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Original Scientific Paper

OSTEOPROTEGERIN AS AN EARLY SIGN OF CHRONIC KIDNEY DISEASE-MINERAL AND BONE DISORDER

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SUMMARY – Chronic kidney disease (CKD) is among the most significant health problems, with the associated cardiovascular disease and bone metabolism disorders being the leading cause of morbidity and mortality in these patients. The aim of the study was to determine markers of bone turnover in patient sera (phosphates, calcium, alkaline phosphatase, parathyroid hormone and osteoprotegerin (OPG)) in all stages of kidney failure including kidney transplant recipients. We also wanted to determine whether dialysis vintage affects recovery of bone markers one year after transplantation. There were 164 study patients, whereas 30 healthy individuals served as a control group. Serum OPG progressively increased with decline of the glomerular filtration rate. The highest OPG concentration was recorded in dialysis group. We observed a statistically significant OPG increase in stage 2 CKD. In kidney transplant group, there was positive correlation between OPG and dialysis vintage. We also found that serum OPG was lower in patients treated with dialysis for less than 4 years prior to transplantation. We confirmed that CKD-mineral and bone disorder began in stage 3 CKD with parathyroid hormone and OPG elevation, and a statistically significant OPG increase in stage 2 CKD might be an early sign of CKD-mineral and bone disorder. Dialysis vintage longer than 4 years is associated with more significant disturbances in mineral and bone metabolism.

Key words: *Renal dialysis; Renal insufficiency, chronic; Kidney transplantation; Osteoprotegerin; Chronic kidney disease–Mineral and bone disorder*

Introduction

Chronic kidney disease (CKD) is one of the major health problems worldwide. Many patients with chronic renal failure and glomerular filtration rate (GFR) below 60 mL/min *per* 1.73 m^2 have mineral and bone disorder. This disorder is called chronic kidney disease-mineral and bone disorder (CKD-MBD) and is manifested by abnormalities in calcium, phosphorus, parathyroid hormone (PTH) and vitamin D metabolism, and abnormalities in bone metabolism or extraosseous calcifications[1]. The leading cause of morbidity and mortality in patients with chronic kidney failure are vascular calcifications and bone turnover disorders[2,3]. The Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD guidelines recommend monitoring serum levels of calcium, phosphorus, PTH an alkaline phosphatase (ALP) beginning in

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stage 3 CKD[1]. However, despite monitoring and treatment recommendations, many patients with advanced CKD have mineral and bone disorder. Also, there are not enough data on bone specific treatment outcomes and bone biopsies in kidney transplant recipients[1].

In a healthy individual, there is a balance between bone resorption and formation in a process called bone remodeling. Many factors such as age, sex, hormones, cytokines and exogenus factors can influence this balance. PTH, vitamin D, FGF-23, osteoprotegerin (OPG) and RANKL coordinate this process in a synergy with the gastrointestinal tract, parathyroid glands, kidneys, and bones[4]. Discovery of the OPG/RANKL/RANK signaling system helped us understand the physiology of bone remodeling, osteoclastogenesis, and cell-to-cell communication between osteoblasts and osteoclasts[5].

In CKD patients, OPG is above the normal range. OPG is higher in patients with lower GFR and longer dialysis vintage[6,7]. Despite the fact that it is not removed through hemodialysis or glomerular membrane, it normalizes after kidney transplantation[8,9]. After kidney transplantation, OPG is comparable to healthy individuals[10].

This study was designed to investigate serum bone turnover markers in all stages of kidney failure, including patients on hemodialysis and kidney transplant patients. The aim was to determine the threshold when it is necessary to start treatment for CKD-MBD. Also, we wanted to determine whether dialysis vintage affects the CKD-MBD improvement one year after transplantation.

The research was carried out according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from all individuals included in the study and the study was approved by the institutional Bioethics Committee.

Patients and Methods

Patients

In this single center study, we enrolled 164 Caucasian patients. Patients were divided into five groups (stage 2, 3 and 4 of chronic kidney failure, hemodialysis, and kidney transplant group). Each group had 15 male and 15 female participants except for the hemodialysis group (25 male and 25 female) and the kidney transplant group (15 male and 9 female). The underlying renal disease was chronic glomerulonephritis in 94 patients, diabetic nephropathy in 33 patients, hypertensive renal injury in 28 patients, polycystic kidney disease in 5 patients, and chronic pyelonephritis in 4 patients. Transplant patients were divided into the group with dialysis vintage <4 years and the group with dialysis vintage ≥4 years because the average waiting time for a kidney at our center is around 4 years. The group with dialysis vintage <4 years included 11 patients (7 male and 4 female) and the group with dialysis vintage ≥4 years included 12 patients (8 male and 5 female). The reason for the unequal number of male and female patients in the transplant group was the insufficient number of female patients meeting our criteria. The inclusion criterion for the transplant group was GFR >60 mL/min/1.73m^2 three months after kidney transplantation. The study exclusion criteria were active malignant disease, acute inflammation, liver failure, peritoneal dialysis, women with menstrual cycles, history of renal transplantation and corticosteroid therapy (except for the kidney transplant group). Thirty healthy individuals (15 male and 15 female) with similar age- and sex-matched to patient characteristics served as the control group. The inclusion criteria for this group were no evidence for kidney, bone or liver disease and no record of taking medications that could affect bone metabolism. The immunosuppressive protocol consisted of mycophenolate mofetil, tacrolimus and corticosteroids. We used the Modification of Diet in Renal Disease (MDRD) study formula for estimating GFR.

Laboratory analysis

Venous blood was drawn in the morning after an overnight fast. Serum concentrations of calcium, phosphate, urea, creatinine, ALP, intact parathyroid hormone (iPTH) and albumin were measured using standard methods at central laboratory, Rijeka University Hospital Center. Blood samples for OPG analysis were centrifuged, sera aliquoted and stored at -80 °C. The ELISA assay was used for measuring serum OPG concentrations. We used a commercially available kit (Biovendor Research and Diagnostic Products, Brno, Czech Republic).

Statistical analysis

Data with normal distribution were expressed as mean ± standard deviation (SD). Data with non-normal distribution were expressed as median with range. The T-test was used to compare data between the two groups. Data with non-normal distribution were evaluated using Mann-Whitney test. Pearson correlation coefficient was used on correlation anal-

ysis. A two-tailed p value less than 0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Analyzer Wizard, version 1.8.15.

Results

Bone turnover markers in predialysis, hemodialysis and kidney transplant patients

Calcium, phosphate, ALP and PTH were within the normal range in stage 2 CKD. Serum OPG was significantly higher in stage 2 CKD compared to the control group (5.7±2 pmol/L *vs.* 4.5±1.6 pmol/L; p=0.01). In stage 3 CKD, calcium, phosphate, and ALP concentrations were also within the normal range. Serum PTH was significantly higher in stage 3 CKD than in stage 2 CKD (9.5**±7**.6 pmol/L *vs.* 4.01±1.82 pmol/L; p<0.001), and so was OPG (7.2±2.8 pmol/L *vs.* 5.7±2 pmol/L; p=0.025). In stage 4 CKD, serum calcium, phosphate and ALP were still in the normal range. PTH was significantly higher than in stage 3 (20.56±17.33 pmol/L *vs.* 9.53±7.62 pmol/L; p=0.002). Serum OPG was also higher (8.2±2.7 pmol/L) but nonsignificantly.

Hemodialysis patients were characterized by GFR <15 mL/min/1.73^2. Calcium and ALP were in the normal range while PO_4 was high (1.73**±0**.51 mmol/L). Serum OPG and PTH increased further. In hemodialysis group, serum OPG was significantly higher compared to predialysis patients (10.4±4 pmol/L *vs.* 7.03±0.6 pmol/L; p<0.001), and so was PTH (59.3±59.1 pmol/L *vs.* 11.4±2.7 pmol/L; p<0.001).

The inclusion criterion for the kidney transplant group was GFR >60 mL/min/1.73 m^2 three months after transplantation. The mean GFR in this study population was 68.5±9.6 mL/min *per* 1.73 m^2. Phosphate and ALP were in the normal range. Calcium was higher than normal (2.6±0.58 mmol/L). PTH was above the normal range (20.5±19.4 pmol/L). Serum OPG was lower in the transplant group than in stage 2 CKD (5.0±1.5 pmol/L *vs.* 5.7±2 pmol/L; p=0.172). Serum OPG did not differ significantly between the kidney transplant group and control group (p=0.191). Clinical and laboratory characteristics of patients are shown in Table 1. Serum OPG levels in predialysis patients are illustrated in Figure 1.

Table 1. Demographic data and serum biochemical bone markers in different stages of chronic kidney disease expressed as mean ± standard deviation

	Control group	Stage 2 CKD	Stage 3 CKD	Stage 4 CKD	HD	Tx
n	30	30	30	30	50	24
Gender (M/F)	15/15	15/15	15/15	15/15	25/25	15/9
GFR (mL/min *per* 1.73 m^2)	95.9±4.6	75.4±8.4	41.1±9.9	21±4.3	<15	68.5±9.6
Ca (mmol/L)	2.28±0.08	2.29±0.17	2.21±0.29	2.22±0.35	2.31±0.19	2.6±0.58
PO_4 (mmol/L)	0.97±0.11	1.01±0.21	1.16±0.38	1.41±0.47	1.73±0.51	0.86±0.22
ALP (U/L)	86.1±21.2	74.2±20.6	73.2±28.5	97.4±26	100±49	84.7±33.7
iPTH (pmol/L)	4.46±1.94	4.01±1.82	9.53±7.62	20.56±17.33	59.3±59.1	20.48±19.4
OPG (pmol/L)	4.5±1.6	5.7±2	7.2±2.8	8.2±2.7	10.4±4	5.0±1.5

CKD = chronic kidney disease; HD = hemodialysis; Tx = kidney transplant recipients; M/F = male/female; GFR = glomerular filtration rate; Ca = calcium; PO_4 = phosphorus; ALP = alkaline phosphatase; iPTH = intact parathyroid hormone; OPG = osteoprotegerin

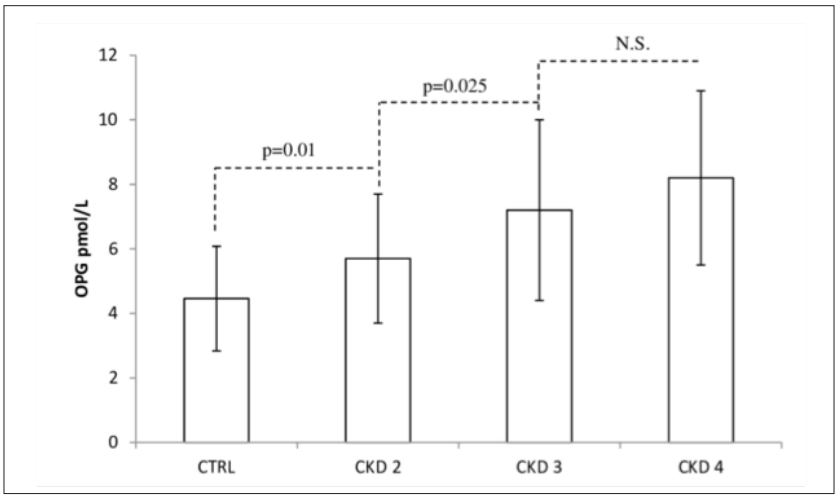

Fig. 1. Serum OPG in control group and CKD stage 2, 3 and 4

OPG = osteoprotegerin; CKD = chronic kidney disease; CTRL = control group; NS = nonsignificant

Osteoprotegerin in predialysis, hemodialysis and kidney transplant groups vs. control group

Serum OPG was significantly lower in the control group compared to predialysis patients (4.5±1.6 pmol/L *vs.* 7.03±0.6 pmol/L; p<0.001). Also, OPG in the predialysis group was lower compared to the hemodialysis group (7.03±0.6 pmol/L *vs.* 10.4±4 pmol/L; p<0.001). There was a significant difference between the hemodialysis and kidney transplant groups (10.4±4 pmol/L *vs.* 5.0±1.5 pmol/L; p<0.001). Comparing the transplant group and predialysis patients, we found lower OPG in the transplant group (5.0±1.5 pmol/L *vs.* 7.03±0.6 pmol/L; p<0.001). Serum OPG was lower in the control group but the difference between the control and kidney transplant group was not statistically significant (Fig. 2).

Serum osteoprotegerin and bone turnover markers one year after kidney transplantation

Transplant patients were divided into a group with dialysis vintage <4 years and group with dialysis vintage ≥4 years. Calcium, phosphate, ALP and PTH did not differ significantly between these groups of

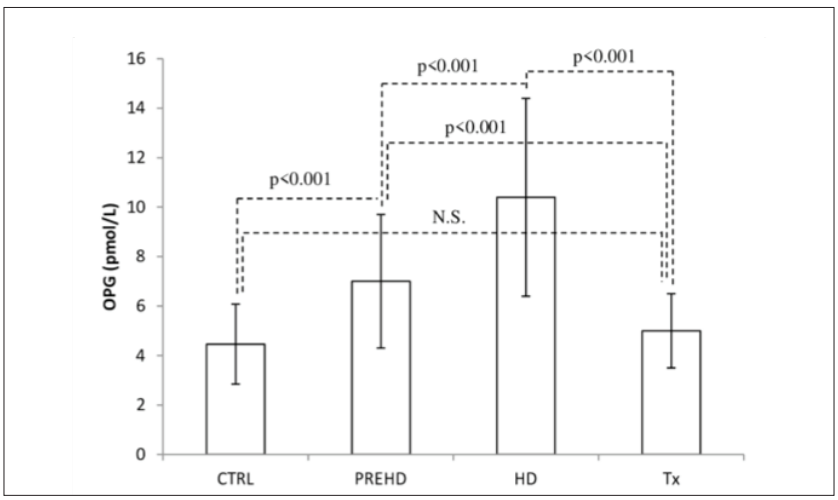

Fig. 2. Serum OPG in control, predialysis, hemodialysis and kidney transplant groups

OPG = osteoprotegerin; CTRL = control group; PREHD = predialysis patients; HD = hemodialysis patients; Tx = kidney transplant recipients; NS = nonsignificant

patients. Serum OPG was lower in the group with dialysis vintage <4 years and almost reached statistical significance (4.4 pmol/L *vs*. 5.6 pmol/L; p=0.06).

Discussion

Almost every person with chronic kidney failure is at an increased risk of developing disturbances of bone and mineral metabolism (CKD-MBD), which can be presented as a disorder of mineral metabolism, as bone turnover disbalance, or as vascular and soft tissue calcifications[11]. These patients often complain of bone pain. Bones are fragile and prone to fractures even after minor trauma. Also, bone deformities and growth retardation are frequently seen in pediatric CKD population[12]. Bone turnover disorders and vascular calcifications significantly increase morbidity and mortality, especially in the elderly, who are most prevalent in CKD population[2,3]. Although there are strict rules for the maintenance of serum calcium and phosphorus concentrations within a narrow range, there still are a lot of patients with a severe clinical picture of bone turnover abnormalities and vascular calcifications.

For the first time, bone turnover markers and OPG were investigated in patients with all stages of kidney failure (stage 2, 3 and 4, hemodialysis patients and transplant patients). Also, for the first time, we investigated the effect of dialysis vintage prior to kidney transplantation on bone turnover markers and OPG.

Bone turnover markers in predialysis, hemodialysis and kidney transplant patients

In stage 2 CKD, calcium, phosphate, PTH and ALP were normal while OPG was significantly higher than in the control group (5.7±2 pmol/L *vs.* 4.5±1.6 pmol/L; p=0.01). We did not find any articles on OPG in stage 2 CKD. A study design almost like ours was the study by Jiang *et al*. They showed the increase in OPG but in stage 3[13]. Calcium and phosphate were still normal in stage 3 and 4 CKD. This is an indicator of good patient management regarding dietary advice and drug treatment (calcium supplements, phosphate binders, vitamin D and its analogs). In stage 3 CKD, PTH levels started to rise[1]. Serum OPG was significantly higher than in stage 2 (p=0.025). In a study on 46 chronic kidney patients, Kazama *et al*. also showed that OPG increased progressively with GFR decline[7].

In stage 4 CKD, PTH was high due to phosphate retention and decreased vitamin D production. Phosphates were normal but at the high end of the normal range (1.41 mmol/L). Serum OPG was higher than in stage 3 CKD but not significantly (p=0.15).

In the hemodialysis group, serum calcium was normal but phosphates were elevated (1.73 mmol/L). These patients need much more dietary control and treatment with phosphate binders to maintain phosphates within the normal range because phosphate absorption from food exceeds phosphate removal during dialysis[14,15]. KDIGO guidelines suggest maintaining iPTH in the range of 2-9 times the upper limit of the normal range[1]. In our group of hemodialyzed patients, serum iPTH was in that range (59.3 pmol/L; normal 1.1-7.3 pmol/L). Higher serum iPTH is important for maintaining high bone turnover. Serum OPG was highest in this group (10.4 pmol/L). Patients on hemodialysis commonly have higher serum OPG although this molecule is not filtered through the glomerular or hemodialysis membrane[8].

In the transplant group, serum calcium was above the normal range. It is known that six months after kidney transplantation, calcium retains at the high end of normal[16,17]. However, hypercalcemia can also be found in <5% to >50% of transplant patients[18]. Hyperparathyroidism and restored renal function are the reasons for low phosphate levels in this group of patients. Serum iPTH remained high (20.48 pmol/L) but significantly lower than in the hemodialysis group of patients (p=0.003). This condition is called tertiary hyperparathyroidism due to parathyroid hyperplasia and low vitamin D_3. The mean serum OPG was lower compared to OPG in stage 2 CKD but nonsignificantly (p=0.172). The serum OPG difference between the control and kidney transplant groups was not significant (p=0.191). Similar results have been reported by other authors[10,19].

Osteoprotegerin in predialysis, hemodialysis and kidney transplant groups

We did not find a study in which OPG was monitored through stages 2, 3 and 4 CKD, in patients on hemodialysis and in transplant patients. Only the study by Jiang *et al*. was conducted on 60 patients grouped from stage 1 to stage 5 CKD. Controls were 18 patients on hemodialysis. They found that an increase in OPG occurred in stage 3 CKD before the elevation of PTH and phosphates[13].

We found that OPG was continuously increasing through CKD stage 2, 3, and 4 compared to the control group. Serum OPG in stage 2 CKD was significantly higher compared to the control group (p=0.01).

This could be an early sign of CKD-MBD since the increase in serum OPG occurred before calcium, phosphate, PTH or ALP alteration. Serum OPG was higher in the hemodialysis group than in predialysis patients ($p<0.001$). One year after kidney transplantation, OPG significantly decreased compared to hemodialysis patients ($p<0.001$) and predialysis patients ($p<0.001$). Serum OPG was even lower than OPG in stage 2 CKD but not significantly ($p=0.172$).

Serum osteoprotegerin and bone turnover markers one year after kidney transplantation

Serum OPG was lower in the group of patients with dialysis vintage <4 years compared to the group of patients with dialysis vintage ≥4 years ($p=0.06$). These results almost reached statistical significance. It is known that hemodialysis is associated with numerous complications but mostly with cardiovascular complications and bone metabolism disturbances[1,20,21]. It is not possible to determine the period of regular dialysis treatment after which bone and mineral metabolism disorder becomes irreversible. In this study, we found higher OPG in kidney recipients with dialysis vintage >4 years. This could mean that dialysis longer than 4 years may be related to more significant CKD-MBD one year after kidney transplantation. Therefore, it is necessary to conduct more studies with a larger number of patients to confirm this thesis.

For the first time, OPG and bone turnover markers were analyzed in a large group of patients with all kidney failure stages, including patients on hemodialysis and kidney transplant recipients. So far, there have been no studies analyzing the impact of dialysis vintage on OPG and bone turnover markers. We confirmed that mineral and bone disorder began in stage 3 CKD with an increase in iPTH and OPG levels. Serum OPG increase in stage 2 CKD was statistically significant compared to the control group and could be an early sign of CKD-MBD. Bone turnover markers were continuously increasing with the progression of kidney failure. Hemodialysis is one of the most significant risk factors for cardiovascular disease and bone metabolism disorders. Dialysis longer than 4 years could be associated with a more significant CKD-MBD. Treatment of CKD-MBD should be initiated as soon as possible but necessarily in stage 3 CKD. It is also mandatory to continue treatment of CKD-MBD in all types of renal replacement therapy.

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Sažetak

OSTEOPROTEGERIN KAO RANI PREDSKAZATELJ MINERALNO-KOŠTANOG POREMEĆAJA U BOLESNIKA S KRONIČNOM BUBREŽNOM BOLESTI

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Kronična bubrežna bolest (KBB) važan je javnozdravstveni problem pri čemu su kardiovaskularne komplikacije i poremećaj mineralno-koštanog metabolizma vodeći uzroci pobola i smrtnosti ovih bolesnika. U ovom istraživanju mjerene su koncentracije biljega koštane pregradnje (kalcij, fosfati, alkalna fosfataza, paratireoidni hormon i osteoprotegerin (OPG)) u različitim stadijima kronične bubrežne bolesti uključujući i bolesnike nakon transplantacije bubrega. Temeljem tih rezultata namjera je bila odrediti u kojem je stadiju KBB potrebno započeti liječenje poremećaja mineralno-koštanog metabolizma. Također smo željeli utvrditi utječe li vrijeme provedeno na dijalizi na oporavak mineralno-koštanog metabolizma nakon učinjene transplantacije bubrega. U istraživanje je bilo uključeno 164 bolesnika te 30 zdravih ispitanika u kontrolnoj skupini. Utvrdili smo kako je koncentracija OPG-a obrnuto proporcionalna glomerularnoj filtraciji. Najviše koncentracije OPG-a utvrđene su u dijaliznoj skupini bolesnika, a statistički značajan porast koncentracije OPG-a utvrđen je već u drugom stadiju KBB. Također je utvrđeno da koncentracija OPG-a pozitivno korelira s vremenom trajanja hemodijalize. Ovim istraživanjem potvrdili smo da poremećaj mineralno-koštanog metabolizma počinje u trećem stadiju KBB. Statistički značajan porast koncentracije OPG-a u drugom stadiju KBB mogao bi biti rani znak poremećaja mineralno-koštanog metabolizma. Trajanje dijalize duže od četiri godine povezano je sa značajnijim poremećajem mineralno-koštanog metabolizma.

Ključne riječi: *Hemodijaliza; Kronična bubrežna bolest; Kronična bubrežna bolest-mineralni i koštani poremećaj; Osteoprotegerin; Transplantacija bubrega*