BANTAO Journal 2017; 15(1): 16-19

BJ

BANTAO Journal

Original article

Influence of Hemodialysis Treatment on Biochemical Markers of Bone Disease

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Abstract

Introduction. Bone disease is a chronic complication of chronic kidney disease and major clinical problem in hemodialysis (HD) patients. The aim of our study was to assess the influence of treatment longevity on biochemical parameters of mineral and bone metabolism in HD patients, and to identify the most important parameters.
Methods. The research was observational and retrospective, involved 70 patients, mean age 58.69±12.54, divided into groups in respect to the duration of dialysis treatment (Group I-5 years, Group II-5-10 years and Group III-over 10 years).
Results. Serum phosphorus was increased, but the values tend to increase along with dialysis duration - (Group I: 1.93±0.45; Group II: 1.97±0.50; Group III: 2.01±0.37; p>0,05). Calcium values were also not significantly increased based on the duration of treatment [Group I: 2.3 (2.2-2.41); Group II: 2.46 (2.15-2.6), Group III: 2.35 (2.10-2.52)]. Dialysis and PTH correlated positively in the first group of patients (Rho=0.470, p=0.013). The values of calcium and alkaline phosphatase correlated positively in all patients (Rho=0.351, p=0.003). PTH was significantly higher in the second and third compared to the first group (p=0.009 and p=0.038, respectively), and there was no significant difference between the second and the third group. Interestingly, parathyroidectomized patients had higher PTH values compared to those without parathyroidectomy (557 vs. 359 pg/ml).
Conclusion. The most reliable marker for clinical monitoring of bone disease in dialysis patients is PTH. The values of calcium and phosphorus are highly variable and not reliable parameters for bone disease follow-up.

Keywords: hemodialysis duration, mineral and bone metabolism, PTH

Introduction

Chronic kidney disease is defined as kidney failure that persists for at least 3 months, caused by structural or functional kidney disorder, manifested by histological abnormalities or disorders characterized by blood, urine or kidney appearance, with decrease in glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for over 3 months [1,2]. It is characterized by different level of uremia but also by changes in the volume and content of body fluids and electrolytes, and imbalance of numerous hormones. In the progression of CKD the disorder in the metabolism of calcium (Ca) and phosphorus (P), and parathyroid hormone (PTH) and vitamin D3 occurs at an early stage [2], according to some studies already with the glomerular filtration rate (GFR) of 60 ml/min/ 1.73m^2, that is in the second stage of CRF [3]. This disorder deteriorates from stage to stage and is therefore significantly represented in patients on dialysis. Complicated causal effects in this electrolyte-hormone imbalance can be explained by the kidney tissue prolapse which results in decrease of active metabolite of vitamin D3 (1.25(OH)2D3) synthesis [4]. It results from the phosphate retention along with a decreased absorption of Ca, and both hyperphosphatemia and hypocalcemia stimulate parathyroid glands with the development of secondary hyperparathyroidism and disordered Ca and PTH regulation. If accompanied by bone resistence to PTH effect, this metabolic imbalance leads to significant disorder in bone metabolism, especially in patients on dialysis [3-6]. Progressive bone abnormalities in patients with CKD are traditionally qualified as renal osteodystrophy (ROD). However, the National Kidney Foundation (NKF) provided new recommendations according to which the term ROD is used to explain modification of bone structure morphology in patients with CKF, based exclusively on histological results obtained from bone biopsy. Clinical, bioche-

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mical and radiological abnormalities associated with ROD should be treated as elements of wider clinical syndrome; Chronic Kidney Disease-Mineral and Bone Disorder, i.e. CKD-MBD Syndrome [5-7]. In dialysis patients the CKD-MBD syndrome is characterized by:

- abnormality in metabolism of Ca, P, PTH and vitamin D3, and/or
- abnormalities in bone turnover, mineralization, volume and bone growth, and/or
- vascular calcifications and calcifications of other soft tissues.

According to some authors, bone biopsy is a "golden" standard in diagnosing and monitoring of bone abnormalities [5-7], but having in mind the invasive character of the procedure, it has been recommended only in cases which from the clinical-biochemical perspective are not clear enough (e.g. in patients with high PHT values and low concentration of alkaline phosphatase).
Clinical symptoms of mineral-bone metabolism occur at a rather late stage of CKD. Some studies have reported that clinical symptoms are present in at least 10% of patients, and histomorphological changes in 35-90% of cases [8]. Given that the mineral-bone metabolism can be diagnosed based on laboratory findings and before the occurrence of the initial symptoms, it is important to primarily monitor the level of parathyroid hormone, but also the level of alkaline phosphatase, Ca, P, and vitamin D, in order to timely administer the appropriate therapy and prevent more severe consequences. It is evident that extended HD treatment can only deteriorate these problems if not timely detected and appropriately treated. With regard to chronology of the problem related to calcium and phosphate metabolism in HD patients, we were interested in selection of the most significant parameters that changed over the time spent on hemodialysis, and could have influenced the bone disease development. The aim of the study was to assess the influence of HD treatment longevity on biochemical parameters of mineral and bone metabolism in HD patients, and to identify the most important monitoring parameters.

Materials and methods

This was an observational, retrospective and cross-sectional study conducted at the Clinic of Hemodyalisis, University Clinical Center Sarajevo (UCCS), from January to December 2015. The study included 70 regular (three times a week) HD patients. The respondents were divided into groups based on hemodialysis treatment duration: Group I-HD duration <5 years; Group II-HD duration from 5-10 years; Group III-HD duration >10 years.
The study did not include patients with malignant and liver diseases, acute infections and septic syndrome. All patients used dialysis solution with 1.25 mmol /L calcium concentration. Also, all patients used the same phosphate binder, calcium carbonate. In the local UCCS laboratory, the following biochemical parameters were regularly monitored: serum calcium, serum phosphate and alkaline phosphates (four times a year), at analyzer Vitros 5600 Integrated System Microslide Technology, using Principles of Spectrophotometry. Determination of intact PTH was performed in the laboratory of the Clinic of Nuclear Medicine at apparatus Cobas 6000 and Cobas 411 (Roche), using an immunoassay analyzer. The reference values were set based on the recommendations of good clinical practice of the American Initiative for the successful hemodialysis outcome (K/DOQI Clinical Practice Guidelines): 150-400 pg/ml for PTH, 2.10-2.60 mmol/l for calcium, from 1.13-1.78 mmol/l for phosphorus and for Ca x P <4.40 $mmol^2/l^2$ [9,10].
Statistical analysis was performed with the SPSS 16 software (version 16.0, SPSS Inc, Chicago, Illinois, USA). Division of variables was tested by the Kolmogorov-Smirnov or Shapiro-Wilk test. The data was presented as median, mean value and interquartile range. For continuous variables, the comparison between the groups was made using the Kruskal-Wallis or Mann-Whitney U-test. Correlation between the continuous variables was tested by Spearman's correlation analysis. P-values less than 0.05 were considered statistically significant [11].

Results

Of the total number of 70 patients, 27 were females (38.5%) with mean age of 59.91±14.73 years, ranging from 19-87 years. The most common basic disease of the patients was pyelonephritis-in 26 patients (37.1%), followed by glomerulonephritis in 14 patients (20%), hypertension in 13 patients (18.5%), diabetes mellitus in 15.7%, polycystic kidney disease in 7.1% and lupus nephritis in 1.6% of patients.

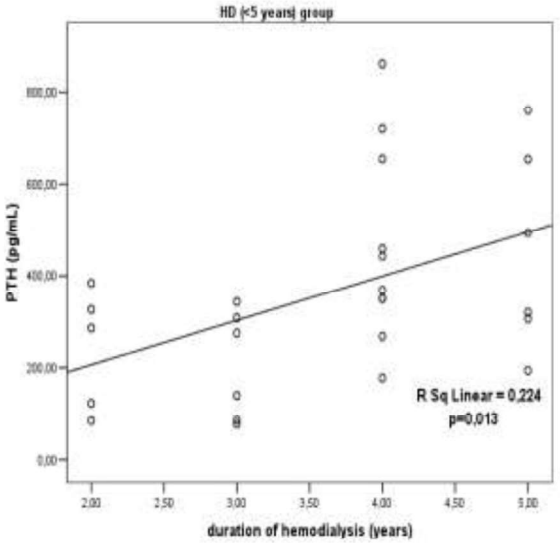

Fig. 1. Correlation of PTH levels and duration of hemodialysis in Group I patients with HD duration <5 years (Rho=0.470; p=0.013)

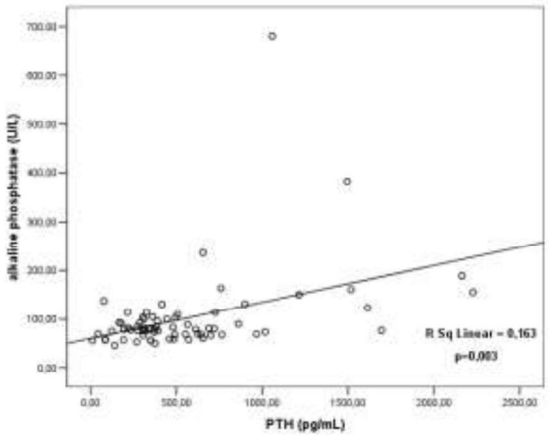

Fig. 2. PTH and alkaline phosphatase correlated positively in all patients (Rho=0.351; p=0.003)

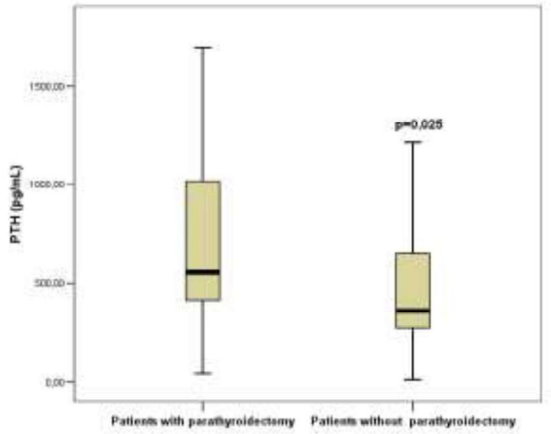

Fig. 3. PTH values in patients with and without parathyroidectomy

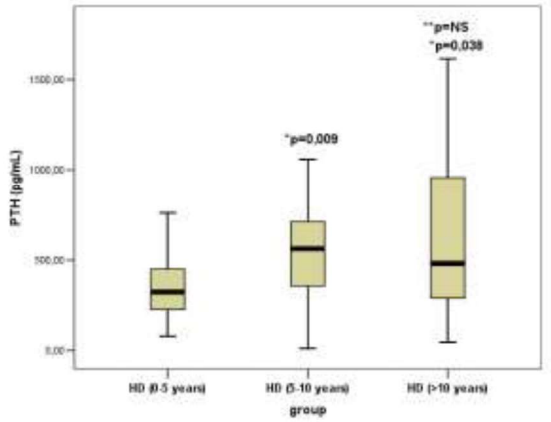

Fig. 4. PTH was significantly higher in the second and third compared to the first group (p=0.009 and p=0.038, respectively), with no significant difference between the second and third group

The highest proportion of patients was in Group I-40%, followed by Group III-31.42% and Group II-17.1%.
There was no significant difference in phosphate levels between the groups (Group I: 1.93±0.45; Group II: 1.97±0.50; Group III: 2.01±0.37; p=ns). The same pattern with similar levels between the groups was observed for calcium [(Group I: 2.3 (2.2-2.41); Group II: 2.46 (2.15-2,6), Group III: 2.35 (2.10-2.52): p=ns].
The duration of hemodialysis treatment and PTH levels correlated positively in Group I, Rho=0.470, p= 0.013 (Figure 1).
PTH and alkaline phosphatase correlated positively (Rho= 0.351, p=0.003) in all patients (Figure 2).
Interestingly, PTH level was higher in parathyreoidectomized patients compared to the others without parathyroidectomy (557 vs 359,5 pg/ml, p=0.025) (Figure 3).
PTH was significantly higher in the second and third compared to the first group (p=0.009 and p=0.038, respectively), while there was no significant difference between the second and third group (Figure 4).

Discussion

Abnormalities of mineral-bone metabolism are frequent both in predialysis patients with CKD and in HD patients. The effective clinical approach to these patients implies the control of phosphate retention and prevention of hyperphosphatemia in order to preserve the serum Ca level within the reference ranges and prevent proliferation of parathyroid gland cells, and subsequent increase in PTH [12].
Of the total of 70 patients, 14(20%) were with parathyroidectomy.
The growth trend of PTH was mainly monitored in Group II (duration of dialysis from 5 to 10 years), as well as increased PTH values mainly in patients with parathyroidectomy. Phosphorus, as the most important parameter of mineral-bone metabolism control, had increased values in all groups of patients, which indicates the possibility of bone disease complications, bone deformities and increased cardiovascular morbidity and mortality.
Although all our patients were on calcium-based phosphate binder therapy, satisfactory phosphate control during hemodialysis treatment was not achieved. There could be various reasons thereof, but the most common are inadequate phosphate intake and irregular treatment with phosphate binders.
Increased production of calcium and phosphorus (increased values of calcium and phosphate) during hemodialysis lead to an increased risk of intravascular calcifications and subsequent increase in cardiovascular morbidity and mortality of these patients [13-16].
Given the high PTH values in the group of patients with parathyroidectomy, there is a question related to the existance of ectopic parathyroid tissue, hyperactivity of other parathyroid glands, which are postoperatively repeatedly connected with longer duration of dialysis.
Some studies allege that bone specific AF (bAF) shows a high statistically significant interdependency with PTH in monitoring the progression of bone disease. It is also alleged that there is statistically significant corre-

lation between the total AF and PTH but to a lesser extent [17,18].

Taking into account that disorder of the mineral-bone metabolism leads to a significant deterioration in quality of life, morbidity, and also mortality, primarily of cardiovascular system, the recommendations of good clinical practice of the American Initiative for successful dialysis outcome (K/DOQI Clinical Practice Guidelines) are that levels of PTH and AF are determined every three months in patients on dialysis, and levels of Ca and P each month, and even more frequently in patients on therapy, [19] in order to ensure adequate control, slow down the progression and improve the quality of life for dialysis patients.

Conclusion

The examination of biochemical markers of mineral-bone metabolism has shown that PTH is the most reliable marker for clinical monitoring of bone disease, as it correlates well with the values of alkaline phosphates and calcium, whereas the levels of calcium and phosphate are highly variable and not reliable indicator of bone metabolism in patients on hemodialysis. Given the high PTH values in the group of patients with parathyroidectomy, there is a question related to the existance of ectopic parathyroid tissue, hyperactivity of other parathyroid glands, which are postoperatively repeatedly connected with longer duration of dialysis (20% of patients were with parathyroidectomy). Increased levels of calcium and phosphates during hemodialysis treatment lead to an increased risk of intravascular calcificates and subsequent increase of cardiovascular morbidity and mortality of these patients. American Initiative for successful dialysis outcome (K/DOQI Clinical Practice Guidelines) recommended that levels of PTH and AF are determined every three months in patients on dialysis, and levels of Ca and P each month, and even more frequently in patients on therapy, in order to ensure adequate control, reduce the progression of bone disease and improve the quality of life for dialysis patients.

Conflict of interest statement. None declared.

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