Correlation between serum parathyroid hormone levels and coronary artery calcification in patients without renal failure

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Abstract. The aim of the present study was to investigate the correlation between serum parathyroid hormone (PTH) levels and coronary artery calcification (CAC) in patients without renal failure, as well as to determine independent risk factors of CAC score (CACS). A total of 157 patients who underwent coronary computed tomography angiographic examination at the 101th Hospital of the People's Liberation Army between December 2013 and February 2015 were retrospectively evaluated. The correlation between PTH levels and CACS was determined using a Pearson correlation analysis. A receiver operating characteristic (ROC) curve was drawn to determine the best cutoff PTH level for prediction of CAC. The independent association between serum PTH levels and CAC was analyzed by using a logistic regression analysis model with the response variable Be binary class. The results revealed that PTH levels in patients in the CAC group were significantly higher than those of patients in the non-calcification group. PTH levels were positively correlated with CACS (r=0.288, P<0.001). The ROC curve suggested that a PTH level of ≥31.05 pg/ml was the best cut-off point for the prediction of CAC, with a sensitivity of 80.88%, specificity of 60.67% and an area under the curve of 0.761. After including predictive factors for CAC (gender, age, smoking status, diabetes, hypertension, hyperlipidemia, body mass index, glomerular filtration rate and calcium, phosphorus, calcium-phosphorus product, magnesium, PTH, total cholesterol, low-density lipoprotein cholesterol, triglyceride, high-density lipoprotein cholesterol and C-reactive protein levels), the odds ratio of the serum PTH levels regarding the prediction of CAC was 1.050 (95% confidence interval, 1.027-1.074; P<0.001). In conclusion, the present study suggested that serum PTH levels are correlated with CAC in patients without renal failure and may thus be used as a reliable predictor of CAC.

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Introduction

Coronary artery calcification (CAC) is a basic pathological change in coronary atherosclerotic heart disease and often indicates further morbidities (1,2). Currently, the most common method of assessment of calcification is multislice computed tomography, and calcification is calculated by using methods such as Agatston, quality and volume integrals. The parathyroid hormone (PTH) is a linear peptide comprising 84 amino acids secreted by parathyroid lord cells, which are mainly implicated in the regulation of calcium phosphorus metabolism. Previous studies have shown that PTH induces high blood pressure and myocardial hypertrophy, is closely associated with heart failure and can even predict the occurrence of coronary heart disease (3-6). In recent years, the association between PTH and CAC has become a research hotspot. The results of previous studies suggested that PTH levels were not associated with the baseline CAC score (CACS), but with CAC progression (7-11). All of the patients included in these studies suffered from kidney failure with or without hemodialysis. However, whether PTH levels are positively correlated with CAC in patients without renal failure has remained elusive. The purpose of the present study was to investigate the correlation between serum PTH levels and CAC in patients without renal failure, as well as independent risk factors of CACS.

Materials and methods

Patients. A total of 225 consecutive patients who underwent coronary CTA examination at the 101th Hospital of the People's Liberation Army (PLA) (Wuxi, China) between December 2013 and February 2015 were retrospectively evaluated. After excluding patients with acute myocardial infarction, heart valve disease, heart failure, a glomerular filtration rate <60 ml/min or transaminase levels three times higher than the upper limit of the 99% reference range, malignant tumors, systemic infection, or autoimmune or connective tissue disease, 157 patients were enrolled. Heart failure was diagnosed according to the Chinese heart failure diagnosis and treatment guidelines from 2014 (12).

Table I. Gender and disease constitution in patients with and without calcification.

Parameter	No calcification group (n=89)	Calcification group (n=68)	χ^2	P-value	CACS≤100 (n=118)	CACS>100 (n=39)	χ^2	P-value
Males, n (%)	49 (55.06)	41 (60.29)	0.432	0.511	67 (56.78)	23 (58.97)	0.058	0.810
CAD, n (%)	23 (25.84)	56 (82.35)	49.241	< 0.001	44 (37.29)	35 (89.74)	32.263	0.000
Hypertension, n (%)	60 (67.42)	54 (79.41)	2.789	0.095	85 (72.03)	29 (74.36)	0.080	0.778
Diabetes, n (%)	12 (13.48)	14 (20.59)	1.408	0.235	16 (13.56)	10 (25.64)	3.096	0.078
Hyperlipaemia, n (%)	17 (19.10)	10 (14.71)	0.523	0.470	22 (18.64)	5 (12.82)	0.698	0.403
Smoking, n (%)	17 (19.10)	24 (35.29)	5.239	0.022	28 (23.73)	13 (33.33)	1.401	0.236
Alcohol, n (%)	2 (2.25)	7 (10.29)	3.250	0.071	7 (5.93)	2 (5.13)	0.035	0.851
Cardiomyopaty, n (%)	0 (0)	0 (0)	-	-	0 (0)	0 (0)	-	-
Atrial fibrillation, n (%)	5 (5.62)	2 (2.94)	0.172	0.678	7 (5.93)	0 (0)	1.229	0.268

CAD, coronary artery disease; CACS, coronary artery calcification score.

The Medical Ethics Committee of The 101th Hospital of the PLA approved the present retrospective study (protocol no. 20150052). Each patient signed a consent form agreeing to the storage of their information in the hospital's database and use for scientific studies.

Experimental methods. Patient data regarding hypertension, diabetes, hyperlipidemia, as well as history of smoking and alcohol consumption were collected and patients were stratified according to their positive or negative status. The body mass index (BMI) was calculated by dividing weight by the square of the height.

A total of 3 ml venous blood had been taken from each patient in the fasting state and subjected to laboratory analysis. Total cholesterol (TC), electrolytes, triglycerides (TGs), C-reactive protein (CRP), creatinine, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and fasting blood glucose (FBG) levels were measured with an automatic biochemical analyzer (AU5800; Olympus, Tokyo, Japan). Serum PTH levels were measured using a chemiluminescence method (PTH ELISA kit; GETEIN Co., Nanjing, China). The glomerular filtration rate (GFR) was calculated by using the equation: GFR (ml/min x 73 m^{-2}) = [140 - age (years)] x weight (Kg)/0.818 x creatinine concentration (μmol/l). For women, the resulting value was multiplied by 0.85.

For coronary computed tomography (CT) scanning, the Toshiba 320 row spiral CT scanner (Toshiba, Tokyo, Japan) was used. The CACS was calculated by using a Toshiba vital 6.2 workstation (Toshiba, Tokyo, Japan) according to the Agatston integral (13), which was operated by a technician. Patients with CACS>0 were assigned to the CAC group.

Heart Doppler examination was performed by cardiac ultrasonography using an ultrasonographic diagnostic instrument (vivid E9; GE Healthcare, Little Chalfont, UK), through which degenerative heart valve disease was diagnosed.

Statistical analysis. All statistical analyses were performed by using SPSS 15.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were presented as the mean ± standard deviation, and analysis of variance and least significant difference tests were applied to compare differences between groups. Categorical variables were presented as percentages and determined by using the χ^2 test. The Pearson rank order was used to analyze the correlations. A receiver operating characteristic (ROC) curve was drawn to determine the predictive value of PTH for CAC. The best cut-off PTH level to predict CAC was determined by using PTH values that provide the maximum sum of sensitivity and specificity. Indicators including gender, age, smoking status, diabetes, hypertension, hyperlipidemia, BMI, GFR, levels of serum calcium, serum phosphorus, calcium-phosphorus product (CPP), serum magnesium, PTH, TC, LDL-C, TG, HDL-C and CRP were assessed using the logistic regression analysis model with the response variable Be binary class in order to determine independent factors correlated with CAC, presented as odds ratio (OR) and 95% confidence interval (CI). P<0.05 was considered to indicate a statistically significant difference.

Results

Patient data. The present study included 68 patients with CAC, comprising 41 men and 27 women, with a mean CACS of 402.49±666.3 and serum PTH levels of 48.70±21.39 pg/ml (range, 20.40-123 pg/ml; normal, 14-72 pg/ml), and 89 patients without CAC, including 49 men and 40 women, with a mean serum PTH level of 31.98±16.03 pg/ml (12.00-86.90 pg/ml). The two groups displayed statistically significant differences in terms of age, PTH levels, GFR and blood phosphorus level, smoking status and frequency of coronary heart disease (P<0.05). However, no significant differences were observed in BMI, calcium, magnesium, CPP, cholesterol, FBG and CRP levels, as well as gender, hypertension, diabetes, hyperlipidemia and alcohol use (P>0.05).

In addition, the 157 patients were further stratified based on the CACS as follows: CACS≤100 (n=118 patients) and CACS>100 (n=39). The two groups only significantly differed

Table II. Clinical and biochemical parameters of patients with and without calcification.

Parameter	No calcification group (n=89)	Calcification group (n=68)	t-value	P-value	CACS≤100 (n=118)	CACS>100 (n=39)	t-value	P-value
Age (years)	59.82±11.50	68.38±10.05	4.879	< 0.001	60.94±11.01	71.36±10.09	5.228	<0.001
BMI (kg/m^2)	24.86±3.28	23.94±3.39	1.725	0.087	24.65±3.28	23.91±3.54	1.203	0.231
PTH (pg/ml)	31.98±16.03	48.70±21.39	5.391	< 0.001	35.87±19.68	49.37±18.76	3.755	<0.001
GFR (ml/min/1.73m^2)	102.16±29.54	84.49±22.47	4.108	< 0.001	98.97±28.43	80.99±22.15	3.603	<0.001
Ca (mmol/l)	2.28±0.13	2.28±0.15	0.088	0.930	2.28±0.13	2.27±0.15	0.725	0.470
Mg (mmol/l)	0.81±0.09	0.82±0.08	0.043	0.966	0.81±0.09	0.83±0.09	1.264	0.208
P (mmol/l)	1.12±0.16	1.07±0.18	2.095	0.038	1.11±0.17	1.06±0.18	1.715	0.088
CPP (mmol^2/l^2)	2.57±0.42	2.43±0.44	1.971	0.050	2.54±0.42	2.40±0.46	1.755	0.081
FBG (mmol/l)	5.36±1.35	5.54±1.40	0.828	0.409	5.41±1.35	5.54±1.44	0.524	0.601
TC (mmol/l)	4.26±0.90	4.11±0.91	1.019	0.310	4.21±0.88	4.17±0.99	0.201	0.841
TG (mmol/l)	1.81±1.26	1.60±1.41	0.962	0.338	1.74±1.15	1.65±1.77	0.393	0.695
HDL-C (mmol/l)	1.23±0.29	1.18±0.26	1.145	0.254	1.22±0.29	1.19±0.25	0.586	0.559
LDL-C (mmol/l)	2.05±0.67	2.04±0.69	0.080	0.936	2.04±0.66	2.06±0.74	0.103	0.918
CRP (mg/l)	3.07±7.05	7.07±18.81	1.668	0.099	4.51±14.60	5.68±9.88	0.467	0.641

Values are expressed as the mean ± standard deviation. CACS, coronary artery calcification score; BMI, body mass index; PTH, parathyroid hormone; GFR, glomerular filtration rate; Ca, calcium; Mg, magnesium; P, inorganic phosphate; CPP, calcium-phosphorus product; FBG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; CRP, C-reactive protein.

Table III. Correlation analysis for parathyroid hormone and biological metabolic parameters.

Parameter	r-value	P-value
GFR	-0.207	0.011
Calcium	0.023	0.778
Magnesium	0.006	0.945
Inorganic phosphate	-0.231	0.005
CPP	-0.225	0.006
FBG	0.139	0.092
TC	0.011	0.892
TG	-0.029	0.726
HDL-C	0.051	0.538
LDL-C	-0.032	0.702
CRP	-0.033	0.690

GFR, glomerular filtration rate; CPP, calcium-phosphorus product; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein.

Table IV. Correlation analysis for parathyroid hormone and calcification scores.

Group	r-value	P-value
Calcification + no calcification	0.288	<0.001
Calcification	0.186	0.130

Table V. Parathyroid hormone levels in patients with three degrees of CAC.

Groups	P-value	95% CI for mean difference Lower	Upper
CACS≤10 and 10<CACS<100	<0.001	-28.19	-10.28
CACS≤10 and CACS>100	<0.001	-23.66	-9.85
10<CACS≤100 and CACS>100	0.626	-7.56	12.52

CACS, coronary artery calcification score; CI, confidence interval.

in terms of age, PTH levels, GFR and the frequency of coronary heart disease (P<0.05) (Tables I and II).

Correlation of PTH levels and calcium score as well as metabolic measures. The results of the Pearson correlation analysis showed that among all of the patients included in the present study, the PTH levels were positively correlated with the CACS (r=0.288, P<0.001), while they were negatively correlated with the GFR, phosphorus levels and CPP (r=-0.207, P=0.011; r=-0.231, P=0.005; and r=-0.225, P=0.006, respectively). However, in the calcification group, no significant correlation was observed in this respect (r=0.186, P=0.130; Tables III and IV).

Serum PTH levels in patients with CACS≤10 (n=98) were significantly lower than those in patients with 10<CACS≤100 (n=20) and CACS>100 (n=39) (P<0.001 for each). However, no significant differences were observed in PTH levels

Table VI. Binary logistic regression analysis of independent predictors for coronary artery calcification.

Indicators	B	Wald	P-value	OR	95% CI
PTH	0.049	18.231	<0.001	1.050	1.027-1.074
Smoking	0.921	4.795	0.029	2.513	1.102-5.731
GFR	-0.025	9.972	0.002	0.975	0.961-0.991

B, regression coefficient; PTH, parathyroid hormone; GFR, glomerular filtration rate; CI, confidence interval; OR, odds ratio.

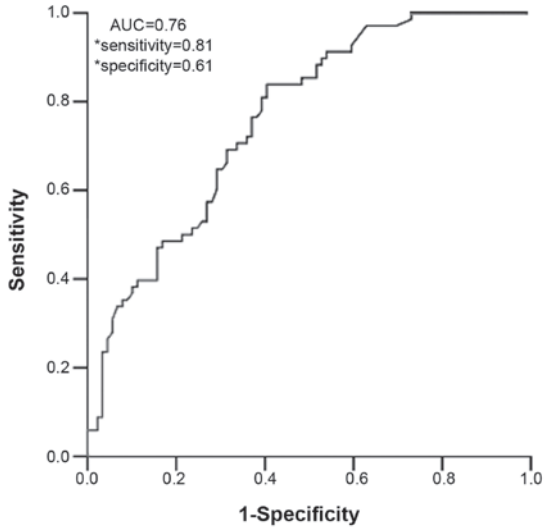

Figure 1. Receiver operating characteristic curve of parathyroid hormone levels for the prediction of coronary artery calcification. *Values were obtained using the optimal cut-off value. AUC, area under the curve.

between patients with 10<CACS≤100 and CACS>100 (P=0.626) (Table V).

Predictive value of PTH for CAC. The ROC curve revealed that PTH levels of ≥31.05 pg/ml are optimal for the prediction of CAC, with a sensitivity of 80.88%, a specificity of 60.67% and an area under the curve of 0.76 (P<0.001; Fig. 1).

Independent predictors of CAC. The results of the logistic regression analysis model with the response variable Be binary class showed that PTH levels (OR=1.050; 95% CI, 1.050-1.074; P<0.001) and smoking (OR=2.513; 95% CI, 2.513-5.731; P=0.029) were predictors of CAC and that the GFR (OR=0.975, 95% CI 0.961-0.991; P=0.002) was negatively associated with CAC (P<0.05; Table VI). None of the other factors assessed had any predictive value regarding CAC (P>0.05). Overall, the results supported the significance of PTH levels in terms of prediction of CAC.

Discussion

CAC arises from calcium salt deposition via atheromatous plaque rupture and hemorrhage-induced composite patches. Previous studies have confirmed that hypertension, diabetes, gender, age and other cardiovascular risk factors are involved in the formation of CAC (14). The results of the present study showed that the mean age and smoking status of the patients in the CAC group were significantly higher than those in the non-calcification group, which was consistent with the results of previous studies (15,16). While in the CAC group, the number of patients with high blood pressure and diabetes, and the proportion of men were higher than those in the group without calcification, the difference did not reach statistical significance, possibly due to factors such as the small overall sample size and the fact that the number of patients without calcification was higher than that of patients with calcification.

The degree of CAC can predict the extent of coronary artery stenosis, affect the therapeutic efficacy of coronary artery intervention and predict the incidence of cardiovascular events, regardless of whether patients had clinical symptoms (17,18). Therefore, an accurate prediction of the degree of CAC is significant in clinical practice. In addition to the most commonly used imaging techniques at present, laboratory indexes, including lipoprotein(a), endothelin 1 and bone morphogenetic protein 2 levels, are also associated with calcification and may be utilized to assess the degree of CAC (19-21). To date, the association between serum calcium, phosphorus, CPP and CAC has been most widely discussed in previous studies (22,23); however, the conclusions are not consistent. The presence of cardiovascular risk factors may affect the results of these studies. According to the present consensus, calcification is considered as the result of calcium phosphorus metabolism disorders, transformation of vascular endothelial cells to osteoblasts and calcium balance disorders (24). PTH mainly regulates calcium phosphorus metabolism and vice versa, suggesting a feedback loop-like association between PTH and calcification.

In fact, the results of a previous study indicated that serum PTH levels were able to predict coronary heart disease in subjects with calcium levels within the normal range (6). Hyperparathyroidism impairs coronary microcirculation and PTH was shown to be independently correlated with abnormal coronary flow reserve (25). Furthermore, several studies have pointed out the important effect of PTH overexpression on cardiovascular disease, including carotid artery, abdominal aortic and valvular calcifications, as well as CAC (26-30), while most of these studies focused on patients with renal failure, which is known to induce secondary hyperparathyroidism. However, the results of previous studies are inconsistent with regard to whether renal insufficiency is associated with CAC. Ix *et al* (31) reported that the association between mild-to-moderate renal insufficiency and CAC was not statistically significant after adjusting cardiovascular risk factors, while Fox *et al* (32) concluded the opposite. Certain studies have argued that the correlation only existed in patients >70 years of age or with stage 3-5 chronic kidney

disease (33,34). Furthermore, it remains elusive whether renal failure influences the association of PTH levels and CAC. In the present study, in order to avoid interference, patients with GFR <60 ml/min were excluded, and PTH remained an independent predictor of CAC after including multiple cardiovascular risk factors; furthermore PTH levels were positively correlated with the CACS in all patients. However, in the calcification group, PTH levels did not show an increasing trend corresponding with the increase in the calcium score, which was different from the results of previous studies (11,23). The small sample size of the calcification group may be one of the reasons for this observation.

All of the abovementioned results indicated that PTH is independently correlated with CAC, irrespective of renal failure being present. Moreover, PTH is easy to detect at low cost, representing advantages over other biomarkers.

The limitations of the present study include, but are not limited to the following points: Patients with heart failure and heart valve disease were excluded; however, the presence of peripheral artery calcification was not known. Calcium metabolism is not only determined by the level of PTH, but vitamin D also has a marked impact on it; however, the levels of vitamin D-associated factors were not available in the present retrospective study. Further limitations of the present study included small sample size and number of parameters available; in addition only a preliminarily analysis of the correlation between PTH levels and CAC was performed. Therefore, the results of the present study only indicated an association, and further studies are therefore required to clarify the detailed mechanisms of the impact of PTH on CAC.

In conclusion, the present study revealed that the serum PTH levels correlated with CAC and may thus be used as a reliable predictor of CAC in patients without renal failure; however, it remains to be determined whether PTH is an independent predictor of CAC.

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