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REVIEW ARTICLE

Impacts of parathyroidectomy on calcium and phosphorus metabolism disorder, arterial calcification and arterial stiffness in haemodialysis patients

Zhuo Gao, Xiaomei Li, Jing Miao, Lide Lun*

Department of Rheumatology and Nephrology, General Hospital of Air Force, Haidian District, Beijing, 100142, China

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Summary *Background:* Secondary hyperparathyroidism (SHPT) and calcium and phosphorus metabolism disorder are important complications in haemodialysis patients. Parathyroidectomy (PTX) may prevent or delay the progress of vascular calcification in haemodialysis patients.
Objective: To investigate the impacts of PTX on calcium and phosphorus metabolism, arterial calcification and arterial stiffness in haemodialysis patients with SHPT.
Methods: Twenty-one SHPT-haemodialysis patients were selected for PTX. The preoperative and postoperative 1-year scores of coronary artery calcification were measured via multislice spiral CT, along with the brachial-ankle pulse wave velocity (baPWV), and preoperative and postoperative 1-year indexes such as calcium, phosphorus, calcium-phosphorus product concentration and parathyroid hormone (PTH) level were compared.
Results: Compared with the preoperative score, the postoperative 1-year coronary artery calcification score was significantly reduced; the mean baPWVs of the bilateral limbs were reduced; and the levels of serum calcium, phosphorus, calcium-phosphorus product concentration and PTH were all reduced; all differences were statistically significant ($P < 0.05$).
Conclusions: PTX can be used to correct calcium and phosphorus metabolism disorder, reduce arterial calcification, and improve arterial stiffness.

* Corresponding author. Department of Rheumatology and Nephrology, General Hospital of Air Force, No. 30 Fucheng Road, Haidian District, Beijing, 100142, China.
E-mail address: lidelunbj@163.com (L. Lun).

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1. Introduction

Secondary hyperparathyroidism (SHPT) and calcium and phosphorus metabolism disorder (CPMD) are important complications in haemodialysis patients. It was previously considered that SHPT and CPMD mainly caused bone lesions, but recent studies have shown that hyperphosphatemia, increased calcium-phosphate multiplication and HPT could increase vascular calcification, arterial stiffness and the risk of cardiovascular events, all of which have been linked to cardiovascular illness and mortality in haemodialysis patients.[1–3] Numerous studies have found that coronary artery calcification (CAC) is a common complication in haemodialysis patients, and cardiovascular diseases are the leading cause of death in haemodialysis patients.[4]

Clinical study of SHPT haemodialysis patients[5] has indicated that parathyroidectomy (PTX) might prevent or delay the progress of vascular calcification. It may also reduce phosphorus, calcium-phosphorus product concentration, parathyroid hormone (PTH) and inflammatory factors, thus reducing the vascular calcification-promoting factor, and controlling vascular calcification. However, the sample size of this study was small, and the observation time was short. We performed PTX on 21 SHPT haemodialysis patients, and compared the preoperative and postoperative 1-year levels of calcium, phosphorus, calcium and phosphorus multiplication, PTH and other parameters of these 21 patients, as well as the preoperative and postoperative CAC score and arterial stiffness index (BaPWV). We was found that PTX surgery could correct calcium and phosphorus metabolism disorder, and reduce arterial calcification and arterial stiffness. PTX may block or delay the vascular calcification process in haemodialysis patients.

2. Subjects and methods

2.1. Subjects

Twenty-one haemodialysis patients who were undergoing long-term regular haemodialysis in our hospital from January 2008 to March 2012 were selected, including 8 males and 13 females, aged 35–74 years old, with a mean age of 50.3 ± 9.7 years; the dialysis durations were 1–20 years, with a mean of 8.8 ± 3.6 years; there were nine cases of chronic glomerulonephritis, four cases of hypertensive nephropathy, three cases of drug-induced kidney injury, two cases of diabetic nephropathy, one case of pregnancy-induced hypertension, one case of lupus nephritis and one case of purpura nephritis. The surgical indications and inclusion criteria were established in our hospital based on the KDOQI guideline,[6] which were as follows: All patients were tested with intact parathyroid hormone (iPTH) $>$ 500 pg/ml, hypercalcemia (Ca^{2+}) $>$ 2.37 mmol/l and (or) difficult-to-control hyperphosphatemia (P^{3-}) $>$ 1.78 mmol/l. The radiological examination revealed an enlarged parathyroid. The imaging examination (ultrasound or CT) found at least 1 enlarged parathyroid nodule, with diameter $>$10 mm and rich blood flow. The exclusion criteria were as follows: serious cardiovascular complications, severe malnutrition, acute infection, hemorrhage and other diseases intolerant of surgery.

2.2. Dialysis method

All enrolled patients underwent dialysis three times a week, for 4.0–4.5 h each time. A Braun dialysis machine was used, and the dialyser was LOPS 15 (polysulfone membranes), with a membrane area of 1.5 m^2, used only once. A bicarbonate dialysate was used, the blood flow rate was set at 250–300 ml/min, and that of the dialysate was 500 ml/min. The urea decreasing rate (URR) was $>$65%, and the urea nitrogen clearance rate by the artificial kidney was $(KT/V) \geq 1.2$.

2.3. Medication and surgical treatment

During the observation period, the dietary intake of the enrolled patients was kept stable, and the use of other medications, such as antihypertensive drugs, vitamins, chalybeate and erythropoietin, was continued. All 21 patients accepted PTX. The surgical procedure was as follows: a transverse neck incision was performed, the superior and inferior flaps were mobilised, and the anterior neck muscle group was longitudinally separated from the midline. After isolating the thyroid medium vein, the thyroid was freed, the recurrent laryngeal nerve was identified at the tracheo-esophageal sulcus, the neck was then thoroughly explored to distinguish the parathyroid glands on the left and right superior and inferior poles, and then total PTX + anterior sternocleidomastoid muscle autograft were performed.[7] After surgery, the drainage was placed. All resected parathyroid glands were histopathologically confirmed. Intravenous and oral calcium therapy were performed postoperatively.

2.4. Definition of surgery success

According to the K/DOQI clinical guidelines, the surgery success was successfully defined as follows: the blood calcium and phosphorus levels after postoperative 6 or later were maintained at normal range; the parathyroid hormone level was less than $<$300 pg/ml; the clinical symptoms were mitigated or disappeared.

2.5. CAC scoring

Evaluation of CAC was performed by multislice spiral CT (MSCT) scanning using Toshiba Aquilion 64CT scanner and Vistra software. The analysis and scoring of CAC were performed by highly qualified doctors. The CAC score was calculated using the Agaston method.[8] The CT value of each calcification focus was multiplied by its area, which generated the score of this focus, and the total CAC score was the accumulation of all foci scores. The score was graded as follows: 0–10 points: non-calcification; 11–100 points: mild calcification; 101–400 points: moderate calcification; $\geq$ 400 points: severe calcification.

2.6. BaPWV detection

An automatic arteriosclerosis analyser (BP-203RPE III type, Omron) was used to detect BaPWV. The subject was in the supine position, and the bilateral brachial artery and

anterior tibial blood pressures (systolic blood pressure, mean arterial pressure, diastolic blood pressure and pressure difference) were measured with a high-precision double-layer cuff, and an automatic waveform recorder was used to record and analyze the relative waveforms. BaPWV was calculated as follows: BaPWV = L/ΔT (L, vessel length; ΔT, pulse transition time from upper arm to foot and head). The calculation was automatically performed by the instrument. Measurements were always made after the subject had rested for at least 10 min. The outlier standards of BaPWV were based on the different age groups.

2.7. Laboratory test

On the morning of dialysis, immediately before surgery and 1 year after surgery, venous blood was extracted from the upper extremity under fasting status. An AXSYM automatic immuno-chemiluminescence analyser (Abbott, USA) was used to detect iPTH; a Hitachi 7060 automatic biochemical analyser was used to detect the levels of calcium (Ca), phosphorus (P), serum albumin (Alb), haemoglobin (Hb) and haematocrit (Hct).

2.8. Statistical analysis

SPSS13.0 software was used for the statistical analysis and mapping. The data were expressed as mean ± standard deviation, and the paired-sample t test was performed. $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Preoperative CAC situation of 21 patients

Among 21 SHPT haemodialysis patients, only 1 case (4.76%) had a CAC score < 10 points, indicating "no calcification". The remaining 20 cases (95.24%) all had CAC: 1 case (4.76%) had a CAC score between 11 and 100 points, indicating mild calcification; 11 cases (52.38%) had a CAC score between 101 and 400 points, indicating moderate calcification; 8 cases (38.10%) had a CAC score ≥ 400 points, indicating severe calcification. Among the 20 patients with CAC, 3 cases (14.29%) had only one branch with calcification, 8 patients (38.10%) had two branches with calcification, 5 cases (23.81%) had three branches with calcification, and 4 cases (19.05%) had four branches with calcification.

3.2. General situation of the 20 CAC patients before PTX

Twenty patients with CAC were divided into mild to moderate and severe calcification groups according to the severity of CAC, and their general preoperative situation was as described in Table 1. Given the small sample size, it was difficult to detect significant differences. However, in general, CAC patients had relatively longer dialysis periods, with the overall average dialysis period being 112.67 months, namely more than 9 years. It was found that CAC patients tended to suffer hypertension and hyperlipidemia. Furthermore, patients with severe calcification also exhibited a high incidence of diabetes.

3.3. Changes in serum calcium, phosphorus, calcium-phosphorus product concentration and iPTH before and after PTX

As shown in Table 2, before PTX, the serum levels of calcium, phosphorus, calcium-phosphorus product concentration (Ca × P) and iPTH were 2.44 ± 0.19 mmol/l, 2.50 ± 0.77 mmol/l, 73.30 ± 22.91 and 1708.72 ± 848.93 pg/ml, respectively. After 1 year from PTX, the serum levels of calcium, phosphorus, Ca × P and iPTH were

Table 1 General situation of the 20 CAC patients before the PTX.

Index	Mild to moderate calcification (10 ≤ score<400) (n = 12)	Severe calcification (score≥400) (n = 8)	Total (score≥10) (n = 20)
Age (years)	50.21 ± 8.72	52.50 ± 14.58	51.22 ± 11.36
Gender (male/female)	4/8	5/3	9/11
Body mass index (kg/m^2)	23.90 ± 1.86	24.10 ± 2.56	23.91 ± 2.17
Smokers (n/%)	2/16.67	3/37.50	5/25.00
Primary cause of CKD (n/%)			
Diabetes	2/16.67	3/37.50	5/25.00
Hypertension	2/16.67	1/12.50	3/15.00
ADPKD	0/0.00	1/12.50	1/5.00
Drug-induced kidney injury	1/8.33	1/12.50	2/10.00
Glomerulonephritis	5/41.67	2/25.00	7/35.00
Other or unknown	2/16.67	0/0.00	2/10.00
Time on dialysis (months)	110.09 ± 35.56	116.25 ± 15.72	112.67 ± 29.26
Co-morbidity (n/%)			
Hypertension	10/83.33	8/100.00	18/90.00
Diabetes	2/16.67	4/50.55	6/30.00
Coronary artery disease	5/41.67	5/62.50	10/50.00
hyperlipidemia	11/91.67	8/100.00	19/95.00

CAC, coronary artery calcification; PTX, parathyroidectomy; CKD, chronic kidney disease; ADPKD, autosomal dominant polycystic kidney disease.

Table 2 Comparison of serum calcium, phosphorus, calcium-phosphorus multiplication and iPTH before and after PTX.

Group	Ca^{2+} (mmol/l)	P^{3-} (mmol/l)	Ca × P	iPTH (ng/L)
Before PTX	2.44 ± 0.19	2.50 ± 0.77	73.30 ± 22.91	1708.72 ± 848.93
After PTX	2.15 ± 0.29*	1.67 ± 0.51*	43.31 ± 15.02*	110.11 ± 136.72*

*P < 0.01 compared with before PTX; iPTH, intact parathyroid hormone; PTX, parathyroidectomy.

2.15 ± 0.29 mmol/l, 1.67 ± 0.51 mmol/l, 43.31 ± 15.02 and 110.11 ± 136.72 pg/ml, respectively. There was significant difference in each index between before and after PTX (P < 0.01).

3.4. Changes in coronary artery score and baPWV before and after PTX

Before PTX, the coronary artery score and baPWV were 1064.85 ± 741.16, 1577.27 ± 265.08 (left) and 1557.83 ± 356.95 (right), respectively. After 1 year from PTX, the coronary artery score and baPWV were 403.70 ± 464.12, 1160.03 ± 459.93 (left) and 1111.23 ± 531.23 (right), respectively. There was significant difference in each index between before and after PTX (P < 0.05) (Table 3).

3.5. Postoperative complications and adverse reactions

During one postoperative year, nine patients presented with hypocalcemia at different stages, and one case exhibited tetany. After supplementary calcium treatment, the serum calcium returned to normal, and no other adverse reactions occurred.

4. Discussion

End-stage renal disease patients, especially those who have already started haemodialysis, will normally exhibit CAC, mainly in the intima and media of large and medium artery walls. The coronary artery is prone to calcification, and contributes to the high morbidity and mortality of cardiovascular diseases in dialysis patients.[9] A previous study[10] has found that, the mortality of haemodialysis patients was l0-20 times higher than that of the age-matched general population, and that death caused by cardiovascular events accounts for more than 50% of all deaths. Another study[8] has showed that, the patients with chronic kidney disease who do not perform dialysis for five courses have a mixture of intima and media calcification within the involved vessels; in patients who maintain haemodialysis, the degree of vascular calcification is more severe than in short-term haemodialysis patients; and over 80% of young haemodialysis patients have CAC, which progresses rapidly with the extension of dialysis time. Some studies[11,12] have also found that many young dialysis patients have very serious vascular calcification. Therefore, CAC threatens the safety of dialysis patients.

The mechanisms of vascular calcification are not yet entirely clear, but it has been proposed that hyperphosphatemia, high calcium-phosphate multiplication and SHPT might contribute towards vascular calcification.[13] Vascular calcification is an active regulatory process that involves multiple factors, including calcification promoting factors and calcification inhibitors.[14–16] When in SHPT, a high parathyroid hormone (PTH) level might increase the cytosolic calcium level, thus causing metastatic calcification. PTH could promote the expression of osteogenesis genes inside bone cells.[17,18] In recent years, studies have suggested that surgical resection of the parathyroid might reduce vascular calcification-promoting factors by reducing the levels of phosphorus, calcium-phosphorus product concentration, PTH and inflammatory factors, etc., thus controlling the progress of vascular calcification.[19,20] It is found that, for patients with severer coronary artery calcification, in the case of normal calcium and phosphorus levels, the improvement of coronary artery calcification score is more obvious.[21] However, in the present study, whether the extent of improvement in serum calcium, phosphorus, calcium-phosphorus multiplication and iPTH abnormality is correlated with the extent of improvement in coronary calcification is not confirmed, which is a limitation of this study, and should be further investigated. Some scholars[22,23] believe that patients with refractory SHPT should be treated with surgical resection of the parathyroid as early as possible, as this might slow the process of atherosclerosis. Bleyer et al[5] compared ten PTX uremic patients with ten patients without PTX, and used MSCT to determine the CAC scores. The average annual change in CAC scores of the PTX patients was significantly lower than in the control group, among whom the scores of two cases that originally had high scores were significantly reduced, and those of the seven cases that originally had low scores were maintained within the preoperative range.

Table 3 Comparison of coronary artery score and baPWV before and after PTX.

Group	Coronary artery score	baPWV	
		left	right
Before PTX	1064.85 ± 741.16	1577.27 ± 265.08	1557.83 ± 356.95
After PTX	403.70 ± 464.12*	1160.03 ± 459.93*	1111.23 ± 531.23*

*P < 0.05 compared with before PTX; baPWV, brachial-ankle pulse wave velocity; PTX, parathyroidectomy.

In this study, PTX was performed in SHPT haemodialysis patients. Preoperative observations revealed that among the 21 patients, 20 patients had preoperative CAC, accounting for 95.24% of all cases: there was one case of mild calcification (4.76%), 11 cases of moderate calcification (52.38%), and eight cases of severe calcification (38.10%). In the majority of patients CAC involved two or more branches. We found that dialysis patients with CAC normally had a relatively longer dialysis period, with an average dialysis period of more than 9 years; CAC patients tended to exhibit hypertension and hyperlipidemia, and patients with severe calcification exhibited a high incidence of diabetes. Given the small number of cases in this study, this general information was not analysed statistically, meaning that more samples will be required for further observational studies.

The follow-up of these 21 PTX haemodialysis patients revealed that, one year after PTX, the patients' serum phosphorus, calcium-phosphorus product concentration and CAC score were significantly reduced; the arterial stiffness index (baPWV of two limbs) was also significantly reduced. Therefore, it is suggested that PTX can correct disorders of calcium and phosphorus, and reduce the extent of atherosclerosis by improving vascular calcification and arterial stiffness, or delaying or blocking artery calcification and hardening. By expanding the sample size and duration of follow-up, the effects of PTX on vascular calcification will be further understood, and the results will be useful in the prevention and treatment of cardiovascular diseases in haemodialysis patients.

Conflict of interest

All authors have no conflict of interest.

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