RENAL FAILURE
2022, VOL. 44, NO. 1, 1409–1416
https://doi.org/10.1080/0886022X.2022.2114369

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Relationship between serum parathyroid hormone levels and abdominal aortic calcification in patients starting hemodialysis who have never taken calcium tablets, calcitriol, or vitamin D analogs

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ABSTRACT

Background: Vascular calcification (VC) and secondary hyperparathyroidism (SHPT) are important causes of the high incidence of cardiovascular events in chronic kidney disease (CKD) patients. The relationship between parathyroid hormone (PTH) and VC is very complex. The aim of this study was to determine the correlation between PTH levels and abdominal aortic calcification (AAC) in patients starting hemodialysis who had not received calcium tablets, calcium-containing phosphorus binders, calcitriol, or vitamin D analogs.

Methods: Seventy-one patients were included. Latero-lateral X-ray lumbar radiography, serum intact PTH (iPTH) levels, and predialysis biochemical parameters were obtained. The degree of AAC was evaluated according to the methods described previously by Kauppila et al.

Results: We found that there was a strong negative correlation between serum PTH and AAC (Spearman's rho -0.76, $p < 0.001$). Receiver operating characteristic (ROC) curve analysis showed that low serum PTH level could predict the presence and extent of AAC (area under the curve values were 0.9013 [$p < 0.0001$] and 0.780 [$p = 0.0041$], respectively).

Conclusions: Our results indicate that serum PTH level is significantly negatively correlated with AAC within a certain concentration range in patients starting hemodialysis who had not received calcium tablets, calcium-containing phosphorus binders, calcitriol, or vitamin D analogs.

ARTICLE HISTORY
Received 17 June 2022
Revised 10 August 2022
Accepted 11 August 2022

KEYWORDS
Chronic kidney disease; vascular calcification; parathyroid hormone; abdominal aortic calcification

Introduction

The incidence and mortality of cardiovascular disease (CVD) are significantly increased in chronic kidney disease (CKD) patients. Even after stratification by age, sex, race, and presence of diabetes, CVD mortality in end-stage renal disease (ESRD) patients treated by hemodialysis or peritoneal dialysis is 10–20 times higher than that in the general population [1].

Vascular calcification (VC), defined as the inappropriate and pathological deposition of minerals in the form of calcium phosphate salts into the vascular tissues, is a very common complication in CKD patients and is associated with significantly increased all-cause and cardiovascular mortality [2–5]. Secondary hyperparathyroidism (SHPT) is another common complication of CKD that has also been associated with increased cardiovascular mortality and CKD progression, especially in CKD stage 3–5 patients [6–8].

The relationship between VC and parathyroid hormone (PTH) is very complex. A study of 1095 hemodialysis patients (aged 65–88) showed that abdominal aortic calcification (AAC) was more severe in male patients with serum PTH levels within the upper-normal range than in patients with serum PTH levels within the lower-normal range [9]. Another study revealed that in nondialysis CKD stage 2–5 patients with AAC score >6 or pelvic arterial calcification (PAC) score >1 had higher serum PTH [10]. In addition, among patients receiving hemodialysis, serum PTH levels were significantly associated with AAC progression [11]. However, in clinical practice, PTH levels do not match the severity of AAC. The present study examined the relationship between PTH levels and AAC in patients starting hemodialysis who have not received calcium, calcium-containing phosphorus binders, calcitriol, or vitamin D analogs to

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determine whether PTH levels are associated with the severity of AAC.

Materials and methods

This study was approved by the Ethics Committee of the Chonggang General Hospital Affiliated with the Chongqing University of Posts and Telecommunications (ethics No.: 2020-SY-04). Written informed consent was obtained from each person at recruitment. Hemodialysis was initiated when the estimated glomerular filtration rate (eGFR) was <15/min/1.73 m^2 of body surface area and was accompanied by uremic-related symptoms that could not be corrected by drugs (such as nausea and vomiting, hyperkalemia, metabolic acidosis, and heart failure). Patients starting hemodialysis who had not used calcium tablets, calcium-containing phosphorus binders, calcitriol, or vitamin D analogs between August 2020 and May 2022 were initially screened for enrollment in this cross-sectional study. Of the 94 hemodialysis patients, patients with malignancy, decompensated liver cirrhosis, lupus nephritis, crescentic glomerulonephritis, and acute kidney injury (AKI) were excluded. Finally, 71 patients were enrolled.

Biochemical data and vascular calcification

Predialysis blood samples and plain radiographs were obtained at the time of enrollment. Serum parathyroid hormone (PTH) concentrations were determined by detecting serum intact PTH (iPTH). iPTH levels were determined by the Chongqing DIAN medical laboratory (reference range 15–65 pg/mL) by electrochemiluminescence assay. AAC was determined by latero-lateral X-ray lumbar radiography using radiographic equipment (Shimadzu 3200 1000MA Digital X-ray Machine, Nishinokyo-Kuwabarachou, Nakagyo-ku, Kyoto 604-8511, Japan). Lateral lumbar films were analyzed in the region of the L1–L4 vertebrae and the Kauppila score (a semiquantitative grading system) was used to assess the severity of AAC [12]. All X-rays were reviewed by two physicians who had the expertise to score them.

Statistical methods

Data are presented as mean ± standard deviation (SD) for normally distributed variables or median [IQR] for nonnormally distributed variables. The normality of the distribution was determined using the Shapiro–Wilk test. The correlation between two continuous variables was analyzed by Pearson's correlation (normal distribution) or Spearman's correction (skewed distribution). Pairs of continuous variables were compared using the unpaired *t*-test (normal distribution) or a nonparametric test (skewed distribution). Receiver operating characteristic (ROC) curves were plotted for serum PTH level and AAC to evaluate the ability of low serum PTH levels to predict the presence and extent of AAC. The area under the curve (AUC) and its 95% confidence interval (CI) were calculated for this ROC curve. A *p*-value of <0.05 was considered statistically significant. All computations were performed using SPSS 20.0 software (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0, Armonk, NY).

Results

The clinical characteristics and biochemistry of all patients are shown in Table 1. There were 48 males (67.6%) and 23 females (32.4%). The mean age was 60.23 ± 1.75 years (23–85 years). The cause of ESRD in our patients was diabetes mellitus in 37, glomerulonephritis in 24, systemic hypertension in 9, and autosomal dominant polycystic kidney disease in 1.

The Shapiro–Wilk test showed that serum PTH, AAC, C-reactive protein (CRP), triglycerides, serum creatinine (Scr) and HbA1c had skewed distributions, while age, serum calcium, serum phosphorus, blood magnesium, serum urea nitrogen (BUN), systolic pressure (SBP), diastolic blood pressure (DBP), hemoglobin (Hb), albumin,

Table 1. Clinical characteristics and biochemistry of whole cohort ($n = 71$).

Age, years (23–85 years)	60.23 ± 1.75
Male, *n* (%)	48 (67.6)
Causes of ESRD	
Diabetes mellitus	37 (52.1)
Glomerulonephritis	24 (33.8)
Systemic hypertension	9 (12.7)
Autosomal dominant polycystic kidney disease	1 (1.4)
SBP (116–196 mmHg)	155.10 ± 20.75
DBP (48–108 mmHg)	83.66 ± 14.31
ACC (score 0–23)	2.00 (8)
iPTH (15.8–594.5 pg/mL)	176.40 (181.10)
BUN (16.37–59.7 mmol/L)	31.41 ± 9.15
Scr (643–1729 μmol/L)	892.00 (315.5)
Serum magnesium (0.88–2.27 mmol/L)	0.96 ± 0.15
Serum calcium (0.88–2.27 mmol/L)	1.79 ± 0.33
Serum phosphorus (0.78–4.15 mmol/L)	2.05 ± 0.70
Hb (39–116 g/L)	76.05 ± 16.47
CRP (1–172 mg/L)	4 (22)
Serum total protein (43.9–80.8 g/L)	61.91 ± 8.58
Albumin (21.9–48.9 g/L)	36.39 ± 6.68
ALP (18–154 U/L)	86.83 ± 36.36
Triglycerides (0.58–5.45 mmol/L)	1.41 (0.79)
Total cholesterol (2.29–6.63 mmol/L)	3.87 ± 1.05
HDL (0.52–1.89 mmol/L)	1.06 ± 0.34
LDL (0.93–4.36 mmol/L)	2.21 ± 0.77
HbA1c (37 diabetes mellitus patients, 6.31–8.45)	6.57 (0.56)

ESRD: end-stage renal disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACC: abdominal aortic calcification; iPTH: intact parathyroid hormone; BUN: serum urea nitrogen; SCR: serum creatinine; Hb: hemoglobin; CRP: C-reactive protein; ALP: alkaline phosphatase; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

serum total protein (TP), alkaline phosphatase (ALP), serum total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were normally distributed. Because AAC had a skewed distribution and Pearson's correlation or multiple linear regression analysis was not suitable, Spearman's rank correlation analysis was employed to analyze the relationship between AAC and other variables.

There was a strong negative correlation between serum PTH and AAC (Spearman's rho −0.76, $p < 0.001$) (Figure 1(A,B); Table 2). Subgroup analysis of patients with diabetes mellitus also suggested that PTH was negatively correlated with AAC (Spearman's rho −0.412, $p = 0.011$) (Figure 1(C,D); Table 3). Receiver-operating characteristic curve analysis (Figures 2 and 3) showed that low serum PTH levels could predict the presence and extent of AAC [AUC values were 0.9013 ($p < 0.0001$) and 0.780 ($p = 0.0041$), respectively]. We also found that there was a moderate negative correlation between Pi and AAC (Spearman's rho −0.536, $p < 0.001$) (Table 2).

To further analyze why there was a negative correlation between serum phosphorus and AAC, the patients were divided into two age groups around the

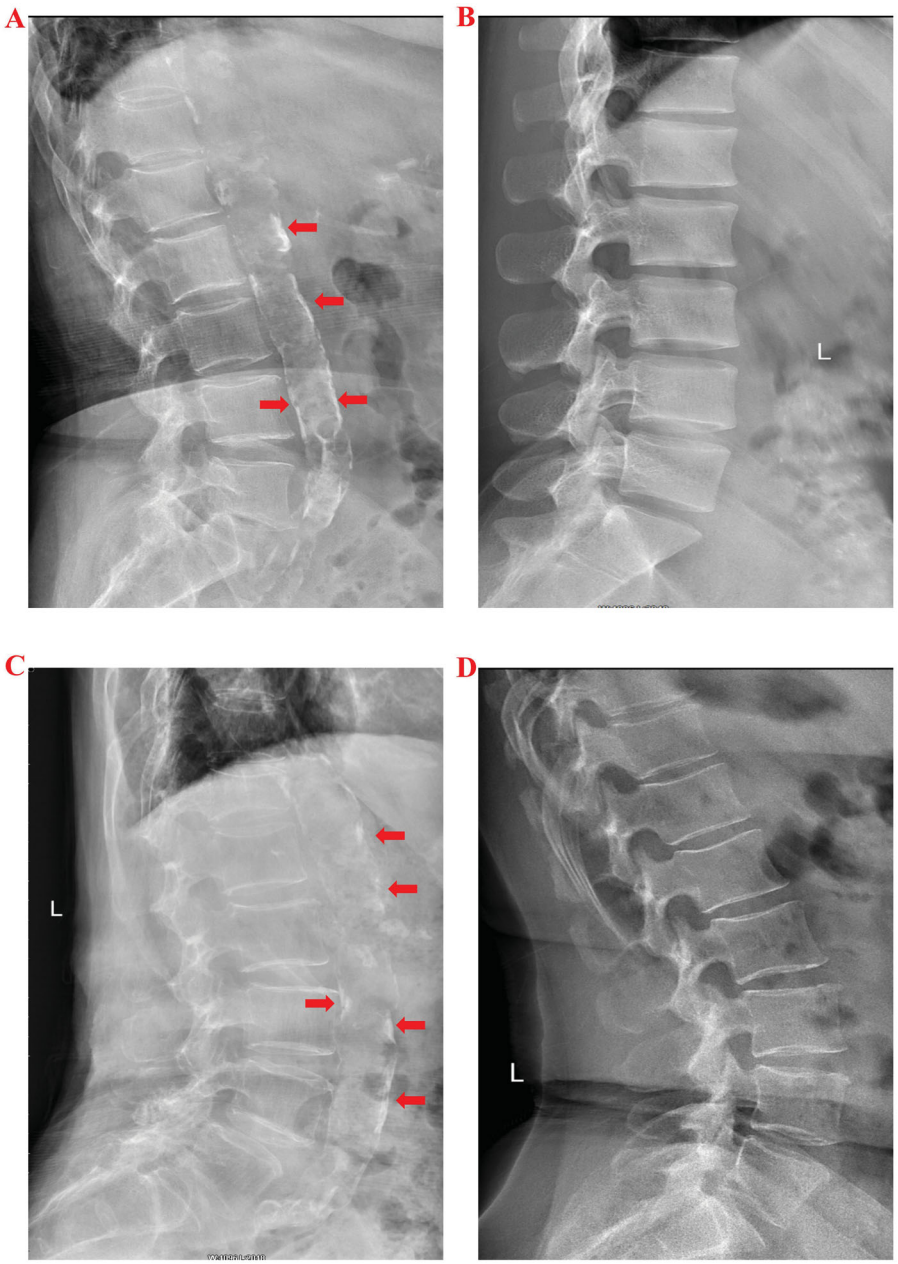

Figure 1. (A) Representative image of AAC in the low-serum-iPTH group of non-DKD patients. (B) Representative image of AAC in the high-serum-iPTH group of non-DKD patients. (C) Representative image of AAC in the low-serum-iPTH group of DKD patients. (D) Representative image of AAC in the high-serum-iPTH group of DKD patients.

Table 2. Spearman's rank correlation analysis for the relationship between abdominal aortic calcification scores and baseline characteristics.

	Spearman's rho AAC	*p*-Value
iPTH (pg/mL)	−0.760	<0.001
Age (year)	0.730	<0.001
Serum phosphorus (mmol/L)	−0.536	<0.001
BUN (mmol/L)	−0.324	0.039
Serum calcium (mmol/L)	0.223	0.160
Serum magnesium (mmol/L)	0.044	0.783
SBP (mmHg)	−0.056	0.728
DBP (mmHg)	−0.270	0.088
Scr (μmol/L)	−0.144	0.369
Hb (g/L)	0.089	0.581
CRP (mg/L)	−0.114	0.478
Serum total protein (g/L)	−0.290	0.066
Albumin (g/L)	−0.036	0.824
ALP (U/L)	−0.216	0.175
Triglycerides (mmol/L)	−0.045	0.781
Total cholesterol (mmol/L)	−0.034	0.831
HDL (mmol/L)	0.002	0.989
LDL (mmol/L)	−0.040	0.846

ACC: abdominal aortic calcification; iPTH: intact parathyroid hormone; BUN: serum urea nitrogen; SBP: systolic pressure; DBP: diastolic blood pressure; SCR: serum creatinine; Hb: hemoglobin; CRP: C-reactive protein; ALP: alkaline phosphatase; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
iPTH, Serum phosphorus, and BUN were negatively correlated with AAC; Age was positively correlated with AAC.

Table 3. A subgroup analysis of patients with diabetes mellitus for relationship between abdominal aortic calcifcation scores and baseline characteristics.

	Spearman's rho AAC Pearson's correlation AAC	*p*-Value
iPTH (pg/mL)	−0.412	0.011
Age (year)	0.436	0.007
Serum phosphorus (mmol/L)	−0.221	0.322
Serum calcium (mmol/L)	−0.536	0.953
CRP (mg/L)	−0.058	0.798
Triglycerides (mmol/L)	−0.227	0.311
HbA1c	0.005	0.976
Serum magnesium (mmol/L)	0.124	0.581
SBP (mmHg)	−0.083	0.713
DBP (mmHg)	0.094	0.676
Scr (μmol/L)	−0.027	0.903
BUN (mmol/L)	0.071	0.754
Hb (g/L)	0.158	0.483
Serum total protein (g/L)	0.182	0.419
Albumin (g/L)	0.236	0.290
ALP (U/L)	−0.343	0.119
Total cholesterol (mmol/L)	−0.059	0.795
HDL (mmol/L)	−0.150	0.505
LDL (mmol/L)	0.029	0.899

ACC: abdominal aortic calcification; iPTH: intact parathyroid hormone; CRP: C-reactive protein; SBP: systolic pressure; DBP: diastolic blood pressure; SCR: serum creatinine; BUN: serum urea nitrogen; Hb: hemoglobin; ALP: alkaline phosphatase; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
iPTH was negatively correlated with AAC; Age was positively correlated with AAC.

cutoff of 50 years. The AAC, serum PTH and serum calcium of the two groups had skewed distributions, and the serum phosphorus was normally distributed, so we used the Mann–Whitney *U*-test and unpaired *t*-test to compare groups.

Our results showed that the serum phosphorus and serum PTH of patients under 50 years old (20/71) were significantly higher (2.74 mmol/L vs. 1.65 mmol/L, unpaired *t*-test, $p < 0.001$; 368.85 pg/mL vs. 173.4 pg/mL, Mann–Whitney *U*-test, $p < 0.001$) than those of patients over 50 years old (50/71), and the AAC score was significantly lower in patients under 50 years old (0.08 vs. 6.87, Mann–Whitney *U*-test, $p < 0.001$). There was no significant difference in serum calcium between the two groups (1.67 mmol/L vs. 1.89 mmol/L, *t*-test, $p = 0.058$) (Table 4).

Discussion

The present study investigated the correlation between PTH levels and AAC in patients starting hemodialysis who had not received calcium tablets, calcium-containing phosphorus binders, calcitriol, or vitamin D analogs. Our results suggested that lower serum PTH levels were associated with higher AAC scores in this population.

Although the prevalence of VC in CKD patients is higher, the incidence of arterial calcification varies between different sites, and the risk factors for arterial calcification in different locations and their influence on cardiovascular events are also different [13–15].

AAC is an independent risk factor for all-cause mortality or CVD events in non-CKD patients, peritoneal dialysis patients, and hemodialysis patients [16–18]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines also suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification in patients with CKD stage 3–5 to guide the management of chronic kidney disease–mineral and bone disorder (CKD-MBD) [19].

Studies have demonstrated that PTH receptors exist in myocardial cells, vascular smooth muscle cells, and endothelial cells, indicating that inappropriate (excessive or insufficient) secretion of PTH may have adverse effects on the cardiovascular system [20,21]. It has been found that PTH perfusion can lead to intense aortic medial calcification in rats with parathyroidectomy, and this effect has nothing to do with uremia or serum phosphorus levels [22]. Another study also found that cinacalcet could inhibit the calcification of the aorta and heart in 5/6-nephrectomized rats by decreasing serum PTH levels [23]. These results suggest that PTH has a direct pro-calcification effect, at least in animal models of CKD.

The exact effects of PTH on AAC in CKD patients are still a matter of debate. Studies have shown that serum PTH level is related to the severity of AAC [9–11], but other studies have found that there is no association

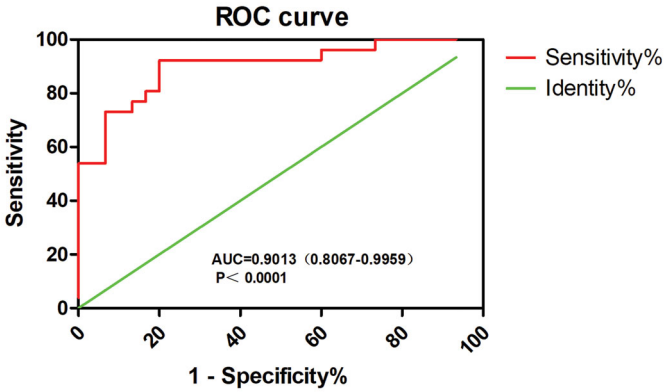

Figure 2. Receiver operating characteristic curve analysis showing the prognostic value of PTH levels in predicting the presence of AAC. The 95% confidence intervals are provided. AUC: area under the curve.

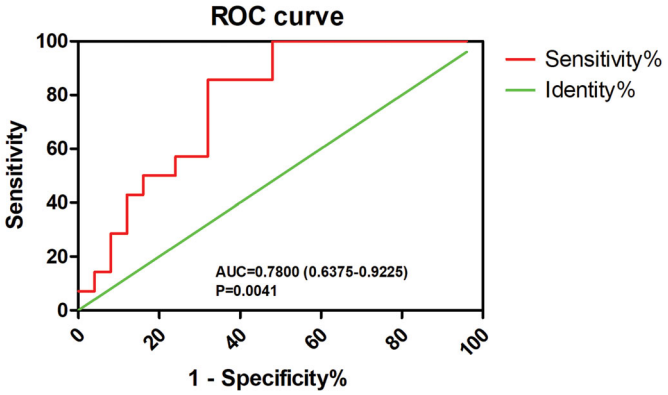

Figure 3. Receiver operating characteristic curve analysis showing the prognostic value of PTH levels in predicting severe and extensive calcification (AAC score $\geq$ 6). The 95% confidence intervals are provided. AUC: area under the curve.

Table 4. Groups analysis between different age groups (<50 years old or ≥50 years old).

	Group 1 (<50) $n = 20$	Group 2 (≥50) $n = 51$	*p*-Value
Age (year)	38.18 ± 8.20	58.73 ± 5.87	<0.001
AAC (score)	0.08 ± 0.25	6.87 ± 5.78	<0.001
iPTH (pg/mL)	368.85 ± 125.87	173.4 ± 122.45	<0.001
Serum phosphorus (mmol/L)	2.74 ± 0.71	1.65 ± 0.34	<0.001
Serum calcium (mmol/L)	1.67 ± 0.44	1.89 ± 0.41	0.058

ACC: abdominal aortic calcification; iPTH: intact parathyroid hormone.
Serum phosphorus and serum PTH of patients under 50 years old was significantly higher than that of patients over 50 years old, and the AAC score was significantly lower than that in patients over 50 years old. There was no significant difference in serum calcium between the two groups.

between the two or even a negative correlation [13–15,24,25]. One possible explanation for these contradictory conclusions is that the widespread use of calcium tablets, calcium-containing phosphorus binders, calcitriol, or vitamin D analogs affects the natural process of AAC.

Currently, calcium tablets, calcium-containing phosphorus binders, calcitriol, and vitamin D analogs are widely used to treat mineral metabolism abnormalities. The DOPPS study found that up to 52% of participants received vitamin D supplementation; 72.9% of participants used calcium-containing phosphorus binders for the control of hyperphosphatemia [8]. However, improper use of the above drugs may lead to adverse clinical consequences. For example, prolonged and disproportionate consumption of vitamin D supplements may lead to excessive inhibition of PTH and aggravation of vascular calcification [26,27]; and the use of high-dose calcium salts (oral calcium tablets or calcium-based phosphate binders) can easily lead to hypercalcemia, resulting in low serum PTH levels and vascular calcification [28,29]. Therefore, it is difficult to draw reliable conclusions about the association between PTH and AAC in the CKD population taking calcium tablets, calcium-containing phosphorus binders, calcitriol, or vitamin D analogs.

In view of this, in this study, we purposely selected patients starting hemodialysis who had not used calcium tablets, calcium-containing phosphorus binders, calcitriol, or vitamin D analogs as the research subjects. Interestingly, even after eliminating interfering factors such as calcium and vitamin D, PTH and AAC were still significantly negatively correlated. One explanation for

the negative correlation is that lower serum PTH levels lead to adynamic bone disease, and adynamic bone disease will impair the ability of patients to handle and buffer calcium loads and thus put them at higher risk of extraosseous calcifications [30,31]. It should be emphasized that although lower serum PTH levels do contribute to the risk of adynamic bone disease, there is currently no evidence that low PTH alone can represent adynamic bone disease. Another possible explanation for the negative correlation between AAC and PTH is that low serum PTH levels may only be a manifestation of malnutrition, inflammation, or cachexia syndrome (MICs), and malnutrition-inflammation is associated with vascular calcification in uremic patients [32,33]. However, in another study that included 97 hemodialysis patients who were followed up for one year, patients with malnutrition and chronic inflammation (defined as serum albumin $<$40 g/L and hs-CRP $\geq$28.57 nmol/L) had significantly higher PTH levels than the control group (241.5 pg/mL vs. 161.8 pg/mL) [11]. Therefore, neither adynamic bone disease nor malnutrition can fully explain why low PTH levels can aggravate AAC. Further studies are needed to elucidate the mechanism of AAC deterioration caused by low PTH levels.

Another surprising finding of the present study is that there was a significant negative correlation between AAC and serum phosphorus. Serum phosphorus plays a very important role in the occurrence and progression of vascular calcification [34]. Subgroup analysis in the MESA study indicated that each 1-mg/dL increment in serum phosphate concentration was associated with a 21%, 33%, 25%, and 62% greater prevalence of coronary artery, thoracic, aortic valve, and mitral valve calcification, respectively [35]. However, other researchers found that there was no significant difference in serum phosphorus levels between the AAC score $>$6 group and AAC score $\leq$6 group of hemodialysis patients [10]. A study on a Chinese hemodialysis population (CDCS study) also found that serum phosphorus was a risk factor for coronary artery calcification (CAC), but not a risk factor for AAC [14]. It should be noted that in the above studies, all participants received hemodialysis or peritoneal dialysis, which is effective in removing serum phosphorus, and a large proportion of participants were taking phosphorus binders (64.6% in the CDCS study). Therefore, it cannot be concluded that there is no correlation between serum phosphorus and AAC. In the present study, serum phosphorus was not affected by dialysis, and the patient did not use any form of phosphorus bonding agent, but there was still a significant negative correlation between AAC and serum phosphorus. This finding is consistent with that of Harin Rhee et al. [32], who also found that the prevalence of baseline AAC and its progression in the low-serum-phosphorus group was significantly higher than that in the high-serum-phosphorus group.

Further analysis of patients' characteristics showed that the serum phosphate of patients under 50 years old was significantly higher than that of patients over 50 years old, but the AAC score was significantly lower in the younger group. We speculate that age may have a greater impact on AAC than serum phosphorus in CKD patients. Indeed, a study of young patients with ESRD who were undergoing dialysis confirmed that there was no significant difference in serum phosphorus between patients with and without CAC [29]. Another study involving 174 Chinese patients also found that age may be the most important factor affecting CAC in maintenance hemodialysis patients, and serum phosphorus had no significant effect on CAC [36].

In our study, the effect of phosphorus on AAC may not have been obvious in young patients. The dietary status of young patients is often better than that of older patients, so they have higher serum phosphorus (without taking phosphate binders); therefore, serum phosphorus may be statistically negatively correlated with AAC, but this does not mean that serum phosphorus has no effect on AAC from a pathophysiological perspective.

There are several limitations to our study. First, the sample size for our study was small. More patients would be necessary to attain adequate power to detect a correlation between serum PTH levels and AAC. Second, we only evaluated the degree of AAC by abdominal radiographs, which are less sensitive and accurate than electron beam computed tomography (EBCT) and multislice CT (MSCT). Due to the relatively high cost and the risk of exposure to high radiation doses, these tests cannot be performed routinely. Third, the serum PTH levels of our observation population were in the range of 15.8–594.5 pg/mL. The correlation between PTH and AAC is not clear in CKD patients with serum PTH levels of 600 pg/mL or higher.

Conclusions

The present study, which is the only study focused on the association between PTH levels and AAC in patients starting hemodialysis who had not taken calcium tablets, calcium-containing phosphorus binders, calcitriol, or vitamin D analogs, demonstrates that PTH levels are significantly negatively correlated with AAC within a

certain concentration range. Inappropriate inhibition of PTH may lead to deterioration of AAC in CKD stage 5 patients.

Ethical approval

All procedures performed on human participants were in accordance with the ethical standards of The Chonggang General Hospital Affiliated with Chongqing University of Posts and Telecommunications and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Each participant signed an informed consent form before entering the study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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