ORIGINAL ARTICLE

Risk factors associated with the development of secondary hyperparathyroidism in dialysis patients

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ABSTRACT

Aim To determine risk factors associated with the development and severity of secondary hyperparathyroidism in dialysis patients.

Methods A cross-sectional study at the Clinical Centre of the University of Tuzla (March 2022) included 104 adult patients (males 51.9%, females 48.1%) with chronic kidney diseases under dialysis treatment. Based on parathyroid hormone (PTH) values, patients were divided into two groups: study group (45/104, PTH >792pg/mL) and control group (59/104, PTH 176-792 pg/mL). The analysis aimed to resolve whether there was a connection between the duration of dialysis, the type of therapy treatment administered, the underlying kidney disease, and the presence of comorbidities with the values of PTH, and a wide spectrum of monitored laboratory parameters.

Results The most common causes of chronic renal failure were undefined kidney diseases (32.7%), followed by diabetic nephropathy (18.3%) and chronic glomerulonephritis (16.3%). In the examined biochemical parameters, a significant difference was found in mean values of alkaline phosphatase ($p<0.001$). The correlation was proved between the duration of dialysis ($p=0.028$), the values of phosphorus ($p=0.031$), and alkaline phosphatase ($p<0.001$) with absolute values of PTH. The most common present comorbidity was hypertension (78.8%), followed by cardiovascular diseases (40.4%) and diabetes (22.1%).

Conclusion A number of factors contribute to the development and severity of SHPT. Modulation of therapy and better control of risk parameters can prolong and reduce the frequency of SHPT in dialysis patients, as well as the occurrence of comorbidities.

Key words: alkaline phosphatase, calcium, chronic kidney diseases, parathyroid hormone, phosphorus

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INTRODUCTION

Chronic kidney disease (CKD) is a major public health concern. It is defined by pathological changes in renal structure and function with reduced glomerular filtration rate (GFR) for at least three months (1). Progressive loss of kidney function leads to an end-stage renal disease (kidney failure), which further leads to dialysis and kidney transplantation. The course of a chronic kidney disease is accompanied by a number of complications, affecting all organ systems (2).

The CKD is the most common cause of secondary hyperparathyroidism (SHPT), but also conversely, SHPT is one of the most common complications in these patients (3). The SHPT occurs as an adaptive pathophysiological process as a response to the aggravation of renal insufficiency. It is characterised by elevated levels of parathyroid hormone (PTH) in the blood, bone and mineral metabolism disorder, primarily calcium and phosphorus (hyperphosphatemia and hypocalcaemia) as the basic characteristics of advanced CKD (4). It is related to an increased morbidity and mortality, and has a negative effect on the quality of life of patients with CKD (5).

Chronic SHPT is associated with several complications, the most common of which are bone and mineral metabolism disorders in kidney diseases and progressive cardiovascular diseases (6). Mineral and bone metabolism disorder in chronic kidney disease (CKD-MBD) includes disorders of calcium, phosphorus, PTH and/or vitamin D, along with disorders of metabolism and bone partitioning with changes in mineralization, linear growth, strength and volume of bone tissue, as well as calcification of blood vessels and soft tissues, which is why CKD-MBD is one of the main indicators of increased morbidity and mortality in haemodialysis patients (7-9).

Over the past several years, clinical studies have shown that by regulating PTH levels and controlling mineral homeostasis (calcium, phosphorus, the product of calcium and phosphorus), morbidity and mortality in patients with SHPT can be reduced (10-12). Current treatment options are related to modulation of calcium and phosphorus balance by haemodialysis, appropriate food intake, phosphorus binders, vitamin D analogues, and new calcimimetics, which reduce PTH values alone or in combination with calcitriol (13). Patients whose elevated PTH values cannot be regulated by medication treatment undergo surgical removal of the parathyroid gland (14).

In addition to the three well-known risk factors (disturbed calcium and phosphorus metabolism and reduced vitamin D values), numerous other factors contribute to the development of SHPT: anaemia, acidosis, inflammation, as well as comorbidities such as cardiovascular diseases and diabetes (15). Likewise, SHPT represents a risk factor for the development of these diseases. Complex interactions of these risk factors with SHPT are still unclear and their early identification could help in prevention and treatment of SHPT in CKD dialysis patients (16).

The aim of this research was to determine the risk factors associated with the development and severity of secondary hyperparathyroidism in dialysis patients undergoing to the treatment at the Haemodialysis Department of the Clinical Centre of the University of Tuzla.

PATIENTS AND METHODS

Patients and study design

This cross-sectional study at the Clinical Centre of the University of Tuzla (March 2022) included 104 patients with chronic kidney disease (≥ 18 years, both genders) who underwent haemodialysis treatment for at least 3 months, who met the clinical practice guidelines for chronic kidney disease (1). Exclusion criteria were the patients who had bleeding or received a transfusion in the last three months, severe infection in the last three months, confirmed HIV infection, primary liver diseases, tumours or autoimmune diseases, primary hyperparathyroidism and parathyroidectomy.

Based on the values of parathyroid hormones, patients were divided into two groups: study group - patients with SHPT whose PTH values were above the recommended values according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) guidelines, which indicate that PTH reference range in dialysis patients is 2-9 times above the upper limit of normal values for the healthy population (>792 pg/mL)(17) and control group - patients whose PTH values were within the recommended reference values (176-792pg/mL).

It was analysed whether there is a connection between the duration of dialysis, the type of therapy treatment administered, the underlying kidney disease and the presence of comorbidities with the values of laboratory tests in these patients. Risk factors affecting the development of SHPT in chronic renal dialysis patients were analysed and identified, as well as a possible relationship between SHPT and its complications, primarily cardiovascular diseases.

This study was carried out in accordance with ethical guidelines as part of a project approved by the Clinical Centre of the University of Tuzla.

Methods

Data from the patients' medical records and laboratory information system were used. The following data were taken from medical history of dialysis patients: basic demographic data for each patient (age, gender), and clinical data including underlying kidney disease, duration of dialysis, presence of comorbidities (hypertension, cardiovascular diseases, diabetes), as well as therapy administered in the last three months.

The values of the following laboratory tests were taken from the laboratory information system: urea, creatinine, calcium, phosphorus, alkaline phosphatase, total protein, albumin, cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), c-reactive protein (CRP), HbA_1C, number of leukocytes, number and percentage of neutrophils, number and percentage of lymphocytes, neutrophil/lymphocyte ratio, haematocrit, haemoglobin, ferritin, transferrin, vitamin D, PTH.

Quantitative determination of serum intact PTH was measured with a 2-site sandwich immunoassay using direct chemiluminometric technology, which uses constant amounts of 2 anti-human PTH antibodies on ADVIA Centaur XP system (Siemens). The first antibody is a monoclonal mouse anti-human PTH (N-terminal) antibody labelled with acridinium ester, and the second antibody is a biotinylated monoclonal mouse anti-human PTH (C-terminal) antibody that is bound to streptavidin-coated paramagnetic latex particles. These assay measures intact PTH concentration from 6.3-2000 pg/mL, with recommended serum reference range for adults apparently healthy individuals from 18.5-88.0 pg/mL.

Statistical analysis

Standard methods of descriptive statistics (frequency, range, median, arithmetic mean, standard deviation) were used. The distribution of variables was determined using QQ and PP graphs, and Shapiro-Wilk and Kolmogorov-Smirnov normality tests. The results were shown as mean values with standard deviation (SD) in case of normal distribution, and in case of non-normal distribution, as median with interquartile range. Parametric and non-parametric tests (Student's t-test, Mann-Whitney test, Fisher's test and $\chi 2$ test) were used to test the statistical significance of the difference between samples. Pearson's and Spearman's correlation coefficient, logistic regression, ANOVA and Kruskal Wallis test were used to determine the linear correlation between the duration of dialysis, the type of therapy treatment, and the type of underlying kidney disease with the values of the laboratory tests. Pearson's and Spearman's correlation coefficient was used to determine the linear correlation between PTH and the values of other examinations and tests (with Kruskal Wallis and Wilcoxon-Mann Whitney test for distribution). The difference between the samples was considered significant if $p<0.05$.

RESULTS

Of the total number of patients who underwent haemodialysis treatment at the Clinical Centre of the University of Tuzla due to chronic renal failure at the time of the study (March 2022), 57% (59/104) had target PTH values for dialysis patients (176-792 pg/mL) and they made up the control group, while 43% (45/104) had PTH values outside the recommended range (>792 pg/mL) and they made up the study group.

The study group had mean value of PTH 1439.4(±557.9) vs. control group 407.9 (±157.2) ($p<001$).

The mean age of all patients was 58.6 (±13.9) years. The youngest patient was 18 and the oldest 88. The study group had a lower mean age than the control group, 55.3(±14.0) and 61.1(±14.2), respectively ($p=0.041$) (Table 1).

The duration from the beginning of dialysis treatment ranged from 4 to 430 months with the average duration of dialysis in all patients of 83.7 (±85.1). The study group spent an average of

Table 1. Demographic and clinical characteristics of 104 patients with chronic kidney disease

Variable	Categories	Control group n=59 (PTH=176-792)	Study group 45 (PTH > 92)	Total	p
Mean age (SD) (years)		61.1 (14.2)	55.3 (13.9)	58.6 (14.3)	0.041
Mean duration of dialysis (SD) (months)		72.0 (80.3)	99.5 (89.7)	83.7(85.1)	0.018
			No (%) of patients		
Gender	Male	28 (47.5)	26 (57.8)	54 (51.9)	0.327
	Female	31 (52.2)	19 (42.2)	50 (48.1)	
Underlying kidney disease	Autoimmune diseases	3 (5.1)	4 (8.9)	7 (6.7)	0.138
	Diabetic nephropathy	15 (25.4)	4 (8.9)	19(18.3)	
	Glomerulonephritis chronic	10 (16.9)	7 (15.6)	17 (16.3)	
	Hypertensive kidney disease	2 (3.4)	7 (15.6)	9 (8.7)	
	Undefined kidney disease	18 (30.5)	16 (35.6)	34 (32.7)	
	Polycystic kidney disease	3 (5.1)	3 (6.7)	6 (5.8)	
Hypertension	Yes	8 (13.6)	4 (8.9)	12 (11.5)	0.190
	No	13 (14.6)	12 (25.0)	25 (18.2)	
	No data	1 (1.1)	1 (2.1)	2 (1.5)	
Cardiovascular diseases	Heart anomalies	2 (3.4)	2 (4.4)	4 (3.8)	0.942
	Hypertensive heart disease	7 (11.9)	4 (8.9)	11 (10.6)	
	Stroke	4 (6.8)	5 (11.1)	9 (8.7)	
	Myocardial infarct	5 (8.5)	2 (4.4)	7 (6.7)	
	Ischemic heart disease	7 (11.9)	4 (8.9)	11 (10.6)	
	No	32 (54.2)	26 (57.8)	58 (55.8)	
Diabetes	No data	2 (3.4)	2 (4.4)	4 (3.8)	0.035
	Yes	18 (30.5)	5 (11.1)	23 (22.1)	
	No	40 (67.8)	39 (86.7)	79 (76.0)	
	No data	1 (1.7)	1 (2.2)	2 (1.9)	
Other diseases	Yes	17 (28.8)	18 (40.0)	35 (33.7)	0.426
	No	40 (67.8)	25 (55.6)	65 (62.5)	
	No data	2 (3.4)	2 (4.4)	4 (3.8)	
Erythropoietin	Yes	52 (88.1)	37 (82.2)	89 (85.6)	0.414
	No	7 (11.9)	8 (17.8)	15 (14.4)	
Calcium preparations pills (1gr)	2x1	17 (28.8)	8 (17.8)	25 (24.0)	0.423
	3x1	7 (11.9)	5 (11.1)	12 (11.5)	
	No	35 (59.3)	32 (71.1)	67 (64.4)	
Calcimimetics (30mg)	1x1	2(3.4)	6 (13.3)	8 (7.7)	0.074
	No	57 (96.6)	39 (86.7)	96 (92.3)	
Vitamin D analoguse pills (1µg)	3x2	1 (1.7)	23 (51.1)	24 (23.1)	<0.001
	No	58 (98.3)	22 (48.9)	80 (76.9)	
Vitamin D analogues amp (5 µg)	3x1	0	11 (24.4)	11 (10.6)	<0.001
	No	59 (100)	34 (75.6)	93 (89.4)	
Active vitamin D (0.25 µg)	1x1	12 (20.3)	1 (2.2)	13 (12.5)	0.019
	2x1	14 (23.7)	14 (31.1)	28 (26.9)	
	No	33 (55.9)	30 (66.7)	63 (60.6)	
Phosphate binders (800mg)	2x1	6 (10.2)	15 (33.3)	21 (20.2)	<0.001
	3x1	10 (16.9)	14 (31.1)	24 (23.1)	
	No	43 (72.9)	16 (35.6)	59 (56.7)	

SD, standard deviation;

27.4 months longer under dialysis treatment than the control group (Table 1).

The most common cause of chronic renal failure in both groups was undefined kidney disease, followed by diabetic nephropathy and chronic glomerulonephritis, without significant differences between groups. Also, some comorbidities were presented in the majority of patients, most common of which was hypertension, followed by cardiovascular diseases and diabetes. Patients were treated with different combination of therapy (Table 1).

The duration of dialysis for all patients was related to the concentration of alkaline phosphatase (r=0.216, p=0.032), albumin (r=-0.268; p=0.008), HbA_1C values (r=-0.341; p<0.001), ferritin (r=0.262; p=0.009), as well as PTH values (r=0.176; p=0.044). In relation to the underlying disease that led to chronic renal failure, a significant difference was found in the mean age (p=0.012) and values of creatinine (p=0.026), as well as HbA_1C (p=0.001) for all patients (data not shown).

In the examined biochemical parameters, a significant difference between groups was found in the mean value of alkaline phosphatase and HbA1c (Table 2).

Table 2. Laboratory findings in dialysis patients with secondary hyperparathyroidism

Parameter (reference value)	**Control group** (PTH=176-792) N=59; Mean (SD or 95% CI*)	**Study group** (PTH>792) N=45 Mean (SD or 95% CI*)	p
Urea (2.1-7.1) (mmol/L)	24.1 (8.3)	25.2 (6.7)	0.455
Creatinine(M:80-115; F:53-97) (μmol/L)	784.4 (213.9)	858.3 (244.9)	0.104
Calcium (2.15-2.50) (mmol/L)	2.18 (0.24)	2.13 (0.18)	0.298
Phosphorus (0.87-1.45) (mmol/L)	1.70 (0.54)	1.84 (0.55)	0.216
Alkaline phosphatase (40-150) (U/L)	71.0 (50.0)	112.0 (121.0)	<0.001
Total proteins (66-81) (g/L)	67.5 (5.4)	67.9 (5.8)	0.686
Albumin(35-52) (g/L)	39.4 (4.6)	38.2 (3.2)	0.134
Cholesterol (<5.18) (mmol/L)	4.47 (1.12)	4.28 (1.07)	0.387
Triglyceride (<1.7) (mmol/L)	1.77 (1.99)	1.86 (1.32)	0.202
Low density lipoprotein) (<3.37) (mmol/L)	2.67 (0.94)	2.50 (0.92)	0.374
High density lipoprotein (≥1.55) (mmol/L)	0.92 (0.24)	1.00 (0.29)	0.122
C-reactive protein (<5.0) (mg/L)	5.6 (10.8)	6.0 (12.0)	0.213
HbA1c (<6.5) (%)	5.3 (1.2)	4.9 (0.40)	0.018
Leukocytes (3.4-9.7) (x109/L)	6.8 (1.9)	6.2 (2.2)	0.151
Neutrophils (2.06-6.49) (x109/L)	4.46 (1.71)	3.96 (1.75)	0.152
Percentage of neutrophils(44-2)	64.7 (8.9)	63.5 (9.15)	0.500
Lymphocytes (1.19-3.35) (x109/L)	1.39 (0.52)	1.39 (0.64)	0.986
Percentage of lymphocytes (20-46)	21.8 (12.45)	22.6 (11.20)	0.369
Neutrophils/ lymphocytes ratio	2.98 (2.16)	2.82 (2.00)	0.379
Haematocrit (M:0.415-0.530; F:0.356-0.470) (L/L)	0.319 (0.056)	0.324 (0.065)	0.693
Haemoglobin (M:138-175; F:119-157) (g/L)	106.8 (18.6)	108.5 (21.8)	0.664
Ferritin (M:22-322; F:10-291) (μg/L)	494.9 (475.8)	512.9 (514.7)	0.806
Vitamin D(nmol/L) (>75)	24.2 (11.9)	23.2 (7.9)	0.997
PTH (18.5-88) (pg/mL)	407.9 (157.2)	1439.4 (557.9)	<0.001

*SD or CI depending of data distribution and statistical test used SD, standard deviation; CI, confidence interval; M, male; F, female; PHT, parathyroid hormone;

The correlation was proved between the duration of dialysis, measured phosphorus values (p=0.010), the values of alkaline phosphatase (p=0.001), HbA_1C and diabetes as underlying disease, as well as administered therapy (calcimimetics, vitamin D and phosphate binders) with absolute values of PTH, for all patients (Table 3). In the study group the correlation was proved between the mean values of alkaline phosphatase (r=0.380; p=0.010), mean neutrophil percentage (r= 0.309; p=0.039), number of lymphocytes (r=-0.306; p=0.041), percentage of lymphocytes (r=-0.373; p=0.012), and neu/lympho ratio (r=0.413; p=0.005) with measured values of PTH (data not shown).

DISCUSSION

The diagnosis and treatment of SHPT are complex, but setting and maintaining PTH target values the basis for it. The very development and progression of SHPT in dialysis patients depends on numerous factors and is associated with numerous pathophysiological mechanisms (3). Along with deterioration of renal function, depending on the stage of CKD, SHPT is found in 20-80% of patients (18,19). Our study also showed that a large number of dialysis patients (43%), despite the administered therapy, still develop SHPT (with PTH values above recommended for dialysis patients), which is somewhat correlated with data from previous studies that showed a slightly higher prevalence of SHPT, which can be explained by the lower reference values for PTH used in these studies (18,19).

In our study, undefined kidney disease was the most common cause of chronic renal failure, followed by diabetic nephropathy and chronic glomerulonephritis, which is not entirely consistent with the results of other studies (5,16,20). This can be explained by the fact that biopsies on all patients with CKD were not performed in our centre in previous years, which is the reason for the lack of definitive pathohistological confirmation of the diagnosis of an underlying disease. The relationship between the underlying kidney disease and PTH values was not proven. Similar results were obtained in a study by Yudan Wei et al. (16).

Most of the patients in our study were elderly, but the incidence of SHPT did not increase with age. Although some studies have shown that the female gender is more prevalent, due to the influ-

Table 3. Correlation of examined variables in all patients with values of parathyroid hormone (PTH)

Parameter (reference value)	**Correlation**	**p**
Urea (2.1-7.1) (mmol/L)	r= -0.013	0.892
Creatinine (M:80-115; F:53-97) (μmol/L)	r= -0.050	0.614
Calcium (2.15-2.50) (mmol/L)	r= -0.045	0.650
Phosphorus (0.87-1.45) (mmol/L)	r= 0.213	0.031
Alkaline phosphatase (40-150) (U/L)	r= 0.460	<0.001
Total proteins (66-81) (g/L)	r= 0.050	0.617
Albumin(35-52) (g/L)	r= 0.134	0.177
Cholesterol (<5.18) (mmol/L)	r= -0.076	0.443
Triglyceride (<1.7) (mmol/L)	r= -0.147	0.139
Low density lipoprotein) (<3.37) (mmol/L)	r= -0.106	0.289
High density lipoprotein (≥1.55) (mmol/L)	r= 0.158	0.114
C-reactive protein (<5.0) (mg/L)	r= -0.067	0.498
HbA1c (<6.5) (%)	r= -0.208	0.039
Leukocytes (3.4-9.7) ($x10^9$/L)	r= -0.173	0.079
Neutrophils (2.06-6.49) ($x10^9$/L)	r= -0.127	0.199
Percentage of neutrophils (44-2)	r= 0.058	0.557
Lymphocytes (1.19-3.35) ($x10^9$/L)	r= -0.114	0.247
Percentage of lymphocytes (20-46)	r= 0.044	0.657
Neutrophils/ lymphocytes ratio	r= -0.020	0.839
Haematocrit (M:0.415-0.530; F:0.356-0.470) (L/L)	r= 0.062	0.529
Haemoglobin (M:138-175; F:119-157) (g/L)	r= 0.048	0.626
Ferritin (M:22-322; F:10-291) (μg/L)	r= -0.012	0.900
Vitamin D(nmol/L) (>75)	r= -0.049	0.647
Age (years)	r= -0.165	0.095
Duration of dialysis (months)	r= 0.221	0.028
Underlying kidney disease	H=7.388	0.286
Hypertension	U=650	0.152
Cardiovascular diseases	H=0.707	0.994
Diabetes	U=647	0.036
Other diseases	U=1038	0.472
Erythropoietin	U=594	0.496
Calcium preparations pills (1gr)	H=1.643	0.440
Calcimimetics (30mg)	U=214	0.038
Vitamin D analogues pills (1μg)	U=282	<0.001
Vitamin D analogues amp (5 μg)	U=113	<0.001
Active vtamin D (0.25 μg)	H=10.852	0.004
Phosphate binders (800mg)	H=21.776	<0.001

M, male; F, female; r, Pearson/Spearman correlation; H, Kruskal-Wallis test; U, Wilcoxon Mann-Whitney test

ence of estrogen on the expression of mRNA for PTH in the parathyroid gland cells (16,21), the results of our study did not confirm this.

Hyperphosphatemia plays a significant role in the development of SHPT. Although the sensor for the secretion of extracellular phosphorus is still unknown, the phagocytic growth factor (FGF23) is believed to participate in the regulation of phosphorus and vitamin D (22). Numerous epidemiological studies have shown a connection between hyperphosphatemia and accelerated deterioration of renal function, and that phosphorus retention in serum is one of the most important factors in the development of SHPT (23-25). Most of our patients also had elevated values of phosphorus in blood, especially in the group with SHPT, but without statistically significant differences by group. It can be explained by the fact that patients in the study group took significantly more phosphate binders and vitamin D analogues. Similar results were obtained in numerous other studies (26-28).

Hyperphosphatemia also lowers the level of ionized calcium and interferes with the production of calcitriol, which results in increased secretion of PTH (22). Serum calcium is an important factor affecting PTH levels (29). Although it was not confirmed by the results of our study, the correlation between phosphorus and calcium values with increased secretion of PTH in dialysis patients was also shown in other studies (30-32). A possible explanation lies in the fact that most SHPT patients are on medications with preparation of vitamin D, which causes increased absorption of calcium from the intestines and mobilization of calcium from the bones, so a certain number of patients may even have hypercalcemia with hyperphosphatemia.

In addition to standard traditional and non-traditional cardiovascular risk factors, CKD itself is associated with an increased risk of cardiovascular diseases acting through its specific uremic factors (anemia, hyperphosphatemia, SHPT, endothelial dysfunction) (8).

The majority of our patients also developed some of the complications, and the most common were cardiovascular diseases, which is in accordance with the reference data (33,34). In our study patients with higher PTH values (study group) did not have more cardiovascular diseases, which was the opposite of what was expected. The probable reason for these results was that patients in the study group were significantly younger compared to the control group and had fewer patients with diabetes.

Although it is not expected, the majority of our patients with diagnosed diabetes had HbA_1C values within reference values, which is related to a decrease in the concentration of total haemoglobin in these patients, which is also reflected in the measured HbA_1C values (35.)

Normocytic normochromic anaemia is a regular and permanent companion of CKD, and is present in more than 90% of patients treated with dialysis (36,37). It is believed that PTH itself acts as a uremic toxin that directly affects bone marrow suppression (reduces erythrocyte production), increases erythrocyte fragility and shortens their

normal lifespan (38). It was confirmed that patients with higher PTH values respond less well to drugs stimulating erythropoiesis, which is one of the causes of anaemia in these patients (39). Also, elevated PTH values are related to the occurrence of anaemia in these patients (40). Although most patients in our study had lower haemoglobin and haematocrit values as compared to those recommended for dialysis patients, no significant difference was found between the study and the control group. This can be explained by the fact that most of our patients were treated with preparations that stimulate bone marrow-erythropoietin. There was no significant difference in the number of patients between the groups on erythropoietin therapy (number of patients), but a probable difference in the administered doses was not calculated, so that can be the reason as well.

Inflammation is also an independent risk factor for the development of cardiovascular complications in dialysis patients and is present in 30-50% of patients under regular haemodialysis treatment (41,42). In our study, a CRP increase was found in both groups, and the correlation was proven between percentage of neutrophils with values of PTH, which is in accordance with the results of other studies (16,42,43).

Previous studies have also shown that in addition to hypoalbuminemia and hypertension, hyperlipidaemia is an important risk factor in CKD (44,45). It was shown that dialysis patients with normal or reduced cholesterol values have a higher risk of mortality (46). Also, it was proved that an elevated ratio of triglycerides to HDL was associated with PTH and phosphorus values (47). However, in our study, the majority of patients in both groups had values of total cholesterol and LDL within the reference values, but they had decreased HDL values and elevated triglyceride values.

Our study has shown a trend toward an association between higher numbers of phosphate binder pills and vitamin D preparations in the therapy, and the measured values of PTH, what can be explained by the fact that these patients also have higher values of phosphate, which is why it is primarily prescribed. It is consistent with literature (17,48,49).

In conclusion, a number of factors contribute to the development of SHPT. Complex interactions of these risk factors with SHPT are still unclear and their early identification could help in prevention and treatment of SHPT in CKD dialysis patients. Modulation of therapy and better control of risk parameters can prolong and reduce the frequency of SHPT in dialysis patients, as well as the occurrence of comorbidities. Intervention could include dietary phosphate restriction, phosphate binder therapy, vitamin D supplementation or a combination, with continuous and more frequent measurement of parathyroid hormone concentration.

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REFERENCES

1. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013; 158:825-30.
2. Murabito S, Hallmark BF. Complications of Kidney Disease. Nurs Clin North Am 2018; 53:579-88.
3. Hou YC, Zheng CM, Chiu HW, Liu WC, Lu KC, Lu CL. Role of calcimimetics in treating bone and mineral disorders related to chronic kidney disease. Pharmaceuticals (Basel) 2022; 15:952.
4. Shlipak MG, Tummalapalli SL, Boulware LE, Grams ME, Ix JH, Jha V, Kengne AP, Madero M, Mihaylova B, Tangri N, Cheung M, Jadoul M, Winkelmayer WC, Zoungas S; Conference Participants. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int 2021; 99:34-47.
5. Melamed ML, Eustace JA, Plantinga L, Jaar BG, Fink NE, Coresh J, Klag MJ, Powe NR. Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. Kidney Int 2006; 70:351-7.
6. Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. Nephrol Dial Transplant 2018; 33:28-34.
7. 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; 15:2208-18.

8. Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, Gill JS, Hlatky MA, Jardine AG, Landmesser U, Newby LK, Herzog CA, Cheung M, Wheeler DC, Winkelmayer WC, Marwick TH; Conference Participants. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. J Am Coll Cardiol 2019; 74:1823-38.
9. Liu X, Chen A, Liang Q, Yang X, Dong Q, Fu M, Wang S, Li Y, Ye Y, Lan Z, Chen Y, Ou JS, Yang P, Lu L, Yan J. Spermidine inhibits vascular calcification in chronic kidney disease through modulation of SIRT1 signaling pathway. Aging Cell 2021; 20:e13377.
10. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, Young EW, Akizawa T, Akiba T, Pisoni RL, Robinson BM, Port FK. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 2008; 52:519-30.
11. Li D, Zhang L, Zuo L, Jin CG, Li WG, Chen JB. Association of CKD-MBD markers with all-cause mortality in prevalent hemodialysis patients: a cohort study in Beijing. PLoS One 2017; 12:e0168537.
12. Fukagawa M, Kido R, Komaba H, Onishi Y, Yamaguchi T, Hasegawa T, Kurita N, Fukuma S, Akizawa T, Fukuhara S. Abnormal mineral metabolism and mortality in hemodialysis patients with secondary hyperparathyroidism: evidence from marginal structural models used to adjust for time-dependent confounding. Am J Kidney Dis 2014; 63:979-87.
13. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 2017; 7:1-59.
14. Lau WL, Obi Y, Kalantar-Zadeh K. Parathyroidectomy in the Management of Secondary Hyperparathyroidism. Clin J Am Soc Nephrol 2018; 13:952-61.
15. Wei Y, Lin J, Yang F, Li X, Hou Y, Lu R, Shi X, Liu Z, Du Y. Risk factors associated with secondary hyperparathyroidism in patients with chronic kidney disease. Exp Ther Med 2016; 12:1206-12.
16. Liu ZH, Li G, Zhang L, Chen J, Chen X, Zhao J, Liang X. Executive summary: clinical practice guideline of chronic kidney disease - mineral and bone disorder (CKD-MBD) in China. Kidney Dis (Basel) 2019; 5:197-203.
17. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, Moe SM, Shroff R, Tonelli MA, Toussaint ND, Vervloet MG, Leonard MB. Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters. Kidney Int 2017; 92:26-36.
18. Sprague SM, Martin KJ, Coyne DW. Phosphate Balance and CKD-mineral bone disease. Kidney Int Rep 2021; 6:2049-58.
19. Andress DL, Coyne DW, Kalantar-Zadeh K, Molitch ME, Zangeneh F, Sprague SM. Management of secondary hyperparathyroidism in stages 3 and 4 chronic kidney disease. Endocr Pract 2008; 14:18-27.
20. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA and Andress DL. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. Kidney Int 2007; 71:3138.
21. Emmanuelle NE, Marie-Cécile V, Florence T, Jean-François A, Françoise L, Coralie F, Alexia V. Critical role of estrogens on bone homeostasis in both male and female: from physiology to medical implications. Int J Mol Sci 2021; 22:1568.
22. Centeno PP, Herberger A, Mun HC, Tu C, Nemeth EF, Chang W, Conigrave AD, Ward DT. Phosphate acts directly on the calcium-sensing receptor to stimulate parathyroid hormone secretion. Nat Commun 2019; 10:4693.
23. Pavlović D, Katičić D, Josipović J. Chronic kidney disease--mineral and bone disorder: why and how to control phosphate. Acta Med Croat 2012; 66:64–7.
24. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO4, Ca × PO4 product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12:2131-38.
25. Ritz E, Hahn K, Ketteler M, Kuhlmann MK, Mann J. Phosphate additives in food-a health risk. Dtsch Arztebl Int 2012; 109:49-55.
26. Saravani R, Qureshi M, Jafari M. Correlation between serum level parathormone, alkaline phosphatase, calcium and phosphorus of patients hemodialysis in Zahedan. J Med Sci 2007; **7**:154–7.
27. Blayney MJ, Pisoni RL, Bragg-Gresham JL, Bommer J, Piera L, Saito A, Akiba T, Keen ML, Young EW, Port FK. High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death. Kidney Int 2008; 74:655-63.
28. Li J, Molnar MZ, Zaritsky JJ, Sim JJ, Streja E, Kovesdy CP, Salusky I, Kalantar-Zadeh K. Correlates of parathyroid hormone concentration in hemodialysis patients. Nephrol Dial Transplant 2013; 28:1516-25.
29. Goodman WG, Quarles LD. Development and progression of secondary hyperparathyroidism in chronic kidney disease: Lessons from molecular genetics. Kidney Int 2008; 74:276-88.
30. Sliem H, Tawfik G, Moustafa F, Zaki H. Relationship of associated secondary hyperparathyroidism to serum fibroblast growth factor-23 in end stage renal disease: a case-control study. Indian J Endocrinol Metab 2011; 15:105.
31. Nakai S, Akiba T, Kazama J, Yokoyama K, Fukagawa M, Tominaga Y, Iseki K, Tsubakihara Y; Patient Registration Committee of the Japanese Society for Dialysis Therapy, Tokyo, Japan. Effects of serum calcium, phosphorous, and intact parathyroid hormone levels on survival in chronic hemodialysis patients in Japan. Ther Apher Dial 2008; 12:49-54.
32. Li J. Correlates of parathyroid hormone concentration in hemodialysis patients. Nephrol Dial Transplant 2013; 28:1516-25.
33. Xu Y, Evans M, Soro M, Barany P, Carrero JJ. Secondary hyperparathyroidism and adverse health outcomes in adults with chronic kidney disease. Clin Kidney J 2021; 14:2213-20.
34. Geng S, Kuang Z, Peissig PL, Page D, Maursetter L, Hansen KE. Parathyroid hormone independently predicts fracture, vascular events, and death in patients with stage 3 and 4 chronic kidney disease. Osteoporos Int 2019; 30:2019-25.

35. Memon I, Norris KC, Bomback AS, Peralta C, Li S, Chen SC, McCullough PA, Whaley-Connell A, Jurkovitz C, Tamura MK, Saab G. For the Kidney Early Evaluation Program Investigators. The association between parathyroid hormone levels and hemoglobin in diabetic and nondiabetic participants in the National Kidney Foundation's Kidney Early Evaluation Program. Cardiorenal Med 2013; 3:120-7.
36. Molnar MZ, Czira M, Ambrus C, Szeifert L, Szentkiralyi A, Beko G, Rosivall L, Remport A, Novak M, Mucsi I. Anemia is associated with mortality in kidney-transplanted patients--a prospective cohort study. Am J Transplant 2007; 7:818-24.
37. Choukroun G, Kamar N, Dussol B, Etienne I, Cassuto-Viguier E, Toupance O, Glowacki F, Moulin B, Lebranchu Y, Touchard G, Jaureguy M, Pallet N, Le Meur Y, Rostaing L, Martinez F; CAPRIT study Investigators. Correction of postkidney transplant anemia reduces progression of allograft nephropathy. J Am Soc Nephrol 2012; 23:360-8.
38. Drüeke TB, Eckardt KU. Role of secondary hyperparathyroidism in erythropoietin resistance of chronic renal failure patients. Nephrol Dial Transplant 2002; 17:28-31.
39. Kalantar-Zadeh K, Lee GH, Miller JE, Streja E, Jing J, Robertson JA, Kovesdy CP. Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in hemodialysis patients. Am J Kidney Dis 2009; 53:823-34.
40. Sonkar SK, Singh HP, Sonkar GK, Pandey S. Association of Vitamin D and secondary hyperparathyroidism with anemia in diabetic kidney disease. J Family Med Prim Care 2018; 7:815-8.
41. Park CW, Shin YS, Kim CM, Lee SY, Kim SY. Incresed C reactive protein following hemodialysis predict cardiac hypertrophy in chronic hemodyalisis patients. Am I Kidney dis 2002; 40:1230-9.
42. Lavín-Gómez BA, Palomar-Fontanet R, Gago-Fraile M, Quintanar-Lartundo JA, Gómez-Palomo E, González-Lamuño D, García-Unzueta MT, Arias-Rodríguez MA, Gómez-Gerique JA. Inflammation markers, chronic kidney disease, and renal replacement therapy. Adv Perit Dial 2011; 27:33-7.
43. Tsirpanlis G, Bagos P, Ioannou D, Bleta A, Marinou I, Lagouranis A, Chatzipanagiotou S and Nicolaou C. Exploring inflammation in hemodialysis patients: Persistent and superimposed inflammation. A longitudinal study. Kidney Blood Press Res 2004; 27:6370.
44. Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol 2006; 17:2006-16.
45. Menon V, Greene T, Wang X, Pereira AA, Marcovina SM, Beck GJ, Kusek JW, Collins AJ, Levey AS, Sarnak MJ. C-reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. Kidney Int 2005; 68:766-72.
46. Kes P, Bašić-Kes V, Furić-Čunko V, Mesar I, Bašić-Jukić N. Dyslipidemia and stroke in patients with chronic kidney disease. Acta Med Croatica 2014; 68:141-9.
47. Sonmez A, Yilmaz MI, Saglam M, Unal HU, Gok M, Cetinkaya H, Karaman M, Haymana C, Eyileten T, Oguz Y, Vural A, Rizzo M, Toth PP. The role of plasma triglyceride/high-density lipoprotein cholesterol ratio to predict cardiovascular outcomes in chronic kidney disease. Lipids Health Dis 2015; 14:29.
48. Fissell RB, Karaboyas A, Bieber BA, Sen A, Li Y, Lopes AA, Akiba T, Bommer J, Ethier J, Jadoul M, Pisoni RL, Robinson BM, Tentori F. Phosphate binder pill burden, patient-reported non-adherence, and mineral bone disorder markers: Findings from the DOPPS. Hemodial Int 2016; 20:38-49.
49. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, Fouque D, Friedman AN, Ghaddar S, Goldstein-Fuchs DJ, Kaysen GA, Kopple JD, Teta D, Yee-Moon Wang A, Cuppari L. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. Am J Kidney Dis 2020; 76:1-107.