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Risk Factors of Parathyroid Dysfunction in Elderly Patients with Chronic Kidney Disease Undergoing Hemodialysis

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Aberrant mineral metabolism and bone diseases, which are commonly seen in chronic kidney disease (CKD), have been considered to be the important causes of morbidity and decreased quality of life.

Objectives. We aimed to investigate the characteristics of calcium-phosphorus metabolism abnormalities and parathyroid dysfunction in elderly patients with chronic kidney disease undergoing hemodialysis.

Material and Methods. A total of 336 patients undergoing maintenance hemodialysis were divided into two age groups: elderly (≥ 65 years) and non-elderly (< 65 years). Before dialysis, fasting blood samples were initially collected, then hemoglobin (Hb), serum creatinine (Scr), blood urea nitrogen (BUN), calcium, phosphorus, intact parathyroid hormone (iPTH), high-sensitivity C-reactive protein (HsCRP) and albumin (Alb) were measured. Serums BUN, ultrafiltration volume, dialysis duration and body weight were measured after dialysis. Finally, well-established formulas were used to obtain the serum albumin corrected calcium (Ac-Ca) and urea removal index (Kt/V).

Results. Elderly patients accounted for 52.7% of our patients; essential hypertension accounted for 35.6% of the cause for chronic renal failure, followed by chronic glomerulonephritis (21.5%) and diabetes mellitus (19.8%) in the elderly group; while in the non-elderly group, 43.4% of the chronic renal failure was due to chronic glomerulonephritis, followed by diabetes mellitus (23.9%) and essential hypertension (12.6%). Significant differences were found in the dialysis duration, blood pressure, concentrations of serum BUN, Scr, P, iPTH, Alb, standard-protein nitrogen present rate (nPNA) and Hs-CRP between the 2 groups. The multiple logistic regression analysis showed that age, plasma phosphorus, albumin and nPNA were independent risk factors for secondary hyperparathyroidism in patients undergoing maintenance hemodialysis.

Conclusions. We conclude that most elderly patients undergoing hemodialysis experience hyperparathyroidism. The risk factors may include age and malnutrition but need further investigation (**Adv Clin Exp Med 2015, 24, 6, 1007–1012**).

Key words: hemodialysis, elderly, chronic renal failure, parathyroid hormone.

Chronic kidney disease (CKD), a public health problem worldwide with increased prevalence, is often associated with various complications, including cardiovascular disease, progressive loss of kidney function and premature death [1]. Aberrant mineral metabolism and bone diseases, which are commonly seen in CKD, have been considered to be the important causes of morbidity and decreased quality of life.

Generally speaking, the term renal osteodystrophy is used to describe the abnormalities of bone morphology in CKD [2–5]. It has been reported that variations in the plasma levels of intact parathyroid hormone (iPTH) may contribute to the renal osteodystrophy. Together with serum calcium, phosphorus, and alkaline phosphatase levels, iPTH levels have been considered as an important indicator for the diagnosis, severity assessment, and treatment of renal osteodystrophy.

The number of patients with CKD has been increasing at a rate of 5–8% per year in spite of the development in preventive measures [6].

The greatest increase in the incidence and prevalence of end-stage disease is now occurring in the elderly, who constitute the majority of dialytic patients [7]. However, little has been reported on calcium-phosphorus metabolism abnormalities and parathyroid dysfunction in elderly patients undergoing hemodialysis. The aim of this study was to investigate the characteristics of calcium-phosphorus metabolism abnormalities and parathyroid dysfunction in elderly patients undergoing hemodialysis.

Patients and Methods

Patients

A total of 336 stabile patients undergoing maintenance hemodialysis for at least 3 months were separately recruited from the Qilu Hospital from January to December, 2010. The study has been approved by and registered with the Qilu Hospital Ethics Committee. All subjects signed a written informed consent form. All work was undertaken following the provisions of the Declaration of Helsinki.

The recruited patients should have no active infection, heart failure, history of malignancy and diseases for immunosuppressive treatment. The patients were divided into two age groups: elderly (≥ 65 years) and non-elderly (< 65 years). Conventional hemodialysis was given to the patients two or three times every week with a blood flow of 230–250 mL/min and dialysate calcium concentration of 1.5 mM/L, most of the patients received hemodiafiltration (HDF) 1–2 times each month. Hemopoietin, rocaltrol or calcium carbonate were also applied according to the situation of each patient, followed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines.

The data of demography (such as age, gender), duration of dialysis, standard indicators of dialysis care (systolic blood pressure, diastolic blood pressure) and laboratory test results were collected from the recruited patients for further analysis.

Blood Sample Collection

After fasting for at least 12 h, 8–10 mL venous blood was initially collected from each patient. The concentrations of hemoglobin (Hb), serum creatinine (Scr), blood urea nitrogen (BUN), calcium, phosphorus, albumin (Alb) and high-sensitive C-reactive protein (hs-CPR) [8] were then measured according to the established protocols. The chemiluminescence method was used to detect iPHT (normal range, 10–69 pg/mL). Ultrafiltration volume, body weight after dialysis and dialysis duration were all recorded, followed by serum BUN detection. Serum albumin corrected calcium (Ac-Ca), urea removal index (Kt/V) and normalized protein equivalent of nitrogen appearance (nPNA) were finally calculated according to the following formula:

$$\text{Ac-Ca} = \text{serum total calcium} + 0.02 \times (40 - \text{Alb}$$

$$\text{Kt/V} = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times \text{UF/BW}$$

$$\text{nPNA} = 0.0229 \times (\text{Kt/V} + 3.74\text{Kr/V}) \times \times (C1 + C2) + 0.17$$

In is the natural logarithm, R is C2/C1, t is the dialysis duration (h), UF is the ultrafiltration volume (L), BW is the body weight after dialysis, C1 and C2 are serum BUN before and after dialysis respectively.

Statistical Analysis

All data was presented as mean ± standard deviation (SD). Continuous variables were initially tested for the normal distribution assumption by using Kolmogorov-Smirnov statistics and then analyzed by Student's *t* test. Categorical variables were analyzed by Chi-square test. Differences were considered to be significant when $p < 0.05$.

Logistic regression analysis was used to test the correlations between parathyroid dysfunction (iPTH) level and various independents (gender, age, dialysis duration, diabetes mellitus, mean blood pressure, haemachrome, urea nitrogen, creatinine, corrected calcium, P, albumin, Kt/V and nPNA). Variables that had a p value of less than 0.1 in the regression analysis were included in the multivariable model. All analyses were performed by using the SPSS 13.0 software for Windows (SPSS Inc., Chicago, IL, USA).

Results

Demographic Data of Elderly and Non-Elderly Groups

A total of 177 patients (93 males, 78 females; mean age of 72.5 ± 5.1 years) were recruited into the elderly group successfully. Another 159 patients (88 males, 71 females; mean age of 50.4 ± 8.2 years) were recruited into the non-elderly group. In the elderly group, essential hypertension accounted for 35.6% of the cause for chronic renal failure, followed by chronic glomerulonephritis (21.5%) and diabetes mellitus (19.8%); while in

Table 1. Clinical characteristics of patients in the indicated groups

	Elderly (n = 177)	Non-elderly (n = 159)	p-value
Gender (m/f)	93/78	88/71	> 0.05
Age (year)	72.5 ± 5.1	50.4 ± 8.2	< 0.01
Primary disease			
chronic glomerulonephritis	38 (21.5%)	69 (43.4%)	< 0.01
essential hypertension	63 (35.6%)	20 (12.6%)	< 0.01
diabetes mellitus	35 (19.8%)	38 (23.9%)	> 0.05
other	41 (23.2%)	32 (20.1%)	> 0.05
Duration of dialysis (month)	23.5 ± 9.6	35.2 ± 15.8	< 0.01
Dry weight (kg)	58.8 ± 7.2	63.7 ± 10.7	< 0.01
Vitamin D supplementation	85 (48.0%)	121 (76.1%)	< 0.01
Calcium supplementation	98 (55.4%)	118 (74.2%)	< 0.01
SBP (mm Hg)	145.7 ± 12.6	135.9 ± 13.3	< 0.01
DBP (mm Hg)	75.7 ± 10.5	80.3 ± 8.2	< 0.01

SBP – systolic blood pressure, DBP – diastolic blood pressure.

the non-elderly group, 43.4% of the chronic renal failure was due to chronic glomerulonephritis, followed by diabetes mellitus (23.9%) and essential hypertension (12.6%).

Patients in the elderly group had shorter duration of dialysis ($p < 0.01$), lighter dry weight ($p < 0.01$), higher systolic blood pressure ($p < 0.01$) and lower diastolic blood pressure ($p < 0.01$) than those of patients in the non-elderly group. Additionally, patients in the elderly group were supplied with vitamin D and calcium supplements at a lower proportion compared to the non-elderly group ($p < 0.01$) (Table 1).

Calcium-Phosphorus Metabolism Abnormalities and Parathyroid Dysfunction

Compared to the non-elderly group, patients in the elderly group had lower concentrations of serum BUN, Scr, P, iPTH, Alb and nPNA with statistical differences ($p < 0.01$); And higher concentrations of Hs-CRP, meanwhile they have a larger proportion of patients with low iPTH (< 150 pg/L). There was no significant difference in Hb, AC-Ca and Kt/V level ($p > 0.05$) between the two groups (Table 2).

Table 2. Biochemical parameters indicating calcium-phosphorus metabolism abnormalities and parathyroid dysfunction in the indicated groups

	Elderly (n = 177)	Non-elderly (n= 159)	p-value
Hb (g/L)	101.3 ± 8.6	104.3 ± 11.0	> 0.05
BUN (mmol/L)	19.2 ± 4.6	21.1 ± 5.5	< 0.01
Scr (umol/L)	627.2 ± 124.1	734.7 ± 179.3	< 0.01
AC-Ca (mmol/L)	2.15 ± 0.24	2.53 ± 0.23	> 0.05
P (mmol/L)	1.63 ± 0.15	1.69 ± 0.15	< 0.02
iPTH (pg/mL)	143.2 ± 112.9	216.3 ± 133.4	< 0.01
Number of low iPTH patients (%)	91 (51.4%)	56 (35.2%)	< 0.01
Alb (g/L)	34.2 ± 2.3	36.2 ± 2.4	< 0.01
Hs-CRP (mg/L)	7.38 ± 2.24	6.33 ± 2.57	< 0.05
Kt/V	1.18 ± 0.05	1.19 ± 0.05	> 0.05
nPNA (g/(kg*d)	1.22 ± 0.18	1.34 ± 0.14	< 0.05

Age, Phosphorus, Albumin and nPNA Were Risk Factors of Parathyroid Dysfunction in Elderly Patients Undergoing Hemodialysis

As we can see from Table 3, the logistic regression analysis showed that age, phosphorus, albumin and nPNA were risk factors of parathyroid dysfunction in elderly patients on maintenance hemodialysis.

Discussion

In the present study, we found that age, P, albumin and nPNA were independently associated with parathyroid dysfunction in elderly patients undergoing maintenance hemodialysis. Up till now, little has been reported about the relationship between the abnormalities of calcium-phosphorus metabolism and parathyroid dysfunction in elderly patients undergoing maintenance hemodialysis.

Patients with CKD often manifest disorders of bone mineral metabolism [9, 10], which is usually defined as chronic kidney disease-mineral and bone disorder (CKD-MBD) by Kidney Disease Improving Global Outcomes (KDIGO) [11]. CKD-MBD is characterized by calcium-phosphorus and vitamin D metabolism abnormalities, as well as parathyroid dysfunction clinically. According to the level of iPTH, CKD-MBD can be divided into three types of bone disease: low conversion type, high conversion type and hybridism type. Adynamic bone disease (ABD) belongs to the low conversion type, wherein the level of iPTH is lower than normal. In the last 20 years, the incidence of CKD-MBD has changed significantly, the incidence of secondary hyperparathyroidism (SHP) and aluminum poisoning bone diseases have decreased. But the incidence of ABD increased to 15–60% [12, 13], and even to 40–70% in patients undergoing peritoneal dialysis [14]. Although the reason of the increase in ABD remains unclear, the epidemiology and experimental data suggest that parathyroid dysfunction and the inhibition of osteoblasts may be the major underlying factors [15].

With the development of economical options, the number of patients received hemodialysis is increasing. According to the report of United States Renal Data System (USRDS), the number of dialysis patients over 65 years old has risen from 5.0% in 1973, to 38.0% in 1990 and to 60.3% in 2004. In China, the number of patients with end-stage renal disease – who need renal replacement therapy – has increased at a rate of 11% per year over the last decade. Chronic renal failure has become a common disease, followed by the result of increasing the number of elderly hemodialysis patients. Our analysis showed that patients from the elderly group exhibited lower concentrations of serum BUN, Scr, phosphorus, iPTH, Alb and nPNA, and higher concentrations of Hs-CRP. The incidence of low iPTH (< 150 pg/L) was higher in the elderly group (55.8%) than the non-elderly group (36.7%).

Table 3. Correlations between parathyroid dysfunction and variables listed in the elderly patients undergoing hemodialysis

	β	OR	OR 95% CI	p-value
Gender	0.068	0.553	0.365~1.290	> 0.05
Age	0.329	1.176	0.861~1.321	< 0.01
Duration of dialysis (month)	1.263	0.947	0.921~1.187	> 0.05
DM/NDM	0.253	0.277	0.228~0.536	> 0.05
Mean arterial pressure (mm Hg)	0.551	1.332	0.987~1.936	> 0.05
Hb (g/L)	0.052	0.665	0.442~1.225	> 0.05
BUN (mmol/L)	0.162	0.976	0.952~1.152	> 0.05
Scr (umol/L)	0.365	0.887	0.772~1.168	> 0.05
Ac-Ca (mmol/L)	0.088	0.984	0.921~1.227	> 0.05
P (mmol/L)	0.843	1.287	0.886~1.331	< 0.01
Alb (g/L)	1.617	1.047	0.935~1.325	< 0.05
Kt/V	1.175	1.159	0.426~2.469	> 0.05
nPNA [g/(kg*d)]	0.288	1.124	0.952~1.238	< 0.01

Low conversion types of bone disease in elderly patients was associated with not only uremia, but also with aging and sex hormone reductions [16]. As sex hormones decrease, the number of osteoblasts and osteoclasts declines, bone formation decreases, osteoblast apoptosis increases, and organism aging acceleretes. Oxidative stress is a core mechanism of bone loss, and also attributes to the low conversion type of bone disease in elderly patients [17]. The reduction in the number of osteoblasts is also related to reduced activity of the growth hormone, down-regulation of Klotho gene expression and the impaired function of Wnt (a secreted glycophosphoprotein). Elderly patients have weakened immunity and lower resistance to infection. They also have decreased gastrointestinal peristalsis and are prone to malnutrition. As a result, elderly patients have low levels of nPNA, plasma albumin and serum phosphate with hypoparathyroidism [18].

The present study showed that age, P, albumin and nPNA were independent risk factors of parathyroid dysfunction in the elderly patients undergoing maintenance hemodialysis. This result indicates that malnutrition may be a major factor behind parathyroid dysfunction in elderly patients on maintenance hemodialysis. With the function of bone formation and reabsorption decreasing, the capacity to buffer excess calcium loads is declining in patients with the low conversion type of bone disease, thus leading to increased ectopic calcification (e.g. arterial calcification), and an increase in mortality rate in dialysis patients [19]. Our study only observed the differences, and further studies are needed to develop effective preventive or intervention therapeutic strategies for elderly patients on maintenance hemodialysis.

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