Medicus 2005; 6(2): 82-85
UDK 616.61-78-06 UDK 616.1
UDK 616.447-008.61
Professional article
Stručni rad

SECONDARY HYPERPARATHYROIDISM – A RISK FACTOR FOR DEVELOPMENT OF UREMIC CARDIOMYOPATHY IN PATIENTS ON HEMODIALYSIS

Goran Balovic[1] and Dejan Petrovic[1,2]
[1]Faculty of Medicine, University of Kragujevac, [2]Clinic of Urology and Nephrology, CC „Kragujevac", Serbia and Montenegro

SEKUNDARNI HIPERPARATIROIDIZAM – FAKTOR RIZIKA ZA RAZVOJ UREMIJSKE KARDIOMIOPATIJE KOD BOLESNIKA NA HEMODIJALIZI

Goran Balović[1], Dejan Petrović[1,2]
[1]Medicinski fakultet, Univerzitet u Kragujevcu, [2]Klinika za urologiju i nefrologiju, KC „Kragujevac", Srbija i Crna Gora

Primljen/Received: 29. 03. 2005. Prihvaćen/Accepted: 11. 04. 2005.

SAŽETAK

Sekundarni hiperparatiroidizam je česta komplikacija kod bolesnika na hemodijalizi i udružen je sa razvojem kardiovaskularnih komplikacija. Rad je imao za cilj da ispita uticaj parathormona na razvoj uremijske kardiomiopatije kod bolesnika na hemodijalizi. U radu je ispitano 48 bolesnika koji se leče redovnim hemodijalizama. U zavisnosti od koncentracije iPTH u serumu bolesnici su podeljeni u tri grupe. Prvu grupu, s koncentracijom iPTH u serumu < 200 pg/mL, činilo je 16 bolesnika (M:Ž 11:5), prosečne starosti 56,88 ± 8,35 godina, s prosečnom dužinom dijaliziranja 3,45 ± 2,86 godina, i prosečnim Kt/V indeksom 1,02 ± 0,26 i URR indeksom 62,84 ± 8,41%. Drugu grupu, s koncentracijom iPTH u serumu od 200–600 pg/mL, činilo je 16 bolesnika (M:Ž 8:8), prosečne starosti 52,63 ± 9,95 godina, s prosečnom dužinom dijaliziranja 4,73 ± 4,01 godina, i prosečnim Kt/V indeksom 1,00 ± 0,24 i URR indeksom 62,20 ± 8,95%. Treću grupu, s koncentracijom iPTH > 600 pg/mL, činilo je 16 bolesnika (M:Ž 9:7), prosečne starosti 45,50 ± 11,12 godina, s prosečnom dužinom dijaliziranja 6,73 ± 3,64 godina, i prosečnim Kt/V indeksom 0,99 ± 0,14 i URR indeskom 62,53 ± 5,37%. Kao parametri za procenu uticaja parathormona na razvoj uremijske kardiomiopatije ispitivani su: koncentracija albumina u serumu, hemoglobin, hematokrit, koncentracija holesterola i triglicerida u serumu, srednji arterijski krvni pritisak-SAP, indeks mase leve komore-LVMi, indeks enddijastolnog volumena leve komore-iEDVLK, frakciono skraćenje-FSLK i ejekciona frakcija leve komore-EFLK. Za statističku analizu dobijenih podataka korišćeni su Student-ov T test, i Mann-Whitni-jev U test. Između ispitivanih grupa bolesnika nema statistički značajne razlike u vrednostima albumina, hemoglobina, hematokrita, holesterola, triglicerida, SAP, iEDVLK, FSLK i EFLK. Bolesnici sa koncentracijom iPTH u serumu > 600 pg/mL imaju statistički značajno ($p < 0,05$) veći LVMi u odnosu na grupu bolesnika sa iPTH < 200 pg/mL.

Ključne reči: hemodijaliza, sekundarni hiperparatiroidizam, uremijska kardiomiopatija

ABSTRACT

Secondary hyperparathyroidism is a frequent complication in patients on hemodialysis, and it is associated with cardiovascular complications. The study was designed to investigate the impact of parathormone on development of uremic cardiomyopathy in patients on hemodialysis. Forty-eight patients treated with regular hemodialyses were investigated. According to serum iPTH concentration, the patients were divided into three groups. The first group, with iPTH levels < 200 pg/mL, included 16 patients (M:F 11:5), with mean age 56.88 ± 8.35 years, mean dialysis duration 3.45 ± 2.86 years, mean Kt/V 1.02 ± 0.26, and mean URR 62.84 ± 8.41%. The second group, with iPTH 200–600 pg/mL, consisted of 16 patients (M: F 8:8), with mean age 52.63 ± 9.95 years, mean dialysis duration 4.73 ± 4.01 years, mean Kt/V 1.00 ± 0.24, and URR 62.20 ± 8.95%. The third group included 16 patients (M: F 9:7) with iPTH levels > 600 pg/mL, mean age 45.50 ± 11.12 years, mean dialysis duration 6.73 ± 3.64 years, mean Kt/V 0.99 ± 0.14, and URR 62.53 ± 5.37%. The parameters investigated to evaluate the influence of parathormone on development of uremic cardiomyopathy were following: serum concentrations of albumin, hemoglobin, hematocrit, cholesterol and triglycerides serum concentrations, mean arterial blood pressure, left ventricular mass index, end-diastolic volume index, left ventricular fractional shortening, left ventricular ejection fraction. Statistical analysis of the results was performed with Student's t-test and Mann- Whitney's U test. The patients with iPTH > 600 pg/mL showed significantly higher left ventricular mass index values ($p < 0,05$), compared to the group of patients with iPTH < 200 pg/mL.

Key words: hemodialysis, secondary hyperparathyroidism, uremic cardiomyopathy

INTRODUCTION

Disturbance of calcium and phosphate ion metabolism and secondary hyperparathyroidism represent a frequent complication in patients with terminal chronic renal failure [1]. Renal osteodystrophy-ROD - develops as a sequel of secondary hyperparathyroidism. Renal osteodystrophy consists of various bone tissue diseases, including high turnover of bone tissue disturbances (HTBDs) in moderate secondary hyperparathyroidism (osteitis fibrosa), and low turnover of bone tissue disturbances (LTBDs), such as osteomalacia and adynamic bone disease (ABD). HTBDs are characterized with increased decay of bone tissue, and LTBDs are characterized by reduced capacity of generating and mineralization of bone matrix. increased serum iPTH concentration (iPTH > 200 pg/mL) and increased concentration of bone alkaline phosphatase (bAP > 20 ng/mL) point to osteodystrophy of high bone turnover [2]. Low bone alkaline phosphatase levels-bAP < 27 U/L, low osteocalcin levels ≤ 14 μg/L, and low iPTH concentration (iPTH < 150 pg/mL) are good indicators of adynamic bone disease [2-4].

Serum aluminum determination, deferoxamine test and serum iPTH determination are used to prove aluminum bone disease. Deferoxamine test should be performed in standard fashion in patients with serum aluminum concentrations > 30–60 μg/L in two successive measurements. If serum aluminum concentration increase is $\Delta S_{Al} > 50$ μg/L, then determination of iPTH concentration is required. The greatest risk of developing aluminum bone disease is found in patients with iPTH < 150 pg/mL [2, 3].

Correspondence:
Ass. dr Dejan Petrovic
Hemodialysis Department, Clinic of Urology and Nephrology,
CC „Kragujevac", 30 Zmaj Jovina St., Kragujevac 34000,
Phone: 034–370–302
e-mail: aca96@eunet.yu

Secondary hyperparathyroidism, hypocalcemia, hyperphosphatemia, increased solubility product and increased iPTH concentration all contribute to development of cardiomyopathy in patients on hemodialysis.

Uremic cardiomyopathy is a primary disease of cardiac muscle, defined by hypertrophy of left ventricle walls, with or without concomitant enlargement of its internal dimensions [5, 6].

Echocardiographic examination is used to evaluate structure and function of left ventricle in hemodialysis patients [6]. M-mode echocardiography is used to evaluate left ventricle hypertrophy and left ventricle systolic function. Based on left ventricle dimensions it is possible to evaluate systolic function, left ventricular mass and left ventricular volume [6-8]. Left ventricular disorder in hemodialysis patients can manifest as systolic dysfunction, concentric left ventricular hypertrophy, eccentric left ventricular hypertrophy, or left ventricular dilatation. Systolic function disorder is defined as left ventricular fractional shortening FS ≤ 25%, concentric hypertrophy as left ventricular mass index LVMi > 131 g/m² in men and > 100 g/m² in women both with normal fractional shortening and relative left ventricular wall thickness – RWT > 45%, eccentric hypertrophy is defined as left ventricular mass index LVMi > 131 g/m2 in men and > 100 g/m2 in women, with normal fractional shortening and relative left ventricular wall thickness – RWT ≤ 45%; left ventricular dilatation is defined as volume of LV > 90 mL/m² with normal systolic function and normal left ventricular mass index [6–8].

AIM

The study intended to investigate influence of parathormone on development of uremic cardiomyopathy (left ventricular hypertrophy, left ventricular dilatation) in patients on hemodialysis.

METHOD

The study included 48 patients of the Hemodialysis Department, Clinic of Urology and Nephrology, CC „Kragujevac“, Kragujevac, in compliance with Helsinki Declaration on Medical Research and with obtained informed consent of the patients.

The study encompassed patients on chronic program of standard bicarbonate hemodialysis (> 6 months) 3 times a week for four hours, dialyzed on polysulfonic membrane, with blood flow of 200–250 mL/min and dialysate flow of 500–550 mL/min, with application of standard intermittent heparinization, with various primary renal diseases (chronic glomerulonephritis, hypertensive nephropathy, obstructive nephropathy, chronic pyelonephritis, polycystic renal disease). Calcium concentration in hemodialysis solution was 1.75 mmol/L.

Basic observed characteristics are following: duration of patient's dialysis, dialysis adequacy parameters – Kt/V index, URR index, serum albumin concentration, hemoglobin and hematocrit concentrations, serum total cholesterol and triglyceride, systolic, diastolic and mean arterial blood pressure, serum intact parathormone concentration, serum calcium and phosphate concentrations, alkaline phosphatase concentration, solubility product, left ventricular mass index, left ventricular end-diastolic volume index, left ventricular fractional shortening, and left ventricular ejection fraction.

According to serum iPTH concentrations, the patients were divided in three groups: group I – patients with iPTH < 200 pg/mL, group II – patients with iPTH 200–600 pg/mL, and group III – patients with iPTH > 600 pg/mL, table 1.

Biochemical blood analyses were performed in Central Laboratory of Clinical-Hospital Center „Kragujevac“, Kragujevac.

Urea values were obtained by purely enzymatic method (urease-glutamate-dehydrogenase). Normal values are 3.5–7.5 mmol/l.

Serum total cholesterol was determined by enzymatic method (cholesterol esterase-cholesterol oxydase). Normal values for total cholesterol are 3.37-6.48 mmol/L.

Serum triglyceride concentrations were determined by enzymatic-colorimetric method. Normal triglyceride values are 0.45–1.88 mmol/L.

Serum albumin concentrations were measured by biuretic method. Normal values are 38-46 g/L.

Serum iPTH determinations were performed in „Inter-light“ Medical-Biochemical Laboratory, Belgrade. Normal serum iPTH concentrations were 10–65 pg/mL. In hemodialysis patients upper normal limit for iPTH is 200 pg/mL.

All investigated patients had their echocardiographic examinations performed on HITACHI EUB 555G machine with 2.5 MHz probe. Due to alterations in left ventricular end-diastolic diameter depending on patient's level of hydration, echocardiographic examinations were performed 15–20 hours following individual dialysis.

Left ventricular fractional shortening (FS%), as an indicator of systolic function, was calculated with following formula:

$$FS = \frac{(EDDLK - EDSDLK)}{EDDLK}\ 100\%,$$

Where EDDLK represents end-diastolic diameter of left ventricle (mm), ESDLK stands for systolic diameter of left ventricle (mm). Normal left ventricle fractional shortening is 42 ± 8%.

Left ventricular hypertrophy was determined by measurement of left ventricular mass index-LVMi:

$$LVMi = \frac{0,00083x\left[(EDDLK + IVSd + ZZLKd)^3 - (EDDLK)^3\right] + 0,6}{TPm^2}\ g/m^2$$

Where IVSd represents interventricular septum thickness in diastole (mm), ZZLKd is posterior wall thickness in diastole (mm), TP represents body surface area (m2). Normal left ventricular mass index is ≤ 131 g/m2 in men and ≤ 100 g/m2 in women.

Left ventricle volume is calculated by the formula:

$$iEDV = \frac{(EDDLK)^3\ x0,001047}{TP}\ ml/m^2$$

where EDDLK represents left ventricle end-diastolic diameter (mm), and TP is body surface area (m^2). Normally, left ventricle end-diastolic diameter is ≤ 90 ml/m^2.

Relative wall thickness of left ventricle – RWT is calculated by the formula:

$$RWT = [(2 \times ZZLKd)/EDDLK] \times 100\%,$$

And ZZLKd is posterior wall thickness in diastole (mm), and EDDLK represents end-diameter of left ventricle (mm).

Hemodialysis adequacy was estimated according to Kt/V index calculated by the formula below:

$$Kt/V = \ln (Co_1/Ct_1)$$

Co1 is urea concentration before hemodialysis, and Ct1 is urea concentration after hemodialysis. Hemodialysis is adequate if Kt/V index is ≥ 1,2.

Extent of urea reduction –URR, as a parameter of hemodialysis adequacy, was calculated with the formula:

$$URR = (1\text{-}R) \times 100\ (\%),$$

And R represents the ratio of plasma urea after and before hemodialysis. Hemodialysis is adequate if URR = 65–70%, and R = 0.30–0.35.

Statistical analysis of the results was performed with Student's t-test, Mann-Whitney's U test and $\chi 2$ tests. Significance threshold was set as probability of 0.05 and 0.01.

RESULTS

The cross-sectional study, whose results are shown in the tables below, was performed at the Clinic of Urology and Nephrology, CHC „Kragujevac", Kragujevac.

Patients with serum iPTH > 600 pg/mL are significantly ($p < 0.01$) of younger age compared to the group with iPTH < 200 pg/mL. Also, the patients with iPTH > 600 pg/mL showed significantly longer treatment with regular hemodialyses, table 1.

There were no significant differences ($p > 0.05$) in parameters of hemodialysis adequacy (Kt/V index and URR index) among the studied groups, table 1.

Table 1. Basic patient data

GENERAL DATA	Groups – iPTH pg/mL		
	I (< 200)	II (200–600)	III (> 600)
	Xsr± Sd	Xsr ± Sd	Xsr ± Sd
Number (N)	16	16	16
Sex (M: F)	11/5	8/8	9/7
Age (years)	56,88 ± 8,35*	52,63 ± 9,95	45,50 ± 11,12
HD length (years)	3,45 ± 2,86	4,73 ± 4,01	6,73 ± 3,64*
Kt/V index	1,02 ± 0,26	1,00 ± 0,24	0,99 ± 0,14
URR (%)	62,84 ± 8,41	62,20 ± 8,95	62,53 ± 5,37
Significance - p	* P I, III < 0,01		

There were no significant differences ($p > 0.05$) in serum albumin, hemoglobin, hematocrit, serum cholesterol and serum triglyceride values and values of mean arterial blood pressure among the studied groups, table 2.

Table 2. Basic investigation parameters according to iPTH concentration

GENERAL DATA	GROUPS – iPTH pg/mL		
	I (< 200)	II (200–600)	III (> 600)
	Xsr± Sd	Xsr ± Sd	Xsr ± Sd
Albumen (g/L)	35,69 ± 3,98	36,94 ± 2,26	38,31 ± 2,41
Hemoglobin (g/L)	91,50 ± 15, 39	90,50 ± 10,63	90,46 ± 16,18
Hematocrit (%)	27,44 ± 3,65	27,49 ± 3,02	27,22 ± 4,65
Cholesterol (mmol/L)	4,04 ± 0,81	4,03 ± 0,72	4,10 ± 0,55
Triglycerides (mmol/L)	1,49 ± 0,46	1,82 ± 0,56	1,85 ± 0,94
Systolic pressure (mmHg)	125,63 ± 25,02	128,13 ± 16,82	136,88 ± 19,22
Diastolic pressure (mmHg)	76,25 ± 13,10	78,75 ± 10,25	82,50 ± 10,00
aMAP (mmHg)	92,71 ± 16,56	95,21 ± 11,15	100,36 ± 12,54

MAP – mean arterial blood pressure

Patients with iPTH > 600 pg/mL showed significantly ($p < 0.01$) lower serum ionized calcium levels, significantly ($p < 0.05$) lower values of serum total calcium, and highly significant ($p < 0.01$) greater values of serum alkaline phosphatase, table 3.

Table 3. Basic parameters for evaluation of calcium and phosphate ion metabolism disturbance.

INVESTIGATED PARAMETERS	Groups – iPTH pg/mL		
	I (< 200)	II (200–600)	III (> 600)
	Xsr± Sd	Xsr ± Sd	Xsr ± Sd
iCa^{2+} (mmol/L)	1,23 ± 0,07	1,20 ± 0,09	1,11 ± 0,06*
tCa^{2+} (mmol/L)	2,41 ± 0,20	2,34 ± 0,24	2,26 ± 0,14**
PO_4^{3-} (mmol/L)	1,50 ± 0,51	1,65 ± 0,45	1,79 ± 0,60
$[Ca^{2+}] \times [PO_{4=}^{3-}]$ ($mmol^2/L^2$)	3,61 ± 1,27	3,82 ± 0,98	4,03 ± 1,31
Alkaline phosphatase (IU/L)	114,38 ± 47,77	155,38 ± 76,49	181,00 ± 77,54*
Significance - p	* P I, III < 0,01, ** P I, III < 0,05		

iCa^{2+} - serum ionized calcium concentration, tCa^{2+} - serum total calcium concentration, PO_4^{3-} - serum phosphate concentration, $[Ca^{2+}]x[PO_{4=}^{3-}]$ - solubility product

Patients with iPTH > 600 pg/mL had greater values of mean solubility product in comparison to the group with iPTH < 200 pg/mL., but that difference was not statistically significant ($p > 0.05$), table 3.

There were no significant differences ($p > 0.05$) in values of left ventricular end-diastolic volume index, left ventricular fractional shortening and left ventricular ejection fraction among the studied groups, table 4.

Table 4. Influence of parathormone on development of uraemic cardiomyopathy.

INVESTIGATED PARAMETERS	Group – iPTH pg/mL		
	I (< 200)	II (200–600)	III (> 600)
	Xsr± Sd	Xsr ± Sd	Xsr ± Sd
LVMi (g/m2)	135,24 ± 31,85	148,62 ± 41,08	157,72 ± 30,22*
iEDVLK (mL/m2)	77,39 ± 23,02	85,69 ± 26,72	84,67 ± 30,07
FSLK(%)	31,21 ± 11,29	31,41 ± 6,99	30,00 ± 6,58
EFLK (%)	65,06 ± 15,17	66,79 ± 9,87	64,83 ± 9,82
Significance - p	* P I, III < 0,05		

LVMi – left ventricular mass index, iEDV – end-diastolic volume index of left ventricle, FS – left ventricular fractional shortening, EF – left ventricular ejection fraction

Patients with iPTH > 600 pg/mL had significantly ($p < 0.05$) greater values of left ventricular mass index than the patients with iPTH < 200 pg/mL, table 4.

DISCUSSION

Cardiovascular diseases are the most frequent cause of mortality in patients with terminal chronic renal failure [9,10]. Main risk factors for development of cardiovascular diseases, susceptible to alterations, in patients with renal diseases are hypertension, hyperglycemia, hyperlipidemia, hyperhomocystinemia, anemia and hyperparathyroidism [10–12]. Secondary hyperparathyroidism-SHPTH in hemodialysis patients is associated with left ventricle hypertrophy and diminished cardiac function. In patients treated with regular hemodialyses, increased serum phosphate concentrations $[PO_4^{3-}] > 6,5$ mg/dL and increased solubility product $[Ca^{2+}] \times [PO_4^{3-}] > 72$ mg^2/dL^2 significantly increase mortality of these patients.

So far, the research have confirmed the assumption that secondary hyperparathyroidism, i. e. increased iPTH concentration, results in development of uremic cardiomyopathy. It has been proven that parathormone-iPTH stimulates fibroblast proliferation of myocardial interstice, followed by increased production of extracellular matrix protein, ventricular wall thickening, recovery of myocardial interstice [5].

Patients with iPTH > 600 pg/ml have significantly greater values of left ventricular mass index in comparison to the patients with iPTH < 200 pg/ml, table 4, and these data are in agreement with the result of published research that showed statistically significant positive correlation between serum parathormone concentration and left ventricular mass in hemodialysis patients [5]. Parathormone level reduction in hemodialysis patients, with application of active vitamin D3 metabolites or after parathyroidectomy, was followed by improvement in systolic function of left ventricle [5].

Having in mind that among studied groups there were no statistically significant differences in albumin, hemoglobin, hematocrit and mean arterial blood pressure, it can be concluded that increased serum iPTH concentration could be responsible for increased LVMi in studied patients with iPTH > 600 pg/mL.

Therefore, therapy for secondary hyperparathyroidism should achieve the following values: $[PO_4^{3-}] \leq 1.8$ mmol/L, $[Ca^{2+}] \times [PO_4^{3-}] \leq 4.4$ $mmol^2/L^2$, and iPTHs=100–200 pg/mL.

CONCLUSIONS

Among the studied groups of patients there were no statistically significant differences in albumin, hemoglobin, hematocrit, cholesterol, triglyceride or mean arterial blood pressure values.Patients with iPTH>600 pg/mL had significantly greater left ventricular mass index compared to the group with iPTH<200 pg/mL. Among the studied groups there were no statistically significant differences in end-diastolic volume of left ventricle, left ventricular fractional shortening and left ventricular ejection fraction. Secondary hyperparathyroidism is an independent risk factor for development of uremic cardiomyopathy.

REFERENCES

1. Goodman WG. Medical management of secondary hyperparathyroidism in chronic renal failure. Nephrol Dial Transplant 2003; 18 (Suppl 3): 2–8.
2. Ferreira MA. Diagnosis of renal osteodystrophy: when and how to use biochemical markers and non-invasive methods; when bone biopsy is needed. Nephrol Dial Transplant 2000; 15 (Suppl 5): 8–14.
3. Cannata-Andia JB. Pathogenesis, prevention and management of low-bone turnover. Nephrol Dial Transplant 2000; 15 (Suppl 5): 15–7.
4. Couttenye MM, D, Haese PC, Van Hoof VO, et al. Low serum levels of alkaline phosphatase of bone origin: a good marker of adynamic bone disease in haemodialysis patients. Nephrol Dial Transplant 1996; 11 (6): 1065–72.
5. Kunz K, Dimitrov Y, Muller S, et al. Uraemic cardiomyopathy. Nephrol Dial Transplant 1998; 13 (Suppl 4): 39–43.
6. Parfrey PS, Collingwood P, Foley RN, et al. Left ventricular disorders detected by M-meode echocardiography in chronic uremia. Nephrol Dial Transplant 1996; 11 (7): 1328–31.
7. Middleton RJ, Parfrey PS, Foley RN. Left Ventricular Hypertrophy in the Renal Patient. J Am Soc Nephrol 2001; 12 (5): 1079–84.
8. Rigatto C, Parfrey PS, London GM. Cardiac hypertrophy in end-stage renal failure. In: Cardiovascular Disease in End-stage Renal Failure. Loscalzo J, London GM (eds), The Oxford University Press, New York, 2000, pp. 157–73.
9. Locatelli F, Pozzoni P, Tentori F, et al. Epidemiology of cardiovascular risk in patients with chronic kidney disease. Nephrol Dial Transplant 2003; 18 (Suppl 7): 2–9.
10. Massy Z. A, Kasiske BL. Prevention of cardiovascular complications in chronic renal disease. In: Cardiovascular Disease in End-stage Renal Failure. Loscalzo J, London GM (eds), The Oxford University Press, New York, 2000, pp. 463-81.
11. Poskurica M. Etiopathogenesis and frequency of cardiovascular diseases in end-stage renal failure. News in nephrology 1998; 3 (1): 1–15 (in serbian).
12. Poskurica M, Miletic D, Lazarevic T, Lazarevic M, Petrovic D. Heart failure in end-stage renal failure. Medical Invest 1999; 33 (2): 27–32 (in serbian).