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Hypoparathyroidism versus hyperparathyroidism in pediatric dialysis patients; a single center study

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ABSTRACT

Background: Abnormalities in calcium, phosphorous and parathyroid hormone (PTH) metabolisms are common in dialysis patients. Reaching target levels for these serologic factors and calcium × phosphorous products is recommended to minimize cardiovascular events.

Objectives: The aim of this study was to examine calcium, phosphorous and intact PTH (iPTH) abnormalities in a group of dialysis patients.

Patients and Methods: Bone minerals status and iPTH levels were assessed in 46 dialysis patients aged 19-300 (165.2 ± 75.73) months. Low and high Ca dialysate solutions routinely were used for hemodialysis (63%) and peritoneal dialysis (30.4%) patients respectively. Comparisons between groups were performed with considering age (≤5, 6-10, and > 10 years), gender and modality of dialysis.

Results: Serum calcium and corrected calcium levels were significantly higher in peritoneal dialysis (PD) patients. Hypoparathyroidism was the most frequent iPTH abnormality (58.7%). It was more prevalent in males. Hyperparathyroidism was more frequent in females.

Conclusions: We found that hypoparathyroidism is the most prevalent PTH abnormality. We also noted that patients on peritoneal dialysis are more prone to develop this form of PTH abnormality. We found that phosphate control is better in peritoneal dialysis vs. hemodialysis cases.

Original Article

Implication for health policy/practice/research/medical education:
In an observational cross-section study in dialysis patients, we found that over suppression of iPTH and hypoparathyroidism was the most common abnormality.

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1. Background

Normal homeostatic regulation mechanisms maintain optimal amounts of calcium (Ca) and phosphorous (P) in serum, intracellular spaces, and in bone via the complex integration of parathyroid hormone (PTH) and vitamin D (1). Maintaining extra- and intracellular phosphate levels within a narrow range is important for energy metabolism, bone integrity, and apoptosis of mature chondrocytes in the growth plate (2,3). Renal osteodystrophy is a common complication of chronic kidney diseases (CKDs) (4). Hypocalcemia, phosphate retention, reduced synthesis of 1, 25-dihydroxy vitamin D, and skeletal resistance to the calcemic action of PTH are responsible mechanisms for secondary hyperparathyroidism in CKD (5). Abnormalities in serum phosphorus, Ca×P products and intact PTH (iPTH) levels increased risk of cardiovascular death (6).

2. Objectives

We aimed to evaluate serum calcium, phosphorous, Ca×P products and PTH abnormalities in dialysis patients with considering the impacts of age, gender, clinical and dialysis characteristics. Also to determine how much the combination of dialysis and medical therapies including phosphate binders for control

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of hyperphosphatemia and calcitriol for improving calcium metabolism are effective to reach target levels for Ca, P, Ca×P products and PTH.

3. Patients and Methods

Laboratory data of dialysis populations including hemodialysis (HD) and peritoneal dialysis (PD) cases analyzed prospectively. Routinely bicarbonate based dialysis solution containing 1.25 mmol/L Ca (low Ca solution) were used in HD and solution containing 1.75 mmol/L (high Ca solution) were applied in PD. Totally 29 (63%) HD and 14 (30.5%) PD patients and 3 subjects (6.5%) undergoing both modalities enrolled the study. They included 27 males (58.7%) and 19 females (41.3%). Patients categorized into 3 age groups: <5, 6-10 and >10 years. Standard definitions for low, reference range and high levels of Ca, P, intact PTH (iPTH), and Ca × P products were used (7).

3.1. Ethical issues

1) The research followed the tenets of the Declaration of Helsinki; 2) written informed consent was obtained (the study was not an interventional one, but as we needed obtain additional blood samples for checking the serum PTH levels for sending the samples to a laboratory outside of our center, so obtaining written informed consent was necessary); and 3) the research was approved by the ethical committee of Mashhad University of Medical Sciences (Ethical code; IR.MUMS.REC. 1388.200).

3.2. Statistical analysis

The normality of the variables was checked by one sample Kolmogorov-Smirnov test. Independent *t* test and Mann-Whitney U test were used for analysis of variables with normal (Ca, P and Ca × P products, doses of calcitriol and Ca carbonate) and abnormal (iPTH and Alp) distributions respectively. Independent *t* test and Mann-Whitney U test were applied for analysis of variables with normal and abnormal distributions between genders and subgroups of dialysis modalities, respectively. The one-way analysis of variance (ANOVA) and Kruskal-Wallis tests were used to compare dependent variables with normal and abnormal distributions in different age groups (3 sub-groups). Chi-square test was used to compare the frequency of Ca, P, Ca× P products and iPTH abnormalities between genders and different dialysis modalities. For all tests, *P* value <0.05 was considered as significant difference.

4. Results

Characteristics of enrolled patients were presented in Table 1. Serologic parameters were compared between genders and also HD with PD cases (Tables 2 and 3). Serum levels of Ca, P, ALP, Ca× P products and iPTH in age subgroups, HD and PD cases were illustrated in Figures 1-4. There were no significant differences in serum P, Alp, Ca×P products and iPTH levels between PD and HD cases. However, albumin corrected Ca levels were significantly higher in PD patients (P=0.001) (Table 2). Serum iPTH levels were higher in females, however, the difference was not significant (P=0.088). The serum levels of P, Alp and Ca × P products, Ca and also albumin corrected Ca levels were the same in males and females (P>0.05). There was not differences of serologic markers among age groups (P>0.05) (Figures 1 and 2).

Of 42 cases, serum P levels were low, normal and high in 1 (2.4%), 14 (33.3%) and 27 (64.3%) respectively. Serum Ca levels were low in 16 (38.1%), normal in 19 (45.25%) and high in 7 (16.7%) cases respectively (Serum Ca and P levels were missed in 4 cases). Seventeen cases (40.5%) had high serum Ca×P products levels (>55 mg^2/dl^2). Despite low doses of calcitriol majority of the patients (58.7%) had low serum iPTH levels (<150 pg/mL). There was no significant difference in doses of calcitriol between cases with low rather than those with normal serum iPTH levels (P=0.438), and also in cases with low compared with high serum iPTH levels (P=0.599). Hypoparathyroidism was more prevalent in males and hyperparathyroidism was more common in females. Mean ±SD serum iPHT levels were higher in females, however it was not significant (P=0.088). Low serum iPTH levels were common finding in males (>2/3 of cases), however 62% of boys were dialyzed with low dialysate Ca solutions (they were HD cases) which potentially resulted to lower PTH suppression and consequently higher serum iPTH levels. We compared mean ±SD of doses of vitamin D and calcium carbonate between genders. Boys were receiving higher doses of vitamin D, but lower doses of calcium carbonate (Table 3).

5. Discussion

Serum phosphate is not effectively reduced by conventional dialysis (7,8). Calcium-based phosphate binders effectively are used for treatment of hyperphosphatemia in CKD (9). Larger dialyzer surface area and higher blood and dialysate flows in the dialysate associated with better phosphate removal (10-12). Short daily, extended daily or three times weekly nocturnal HD allow higher phosphate removal (12,13). Long dialysis in nocturnal dialysis may correct hyperphosphatemia (14). Impacts of

Table 1. Characteristics of enrolled cases

Variable	Minimum-maximum (mean ± SD), Median, 25 percentile, 50 percentile, 75 percentile
Age (month)	19-300 (165.2±75.73), 183, 105, 183, 229
Gender (male, female) (N/%)	(27;58.7),(19;41.3)
Modality of dialysis (HD, PD, both modalities) (N/%)	(29; 63), (14; 30.5), (3; 6.5)
Duration from onset of dialysis (month)	1-128 (44.3±31.26) ,32.5, 21, 32, 66
Serum calcium levels (mg/dL)	6.5-11.1 (8.8±1.05), 8.7, 8.1, 8.7, 9.7
Serum phosphorous levels (mg/dL)	5.1-10 (6.1±1.67), 5.6, 4.97, 5.6, 7.67
Serum Ca × P products levels (mg^2/dL^2)	31.3-86.67 (53.2±12.4), 50.2, 44.6, 50.2, 59.8
Serum albumin levels (g/dL)	2.5-4.6 (3.43±0.52), 3.4, 3.1, 3.4, 3.8
Serum PTH concentration (pg/mL)	11.5-1650 (260.6±358.45), 120, 18.7, 120, 340.5
Serum alkaline phosphatase levels (U/L)	135-2897 (879.8±730.1) 588, 197, 588, 1253
Albumin corrected calcium levels (mg/dL)	6.7-11.9 (9.17±1.4), 9.5, 8.3, 9.5, 10.1
Characteristics of dialysis sessions in HD cases	1-5 (2.89±0.73) sessions/weekly 3-4 (3.7±0.46) hours/session Standard dialysis (12 h/wk) 13 cases (44.8%) Dialysis doses < standard (8-9 h/wk) 14 cases (48.3%) Dialysis dose > standard (16 and 20 h/wk) 2 cases (6.9%)
Characteristics of dialysis sessions in PD cases	4-6 (4.82±0.52) dialysis cycles/day Dwelling times of 2-4 (3.8±0.71) hours Dialysis volumes 27-77 (39.65±16.14) cc/kg/cycle
Etiologies of CKD (N/%)	Vesicoureteral reflux (20; 43.5), idiopathic (6 ;13), nephrotic syndrome (5;10.9), neurogenic bladder (5;10.6), glomerulonephritis (4; 8.7), Polycystic kidney disease (2; 4.3), stone disease (2, 4.3), familial juvenile nephronophtisis and cystinosis (each 1, 2.2)

Table 2. Comparing characteristics and serologic findings based on modality of dialysis

Variable	HD patients	CAPD patients	P value
Gender[a]			0.238
Male	15	9[b]	
Female	14	5	
Age (month)[c]	198.4±53.7	80.6±47	0.0001
Duration from onset of dialysis (month)[c]	42.6±33.1	35.3±15.7	0.447
Serum calcium levels (mg/dL) [c]	8.5±1	9.46±0.85	0.006
Serum phosphorous levels (mg/dL) [c]	6.5±1.7	5.7±1.66	0.176
Serum Ca × P products (mg^2/dL^2) [c]	54.5±12.8	52±12.4	0.557
Serum albumin levels (g/dL)[c]	3.8±0.38	3.35±0.5	0.055
Serum PTH concentration (pg/mL)[d]	313.7±398.3	106.1±166.1	0.06
Serum alkaline phosphatase levels (U/L)[d]	785.6±801.6	719.5±258	0.768
Albumin corrected calcium levels[c] (mg/dL)	7.4±0.68	10±0.94	0.0001
Dose of calcitriol (ng/kg)[c]	11.9±17.3	15.3 ± 15.5	0.537
Dose of Ca-carbonate[c] (mg/kg/elemental calcium)	38.12±48.7	94.3±100.75	0.066
Dialysate Ca concentrations (mmol /L)	1.25-1.5	1.75	
Total number	29(67.5)	14(32.5)	

[a] Chi square test; [b] Three males were placed on the both modalities at the same time; [c] Independent *t* test; [d] Mann-Whitney test.

dialysis modalities on serum P levels have been evaluated in HD and hemodiafiltration (11,12,15-17). Hemodiafiltration may allow better P control (15), but some studies did not confirm this finding (11,12,16). In PD cases, phosphate clearance influenced by types of PD modalities and membrane transport characteristics (17). Longer dwell times may help control hyperphosphatemia (18). Better and more effective phosphate clearance can be achieved with continuous ambulatory peritoneal dialysis (CAPD)

Table 3. Comparing characteristics and serologic findings based on gender

Variable	Males	Females	P value
Modality of dialysis			
HD	15	14	
CAPD	9	5	
Age (month)[1]	156.4±78.3	177.68±72.14	0.354
Duration from onset of dialysis[a] (month)	42.87±28.69	76.16±35.17	0.74
Serum calcium levels (mg/dL)[a]	8.98±1	8.5±1	0.18
Serum phosphorous levels (mg/dL)[a]	6.28±1.88	5.98±1.34	0.578
Ca ×P products(mg^2/dL^2)[a]	54.2±13.8	51.7±10.1	0.531
Serum albumin levels (g/dL)[a]			
Serum PTH concentration (pg/mL)[b]	162±216.9	400.7±466.8	0.088
Serum alkaline phosphatase levels (U/L) [2]	888.56±924.12	844.26±806.57	0.988
Albumin corrected calcium levels[a] (mg/dL)	9.18±1.4	9.17±1.5	0.988
Dose of Calcitriol(ng/kg)[a]	15.7±16.3	8.9±15.6	0.165
Dose of Ca-carbonate (mg/kg/elemental calcium)[a]	46.4±46.8	72.7±96	0.281

[a] Independent *t* test; [b] Mann-Whitney test.

Table 4. Types of Ca, P, Ca ×P and iPTH abnormalities in different groups of enrolled cases

Type of disorder	Male (N/%)	Female (N/%)	P value
Low serum PTH (< 150 pg/mL)	19 (70.4)	8 (42.1)	0.358
High serum PTH (>300 pg/mL)	5 (18.5)	7 (36.8)	0.364
High serum P levels (>5.5 mg/dL)	12 (44.4)	8 (42.1)	0.321
Low serum Ca levels (<8.4 mg/dL)	6 (22.2)	6 (31.6)	0.333
High serum Ca levels (>10.5 mg/dL)	1 (3.7)	1 (5.2)	0.157
High serum Ca × P products (>55 mg^2/dL^2)	12 (44.4)	5 (26.3)	0.386
Total number	27 (58.7)	19 (41.3)	
Type of disorder	**HD cases (N/%)**	**CAPD cases (N/%)**	**P value**
Low serum PTH (< 150 pg/mL)	15 (51.7)	11 (78.6)	0.574
High serum PTH (>300 pg/mL)	9 (31)	2 (14.3)	0.358
High serum P levels (>5.5 mg/dL)	15 (51.7)	5 (35.7)	0.333
Low serum Ca levels (<8.4 mg/dL)	9 (31)	2 (14.3)	0.366
High serum Ca levels (>10.5 mg/dL)	1 (3.45)	1 (7.15)	0.157
High serum Ca × P products (>55 mg^2/dL^2)	11 (37.9)	5 (35.7)	0.382
Total number	29 (63)	14 (30.4)	
Type of disorder	**< 5 years (N/%)**	**6-10 years (N/%)**	**>10 years (N/%)**
Low serum PTH (< 150 pg/mL)	4 (66.6)	6 (85.7)	17 (51.5)
High serum PTH (>300 pg/mL)	1 (16.6)	1 (14.3)	11 (33.3)
High serum P levels (>5.5 mg/dL)	5 (83.3)	1 (14.3)	21 (63.6)
Low serum Ca levels (<8.4 mg/dL)	0	0	16 (48.5)
High serum Ca levels (>10.5 mg/dL)	2 (33.3)	4 (57.1)	1 (3)
High serum Ca × P products (>55 mg^2/dL^2)	4 (66.6)	2 (28.6)	11 (33.3)
Total number	6 (13)	7 (15.2)	33 (71.8)

prescription (19). All of our PD patients used CAPD regimen with different dwell times (2-4 [3.8±0.71] hours). We compared serum P levels in cases with dwell time ≥4 hours versus those <4 hours. The serum P levels were 4.96 ± 1.11 mg/dL and 6.5 ± 1.37 mg/dL respectively (P = 0.04). In deed, PD patients receiving dwell time of ≥4 hours reached a better P control. However serum P levels were lower in PD cases (Table 2), the difference was not significant (P = 0.176). An extended study compared achieving target levels of Ca, P and Ca ×P products between HD with hemodiafiltration (HDF) groups (8). Reaching target levels of Ca × P products, Ca and P were 80%, 50% and 50% respectively and <25% achieved three targets. In present study P target levels were achieved in one-third of HD and two-thirds of

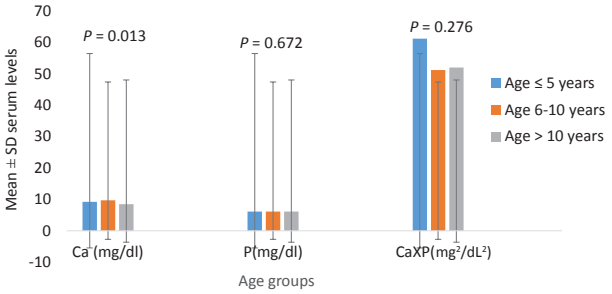

Figure 1. Comparing mean ± SD serum levels of Ca, P and Ca ×P Products in different age groups (ANOVA test).

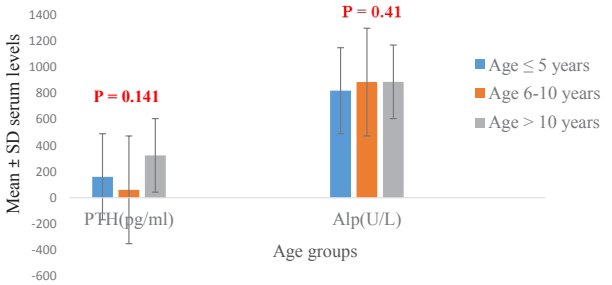

Figure 2. Comparing mean ± SD serum levels of PTH and ALP in different age groups (Kruskal-Wallis test)

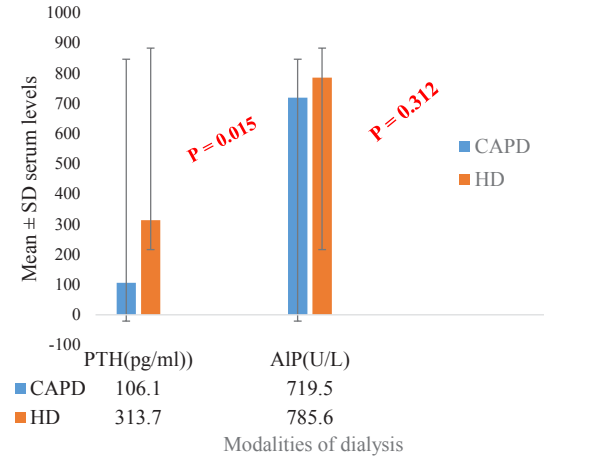

Figure 3. Mean ± SD concentrations of serum PTH and ALP in CAPD versus HD patients (Mann–Whitney test)

PD patients. About half of HD and two-thirds of PD cases had a target levels for Ca ×P products. Just 7% of PD and 17% of HD patients achieved target PTH levels. Also 42% of PD and 38% of HD cases reached the target levels for calcium. Reaching target levels for P, albumin-corrected Ca, Ca × P product and iPTH regarding U.S. (NKF K/DOQI™) and European (EBPG) guidelines have been reported in 40%, 41%, 56%, 22% of patients respectively (20-22). In our series target levels of Ca, P, Ca × P products, and PTH achieved in 17 (40.5%), 18 (42.8%), 25 (59.5%) and 6 (13%) cases respectively. Low dialysate Ca solutions can avoid positive or negative calcium

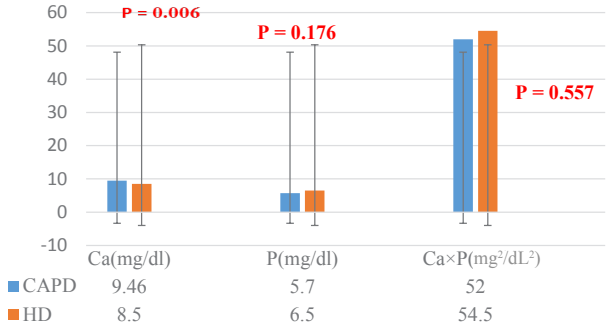

Figure 4. Mean ± SD concentrations of serum Ca, P and Ca ×P products in CAPD versus HD patients (chi-square test) .

balance (23,24). Hypercalcemia, hyperphosphatemia and increased serum Ca × P products and PTH levels increase mortality in CKD (25-29). Low PTH and calcium levels associate with higher mortality or no association at all (30, 31). PD patients benefit using low-calcium dialysate solutions (32-35), which prevent excessive PTH suppression and development of adynamic bone disease (ABD) (32,35-37). The combination of low iPTH and alkaline phosphatase levels (ALP) <100 U/L is suggestive of adynamics bone diseases (ABD) (38). All of our cases with low serum PTH had serum ALP levels >100 IU/L. The prevalence of ABD in dialysis patients is increasing (39,40) due to over suppression of PTH and skeletal resistance to its actions (41).

In our series, high frequency (2/3 of cases) of hypoparathyroidism in males, who majority were used HD modality and dialyzed with low dialysate Ca solutions, suggest that factors other than Ca concentrations in dialysis solutions play role in inducing PTH suppressions. It may be suggested that higher intakes of Ca containing phosphate binders and calcitriol are additional factors that resulted to more PTH suppression in our cases. The response is that in comparison with girls, boys enrolled in the study were receiving higher doses of calcitriol but lower doses of Ca containing phosphate binders (Table 3). Dose higher doses of calcitriol was responsible for severe PTH suppression in boys? This hypothesis (effects of higher intakes of Ca containing phosphate binders and Calcitriol in PTH suppression) may be partially true because hypoparathyroidism was more common in PD patients (78.6%) versus HD subjects (51.7%) (Table 4) .Higher doses (mg/kg) of Calcitriol and Ca containing phosphate binders were recommended in PD patients (Table 2).

We found hypercalcemia twice more common in PD compared with HD cases (7.15% versus 3.5%). Differences in Ca dialysate solutions may be the main etiology for higher frequency of low PTH and

hypercalcemia in PD cases. It seems high dialysate Ca solutions can lead to more PTH suppression and also higher risk of hypercalcemia, even if low doses of calcitriol and Ca-based phosphate binders are used. A highly significant inverse correlation between serum PTH with serum magnesium (Mg) levels in HD and PD patients have been found (42). We did not check the serum Mg levels in our subjects and it may be that high serum Mg level acts as an additional factor in oversupression of PTH levels in our cases. Low dialysate Ca solutions are used throughout the world. When longer and more frequent dialysis such as short-daily and nocturnal HD are prescribed, optimal dialysate Ca levels are challengeable and higher levels (1.75 mmol/L) are probably preferable. The best approach for selecting dialysate Ca concentration is to individualize the prescriptions (43). To prevent ABD, a target level for PTH higher than that in the normal population is recommended (44). Different definitions for low serum PTH has been used (8,43,44). Similar to our findings, hypoparathyroidism has been reported as a common finding in dialysis patients (45). In our series absolute and relative (serum PTH <60 pg/mL and 60-160 pg/mL respectively) deficiencies of PTH were reported in 31.3% and 31.4% of CAPD and 31% and 33.4% HD cases respectively. In present study 17 (63%) cases had absolute and 10 (37%) had relative PTH deficiencies. Low serum PTH levels in dialysis patients can be found in association with aluminum toxicity, manlutrion, PD modality, using Ca containing phosphate binders and overuse of vitamin D (46,47), and may be linked to hypercalcemia (48). It is the most common PTH abnormalities found in 45% of cases (49,50). Majority of our PD cases had low serum PTH levels (78.6%). There was no significant difference in serum P, Ca and doses of recommended calcitriol between cases with low versus those with normal PTH levels (P= 0.414, 0.758 and 0.438 respectively). Reaching target levels for Ca, P and Ca × P products were more common in PD (42.8%, 64.3% and 64.3% respectively) compared with HD (38%, 31% and 48.3% respectively) cases. In contrast, more HD subjects reached target levels for PTH compared with PD patients (17.2% versus 7.15%).

6. Conclusions

Regarding to our findings, we concluded that in dialysis patients:

1) Age and gender have no significant impact on serum bone minerals and PTH levels.

2) Hypoparathyroidism is the most common PTH abnormality.

3) A gender difference in types of PTH abnormalities might be present with higher frequency of hyperparathyroidism in females and hypoparathyroidism in males.

4) Additional factors rather than doses of calcitriol and Ca containing phosphate binders, and dialysate Ca concentration might play role in severe PTH suppression.

5) Hyperparathyroidism and hyperphosphatemia are more frequent in HD and hypoparathyroidism in PD subjects.

6) PD modality can result to a better P control, especially those with longer dwelling times (≥4 hours).

Limitations of the study

Lack of checking serum levels of 25 hydroxyl vitamin D3, Mg and aluminum were the main limitations of our study. Studies with considering impacts of serum levels of 25 hydroxyl vitamin D3, Mg, aluminum and different dialysate calcium concentrations on calcium, phosphorous and PTH metabolism in dialysis patients is recommended to define whether changes in serum levels of these parameters and also concentration of calcium on dialysate solution can prone patients to over suppression of parathyroid gland or other factors are responsible in pathogenesis of hypoparathyroidism in dialysis cases.

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Author's contribution

MN is the single author of the paper.

Conflicts of interest

The author declared no competing interests.

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