0,48, 95% CI (0,24-0,95), p=0,04), ali i za kardiovaskularni mortalitet (RR=0,34, 95% CI (0,12-0,93), p=0,034). Ovi bolesnici imaju značajno veće vrednosti fosfora u poređenju sa bolesnicima koji imaju normalne vrednosti PTH-a (1,72±0,42 vs. 1,39±0,36, p=0,032). Vrednosti fosfora veće od 2,10 mmol/L povećavaju relativni rizik za opštu smrtnost za 60% (RR=0,59, 95% CI (0,35-0,89), p=0,049). Bolesnici sa vrednostima proizvoda CaxP>4,50 mmol^2/L^2 imaju dva puta veći rizik za opštu smrtnost od bolesnika sa normalnim vrednostima CaxP (RR=2,00, 95% CI (0,92-4,36), p=0,048) i čak tri puta veći rizik za kardiovaskularni mortalitet (RR=3,03, 95% CI (0,71-1,29), p=0,039).

Trogodišnja stopa smrtnosti bolesnika na hroničnom programu hemodijalize je 36,02%, polovina od ukupnog broja bolesnika umire od kardiovaskularnih bolesti. Bolesnici sa hiperparatireoidizmom i oni sa povišenim vrednostima proizvoda kalcijum fosfora imaju najveći rizik, kako za opštu tako i za kardiovaskularnu smrtnost, dok bolesnici sa hiperfosfatemijom imaju povećan rizik od opšte smrtnosti. *Acta Medica Medianae 2015;54(4):37-45.*

Ključne reči: *hemodijaliza, preživljavanje, kardiovaskularni mortalitet, mineralno-koštani metabolizam*