

THE IMPACT OF SECONDARY HYPERPARATHYROIDISM ON ECHOCARDIOGRAPHIC PARAMETERS IN HEMODIALYSIS PATIENTS

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Cardiovascular diseases are the leading cause of mortality in hemodialysis patients. Patients are exposed to a number of risk factors for cardiovascular complications, which are the result of uremia and dialysis. Aim of our study was to examine the incidence of secondary hyperparathyroidism and left ventricular hypertrophy, the interplay between them as predictors of mortality. This prospective study included 53 patients. All patients had measured echocardiographic parameters of left ventricular hypertrophy and laboratory parameters of bone metabolism. We followed the death rate of patients over two years. Elevated levels of PTH in the serum was present in 79.24% of patients, hypertrophy of the left chamber was recorded in 81.13% of patients. The survivors had lower values of PTH and phosphate levels which were significantly lower ($p < 0.05$) in relation to deceased patients. Patients with poor outcome had higher LV mass index, lower EF and FSLV, larger diameters of interventricular septum and posterior wall ($P < 0.05$). Left ventricular hypertrophy is premature cardiovascular disorder that develops rapidly during the progression of CKD and is based of uremic cardiomyopathy. Left ventricular hypertrophy is a strong indicator of mortality in patients with ESRD.

Key words: PTH, echocardiographic parameters, cardiovascular disease, hemodialysis.

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INTRODUCTION

Patients with the end-stage renal disease (ESRD) have a high mortality rate^(1,2) that far exceeds the mortality rate for the non-ESRD population⁽³⁾. Cardiovascular diseases are the leading cause of death in patients on hemodialysis (HD). The annual mortality rate from cardiovascular disease (CVD) in these patients is 9%. Cardiovascular system in HD patients is affected by a number of well-known risk factors (RF) dependent of uremia and dialysis. All these RF predisposing to atherosclerosis, which underlies CVD⁽⁴⁾.

The high risk of cardiovascular morbidity and mortality in ESRD patients is associated with a high prevalence of classic cardiovascular RF (hypertension, diabetes mellitus, dyslipidemia, smoking, and advanced age). In addition, several uremia-related factors may also play an important role, namely, the presence of multiple comorbid conditions, fluid overload, secondary hyperparathyroidism (SHPT), hyperphosphatemia, high

calcium-phosphorous product, anemia, left ventricular hypertrophy (LVH), inflammation, oxidative stress, endothelial dysfunction, insulin resistance, hyperhomocysteinemia, high levels of lipoprotein(a) and increased asymmetrical dimethylarginine⁽⁵⁻⁸⁾.

Disruption of calcium and phosphate metabolism occurs when the level of glomerular filtration rate (GFR) falls below 60 ml/min. With the decline of GFR is reduced formation of the active metabolite of vitamin D (calcitriol). This results in decreased reabsorption of calcium from the gastrointestinal tract, and an increased secretion of the parathyroid hormone (PTH). Increased phosphate concentration in the serum stimulates the parathyroid gland to produce and secrete increased PTH and this has resulted in the development of SHPT^(9,10). SHPT contributes to the development of vascular and valvular calcification and cardiovascular complications. Calcification of the arteries can affect intima and/or medium arterial walls of blood vessels and is associated with an increased deposit of calcium in atherosclerotic plaques,

increase in arterial stiffness, the development of ischemic heart disease and concentric LVH⁽¹¹⁾. Elevated phosphate levels is important in triggering artery calcification of media^(12,13). Clinical trial results indicate a correlation between hyperphosphatemia, increased product solubility and left ventricular mass index (LVMI). Patients on HD are at higher risk for sudden cardiac death⁽¹⁴⁾.

The aim of this study was to determine the prevalence of left ventricular hypertrophy, dilatation and systolic dysfunction, prevalence of SHPT and the impact of SHPT on left ventricular remodeling and cardiovascular morbidity. Furthermore, we aimed to determine other cardiovascular mortality predictors in patients on regular HD.

METHODS

The study included 53 patients (25 men and 28 women) treated with regular HD three times a week for four hours in Haemodialysis center/Nephrology department of Clinical center of Montenegro. Investigation included hemodynamically stable patients with different primary kidney disease. Patients were followed prospectively for two years.

During the examination analyzed parameters were: gender and age structure of patients, PTH and bone-mineral metabolism, homocysteine(Hcy), high-sensitive C-reactive protein (hsCRP), nutritional (albumins) and dialysis parameters (KT/V), serum lipid levels, natriuretic brain peptid(BNP), level of anemia and anthropometric parameters. We analyzed the echocardiographic parameters of the left ventricle: LVMI (g/m^2), end-diastolic left ventricular volume index-iEDVLV, posterior wall (PWLVD) and interventricular septum diameter (IVSd) of left ventricle, ejection fraction of left ventricle- LVEF and left ventricular fractional shortening- FSLV. PTH (11-67 pg/ml) was determined from serum on automated system IMMULITE 2000, chemiluminescent immunoassay. Calcium (Ca 2.15-2.55 mmol/l, Schwarzenbach method), phosphate (Phos 0.74-1.52 mmol/l, phosphometric method), Alkaline phosphatase (Alp 40-129 U/l men, 35-104 U/l women, colorimetric method), Albumin (Alb 35.6-46.1 g/l, immunoturbidimetric test), cholesterol (CHOL, 3.80-5.17 mmol/l), triglycerides (TRIG, 0.00-1.69 mmol/l), low density lipoproteins (LDL, 0.00-3.90 mmol/l) and high density lipoproteins (HDL, 0.9-1.45 mmol/l) were performed from the serum of the appliance Roche Integra 400. Lipidogram was determined using enzymatic colorimetric test. Blood parameters were performed on the hematology analyzer Cell-Dyn 3700 (Abbott). NTproBNP was performed from serum on automated system IMMULITE 2000, chemiluminescent immunometric assay (ref. values 0.0-53.1 pmol/l).

Echocardiography was performed on the appliance Philips, the probe of 2.5 MHz transthoracic approach. LVH was determined by measuring LVMI:

$$\text{LVMI} = (0.00083x ((+ \text{EDDLK IVSd ZZLKd} +) - (\text{EDDLK} 2) + 0.6) / \text{TP g}/\text{m}^2$$

The volume of left ventricle is calculated by the following formula:

$$\text{iEDVLV} = ((\text{EDDLK}) x 0.001047 3) / \text{TP ml}/\text{m}^2$$

LVEF is calculated on the basis of the following formula:

$$\text{LVEF}(\%) = (\text{EDVLV} - \text{ESVLV}) / \text{EDVLV} x 100\%$$

(ESVLV - end-systolic left ventricular volume, EDVLV - end-diastolic left ventricular volume, EDVLV- end-diastolic ventricular volume)

Left ventricular fractional shortening (FSLV) is calculated on the basis of the following formula:

$$\text{FSLV} = (\text{EDDLK} - \text{ESDLK}) / \text{EDDLK} x 100\%$$

Normal values of echocardiographic parameters were: LVMI is $\leq 131 \text{ g}/\text{m}^2$ for men and $\leq 100 \text{ g}/\text{m}^2$ in women, iEDVLV is $\leq 90 \text{ mL}/\text{m}^2$, LVEF $67 \pm 9\%$ and FSLV $42 \pm 8\%$. Systolic dysfunction is defined as a FSLV $\leq 25\%$ and LVEF $\leq 50\%$. LVH is defined as the thickness of IVSd $> 11 \text{ mm}$, PWLVd $> 11 \text{ mm}$, LVMI $> 131 \text{ g}/\text{m}^2$ in men $> 100 \text{ g}/\text{m}^2$ in women. Left ventricular dilatation is defined as the inner diameter of the LV end-diastolic $> 57 \text{ mm}$, and LV volume $> 90 \text{ mL}/\text{m}^2$, with normal systolic function and normal left ventricular mass index. Adequacy of dialysis was evaluated based on Kt/Vsp calculated according to following formula

$$\text{Kt} / \text{Vsp} = -\ln (C2 / C1 - 0.008 x T) + (4 - 3.5x C2 / C1) x \text{UF} / \text{W}$$

where: C1 - predialysis urea value, C2 - postdialysis value of urea (mmol/L), T - duration hemodialysis (h), UF - between dialysis yield (l), W - body weight after hemodialysis (kg).

For the statistical analysis we used Student's t test and Spearman's rank test, using IBM SPSS 20. The threshold of significance was $p < 0.05$.

RESULTS

Our investigation included 53. patients undergoing dialysis. The average age was 56.47 ± 11.79 years and average time on dialysis 5.33 ± 4.48 years. General patients data are shown in Table 1.

According to the monitoring of patients in the two-year period, patients were divided into two groups: alive group (41 patients) and deceased group (12 patients). In our study total biannual mortality was 22.64%.

In group of deceased patients biannual mortality was 30% in patients with CKD and DM, 16.5% in patients with hypertensive nephroangiosclerosis, 37.5% IN CKD

caused with polycystic kidney disease and 75% in endemic nephropathy CKD.

The patients with poor outcome had significantly lower hemoglobin(Hgb) levels, lower levels of albumin and higher brain natriuretic peptide($p < 0.05$). Furthermore, deceased patients had lower levels of total CHOL and LDL, higher levels of serum Trig and ferritin (Table 2).

Table 1.
General patients data

Patients data(total)		Xsr±SD	
Number (N)		53	
Age (Years)		56.47±11.79	
Time on dialysis (years)		5.33±4.48	
BMI (kg/m ²)*		23.53±3.65	
KT/Vsp indeks**		1.12±0.15	
Outcome			
Variables	Alive (41 patients) Xsr±SD	Deceased (12 patients) Xsr±SD	p
Gender (M/F)	20/21	5/7	0.664
Age (Years)	55.44±11.12	60.00±14.27	0.247
Time on dialysis (years)	5.45±4.81	4.91±3.50	0.716
BMI (kg/m ²)*	23.67±4.12	23.04±1.48	0.604
KT/Vsp index	1,13±0.16	1.10±0.10	0.603

*Body mass index

Figure 1.
The distribution of patients according to the LVMI

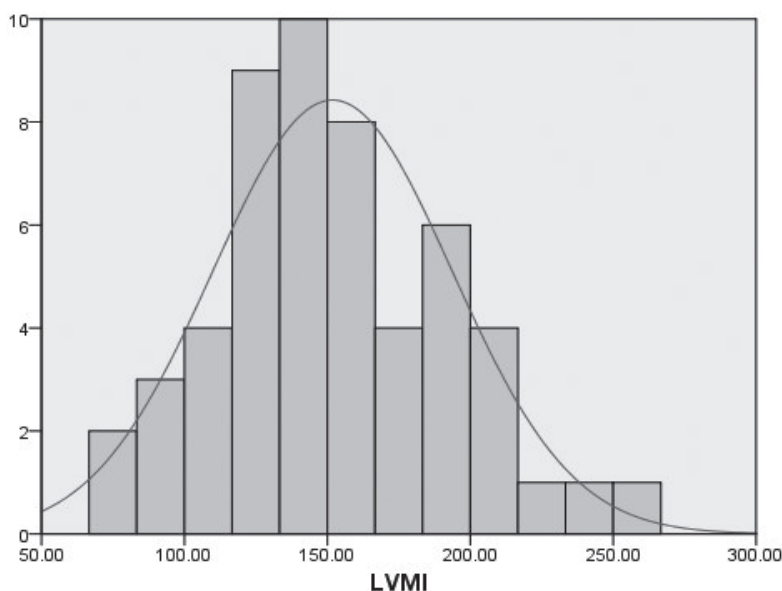


Table 2.
Basic patients parameters based on outcome during the two-year follow-up

Variables	Outcome		p
	Alive (41 patients) Xsrt±SD	Deceased (12 patients) Xsrt±SD	
Hgb (g/l)	104.50±14.12	94.50±15.46	0.040
Hematocrit (%)	0.33±0.04	0.30±0.04	0.031
MCV	91.79±6.37	86.9±8.13	0.035
Alb (g/l)	38.23±2.79	35.53±3.07	0.006
hsCRP (mg/l)	13.39±46.12	13.08±16.68	0.982
Hcy (µmol/l)	30.77±10.90	25.68±12.36	0.173
Total CHOL (mmol/l)	4.28±1.01	3.97±0.92	0.344
Trig (mmol/l)	1.40±0.59	1.51±0.64	0.576
LDL (mmol/l)	2.67±0.83	2.39±0.89	0.313
NT proBNP (pmol/l)	1274.41±1237.71	2200.97±1799.95	0.046
Feritin (µG/L)	74.60±69.18	100.85±100.22	0.303

Elevated PTH levels in serum was present in 42 (79.24%) patients. LVH had the 43 (81.13%) patients. Of them 18 (33.96%) patients had concentric LVH and 25 (47.16%) had eccentric LVH. Dilation of the left ventricle had 4 (7.54%) patients, while 6 (11.32%) had normal left ventricle. Disorder of systolic dysfunction (FSLK <25%) had 5 (9.43%) patients. Th distribution of patients according to the LVMi values is shown in Fig. 1.

Between the serum concentration of PTH and IVSd, LVPWd exists positive correlation ($p < 0.01$). Between concentrations of serum PTH and LVMi there is a positive correlation ($p < 0.05$). Between PTH levels and other echocardiographic parameters for the assessment of hypertrophy, dilatation and systolic function of the left ventricle there is no correlation ($p > 0.05$). (Figure 2.) (Table 3.)

Figure 2.
The correlation between PTH and LVMi values

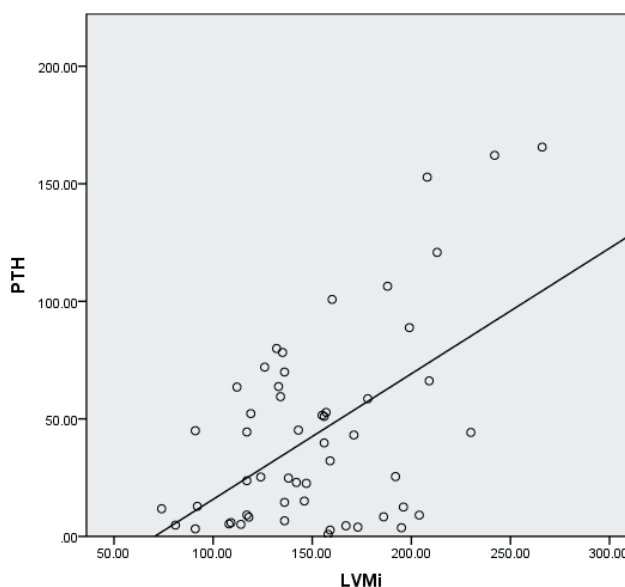


Table 3.

The relationship between PTH and echocardiographic parameters for the assessment of hypertrophy, dilatation and systolic function of the left ventricle

Test parameters	Xsr±Sd	Značajnost - p
LAd (mm)**	41.67±5.67	<i>p</i> _{emp} =0.287
PTH (pmol/l)	43.44±41.86	<i>p</i> =0.037 < 0.05
EDDLV (mm)***	55.24±6.47	<i>p</i> _{emp} =0.281
PTH (pmol/l)	43.44±41.86	<i>p</i> =0.041 < 0.05
ESDLV (mm)****	37.11±5.86	<i>p</i> _{emp} =0.164
PTH (pmol/l)	43.44±41.86	<i>p</i> =0.241 > 0.05
IVSd (mm)	11.90±1.62	<i>p</i> _{emp} =0.389
PTH (pmol/l)	43.44±41.86	<i>p</i> =0.004 < 0.01
PWLVD (mm)	11.60±1.56	<i>p</i> _{emp} =0.378
PTH (pmol/l)	43.44±41.86	<i>p</i> =0.005 < 0.01
RV (d/mm)*****	24.60±3.91	<i>p</i> _{emp} =0.430
PTH (pmol/l)	43.44±41.86	<i>p</i> =0.001 < 0.01
LVMi (g/m ²)	151.79±41.82	<i>p</i> _{emp} =0.315
PTH (pmol/l)	43.44±41.86	<i>p</i> =0.022 < 0.05
iEDVLV (ml/m ²)	101.49±32.32	<i>p</i> _{emp} =0.172
PTH (pmol/l)	43.44±41.86	<i>p</i> =0.218 > 0.05
FSLV (%)	33.03±6.34	<i>p</i> _{emp} =0.008
PTH (pmol/l)	43.44±41.86	<i>p</i> =0.952 > 0.05
LVEF (%)	64.54±8.20	<i>p</i> _{emp} =-0.026
PTH (pmol/l)	43.44±41.86	<i>p</i> =0.851 > 0.05

** left atrium diameter, *** left ventricular end-diastolic diameter,

**** left ventricular end-systolic diameter, ***** right ventricular diameter

Alive patients had lower PTH and lower values of Phos levels in relation to the deceased. The Phos levels are significantly lower in alive patients against the deceased patients (*p*<0.05). Considering echocardiographic parameters, patients with poor outcome had significantly higher LVMi, lower LVEF and FSLV, less IVSd and PWLVd(*p*<0.05) (Table 4).

DISCUSSION

Patients on HD are exposed to many traditional and tra-

ditional risk factors for CVD^(15,16). Non-traditional risk factors are consequences of uremic environment and can be connected also with the type of dialysis. These risk factors cause LVH and accelerate atherosclerosis, and that results in increased cardiovascular morbidity and mortality in patients on HD. The monitoring of risk factors for CVD, can significantly improve cardiovascular outcome in patients treated with HD.

Hemodialysis patients are often accompanied by SHPT, which consists of three components: hypocalcemia, hyperphosphatemia and calcitriol deficiency.

Table 4.

Echocardiographic parameters and calcium disorders parameters based on outcome during the two-year follow-up

Variables	Outcome		p
	Alive (41 patients) Xs±SD	Deceased (12 patients) Xs±SD	
PTH(pmol/l)	39.56±39.83	56.69±47.62	0.216
Ca(mmol/l)	2.31±0.31	2.33±0.23	0.0887
Phos(mmol/l)	1.72±0.39	2.07±0.49	0.025
Alk P(mmol/l)	81.59±68.68	90.58±99.39	0.721
LVMi(g/m ²)	145.56±39.06	173.08±45.60	0.044
iEDVLV(ml/m ²)	99.09±30.52	109.71±38.17	0.322
IVSd(mm)	11.51±1.59	12.58±1.31	0.039
PWLVD(mm)	11.36±1.59	12.41±1.64	0.039
LVEF(%)	66.05±7.68	60.61±5.72	0.028
FSLV(%)	34.30±5.97	29.66±3.84	0.014

This association plays an important role in causing cardiovascular disease, arterial calcification, disorders of the immune system, neurobehavioral changes and inadequate erythropoiesis⁽¹⁷⁾. Arterial calcification lead to an increase in afterload and consecutive result in remodeling of cardiac muscle in the direction of LVH. In patients with 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⁽¹⁸⁾. 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)⁽¹⁹⁾. Even with the increasing knowledge on phosphate metabolism and its role in renal failure patients, interventional measures are still limited. PTH has a permissive role for fibroblast activation and myocardial fibrosis. Thus, it has been observed that elevated PTH levels in ESRD cause irreversible interstitial fibrosis with collagen deposition⁽²⁰⁾.

The fact that progression of LVH was strongly linked to subsequent mortality and cardiovascular events independently of baseline LVMi and of a large series of traditional and emerging risk factors is of relevance because it indicates that assessing changes in LVMI is at least as important as estimating LVMI. Like in the study by Foley *et al*⁽²¹⁾, we found that LVH worsens with time. CVD is the most common cause of morbidity and mortality in patients on chronic HD. During the follow-up period, in our study, biannual mortality was 22.64%. Cardiovascular mortality in CKD patients is approxi-

mately 9% annually^(22,23). Our results are similar to the results of Sameiro-Faria and associated. In their study, during the follow-up period, 18.5% died⁽²⁴⁾.

In our study, the prevalence of SHPT was 79.24%, while the prevalence of SHPT in the works of Owda and associates was 79%⁽¹⁷⁾.

The prevalence of LVH in HD is high. In our study LVH had the 43 (81.13%) patients. Of them 18 (33.96%) patients had concentric LVH and 25 (47.16%) had eccentric LVH. Compared to our results, the Canadian Prospective Cohort Study 25, which followed 433 patients with terminal renal disease, 74% of patients had LVH, 35% had left ventricular dilatation, while 15% had systolic dysfunction. In the group of patients LVH, 44% had concentric, while 30% of patients had eccentric hypertrophy of the left chamber. Results of echocardiographic parameters of our patients were consistent with the results of Foley and associates, who followed 227. patients. In their study were given the following values of ultrasonography parameters: LVMi 161 (g/m²), iEDVLv 88 ml/m² and FSLv 34%⁽²¹⁾. In our study, those parameters are equalled LVMi 151.79 (g/m²), iEDVLv 101.49 mL/m² and FSLV 33.03%.

Concentric hypertrophy of left ventricular diastolic function disturbs the heart. As a consequence HD patients can have pulmonary edema and development of hypotension during hemodialysis⁽²⁶⁻²⁸⁾. Diastolic dysfunction occurs in 50-60% of patients treated with regular HD. When you increase the stiffness of the LV and LV load volume, significantly increase the pressure in it. A small increase of volume can be accompanied by the development of pulmonary capillary congestion and the development of pulmonary edema⁽²⁹⁾. In HD pa-

tients the risk of de novo development of ischemic heart disease is significantly higher if the LVMi >160 g/m², relative to LVMi <150 g/m². Concentric LV hypertrophy, LV dilatation and impaired systolic function are independent risk factors for de novo development of ischemic heart disease⁽³⁰⁾. Increase LVMi for more than 1 g/m² per month increases the risk of developing cardiovascular complications⁽²⁵⁾. In patients with normal volume and normal LV systolic function, high index of left ventricle (LVMi >120 g/m²) and the relationship of weight/volume of left ventricle >2.2 g/ml, are independently associated with late mortality (after 2 years starting hemodialysis). In patients with LV dilatation and normal LV systolic dysfunction, the increased volume of the left LV (iEDVLV >120 mL/min) and LVMi/iEDV <1.8 mL see, are also associated with an increased risk of late mortality⁽³¹⁾.

In our work, between total serum PTH and LVMi, IVSd, PWLVd there is a statistically significant correlation. This leads to the conclusion that patients with higher values of PTH have a more pronounced LVH, as compared to those with normal or subnormal levels of PTH. Secondary hyperparathyroidism is associated with LVH and impaired heart function^(32,33). Patients on HD also follows increased concentration of phosphate. Increased serum phosphate levels >2.10 mmol/l, increased solubility equilibrium >5.65 mmol/l and increased PTH >500 pg/ml significantly increase the risk of mortality in patients treated with regular HD^(33,34). Reduced aortic velum opening leads to the development of concentric LV hypertrophy. The mass of the left ventricle may be increased due to a significant increase of myocardial fibrosis of interstitium (fibroblast proliferation, increased production and deposition of extracellular matrix proteins in interstitium infarction). In dialysis patients, increased concentration of PTH leads to the development of myocardial fibrosis of interstitium⁽¹⁶⁾. The reduction of PTH levels to normal ranges may have beneficial effect to reduce left ventricular hypertrophy and improve heart function. Thus, among hemodialysis population, higher parathyroid hormone concentrations were associated with higher all-cause mortality risk, mostly explained by fatal cardiovascular events⁽³⁵⁻³⁹⁾.

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^(40,41).

CONCLUSION

In conclusion, SHPT, hyperphosphatemia and high Ca \times P product are risk factors for adverse outcome in patients on HD. Regular monitoring and maintaining of PTH, serum calcium, phosphorus and Ca \times P product within the target range contribute to lowering the cardiovascular morbidity

and mortality and improving the quality of life of HD patients. Patients on HD have high risk for cardiovascular morbidity and mortality. Echocardiographic assessment for cardiovascular status in patients on HD identifies those with increased risk of cardiovascular complications, LVH, congestive heart failure, and heart valve calcification. Establishing the most sensitive parameters for identifying patients at risk for cardiovascular complications enables successful treatment.

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SAŽETAK

UTJECAJ SEKUNDARNOG HIPERPARATIREOIDIZMA NA EHOKARDIOGRAFSKE POKAZATELJE U HEMODIJALIZIRANIH BOLESNIKA

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Srčanožilne (SŽ) bolesti su vodeći uzrok smrtnosti u bolesnika na hemodijalizi. Bolesnici su izloženi brojnim čimbenicima rizika za SŽ komplikacije, koje su u prvom redu posljedica uremije i dijalize. Cilj našeg prospektivnog istraživanja jest ispitati učestalost sekundarnog hiperparatireoidizma i hipertrofije lijeve klijetke, i njihovu međuigru kao predskazatelja smrtnosti u bolesnika na hemodijalizi. Istraživanje je uključilo 53 bolesnika. Svim bolesnicima su mjereni ehokardiografski parametri za procjenu hipertrofije lijeve klijetke i laboratorijski parametri koštanog metabolizma. Pratila se smrtnost bolesnika tijekom dvije godine. Povišena razina PTH u serumu bila je prisutna u 79,24% bolesnika, hipertrofiju lijeve klijetke imalo je 81,13% bolesnika. Preživjeli su imali niže vrijednosti PTH i serumske fosfora ($p < 0,05$) u odnosu na preminule bolesnike. Analizirajući ehokardiografske parametre, bolesnici s lošim ishodom imali su značajno viši indeks mase lijeve klijetke, niže frakcije izbacivanja i frakcijskog skraćivanja lijeve klijetke, veće promjere interventrikularnog septuma i stražnje stijenke lijeve klijetke ($P < 0,05$). Hipertrofija lijeve klijetke je rani SŽ poremećaj koji se razvija brzo tijekom napredovanja kronične bolesti bubrega i u osnovi je uremijske kardiomiopatije. Hipertrofija lijeve klijetke je jak pokazatelj smrtnosti u bolesnika u završnoj fazi kronične bubrežne bolesti.

Ključne riječi: PTH, ehokardiografski parametri, srčanožilna smrtnost, hemodijaliza