

Coronary Artery Calcium Score and Arterial Stiffness in Mild Primary Hyperparathyroidism: an Exploratory Cross-sectional Study

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Abstract

Background

Evidence suggests a potential association between primary hyperparathyroidism (PHPT) and cardiovascular alterations. However, data on arterial stiffness in PHPT are heterogeneous, and studies evaluating the coronary artery calcium score (CACS) are limited and report conflicting results. This study compared CACS and arterial stiffness parameters between patients with hypercalcemic PHPT and control subjects and evaluated correlations among these markers and their associations with serum parathyroid hormone (PTH) and calcium levels.

Methods

This exploratory study included 20 patients with PHPT and 25 control subjects. CACS was evaluated by non-contrast cardiac computed tomography. Arterial stiffness indices— augmentation index (Alx), and pulse wave velocity (PWV)—were estimated using an oscillometric device.

Results

Forty-five participants were evaluated, with similar age distribution between groups and a predominance of women. No significant differences were observed between PHPT and controls for CACS (median 0.00 [0.00–52.00] vs. 7.00 [0.00–256.50]; $P = 0.443$), CACS percentile (0.00 [0.00–79.25] vs. 70.00 [0.00–92.00]; $P = 0.418$), Alx (24.55 ± 11.26 vs. 26.72 ± 10.73 ; $P = 0.513$), or PWV (9.13 ± 1.22 vs. 9.07 ± 1.10 m/s; $P = 0.868$). In PHPT participants with CACS > 0, mean CACS percentile was elevated (77.78 ± 19.27). In PHPT patients, CACS, Alx, and PWV were not correlated with serum PTH or calcium. A positive correlation between CACS and Alx was observed exclusively in the PHPT group ($r = 0.472$; $P = 0.035$), with no such association among controls ($r = -0.012$; $P = 0.956$).

Conclusions

CACS correlated positively with Alx in patients with PHPT but not in controls. This finding may suggest a potential disease-specific interplay between central hemodynamics and subclinical atherosclerosis in the context of primary hyperparathyroidism.

Introduction

Primary hyperparathyroidism (PHPT) is the leading cause of hypercalcemia in ambulatory patients [1]. Although it is classically associated with renal and skeletal complications—such as nephrolithiasis, chronic kidney disease, and osteoporosis [1–3]—growing evidence suggests broader systemic complications, including potential cardiovascular involvement [4–12].

Arterial stiffness is an early and independent marker of cardiovascular risk and reflects functional and structural changes of the arterial wall [13–15]. These changes may be influenced by chronic excess parathyroid hormone (PTH) and disturbances in calcium metabolism. However, studies evaluating arterial stiffness in PHPT have yielded heterogeneous results, and there is no consensus regarding the presence or magnitude of these alterations. Some investigations have reported increased arterial stiffness—assessed by pulse wave velocity (PWV) and/or augmentation index (AIx)—in patients with PHPT compared with control subjects [16, 17], although substantial methodological variability limits comparability.

Data on the coronary artery calcium score (CACS) in PHPT is also limited. A small cross-sectional study involving patients with hypercalcemic PHPT found no significant difference in CACS compared with population-based controls from the MESA cohort [18]. In contrast, a French cross-sectional study reported higher CACS percentiles in individuals with PHPT compared with MESA controls, suggesting greater severity of subclinical atherosclerosis [19].

A systematic review and meta-analysis suggested an association between PHPT and adverse cardiovascular outcomes, including cardiovascular mortality, but highlighted major methodological limitations such as heterogeneity and the predominance of retrospective designs [20]. In line with these uncertainties, the Fifth International Workshop guidelines adopt a cautious position regarding cardiovascular involvement in PHPT: findings are not uniformly reversible after parathyroidectomy, and routine cardiovascular assessment is not recommended [3].

Therefore, this exploratory cross-sectional study aimed to evaluate the coronary artery calcium score and arterial stiffness parameters in patients with PHPT compared with control subjects and to investigate correlations between these vascular markers and serum PTH and calcium concentrations

Methods

This cross-sectional study was conducted at the outpatient clinic of a tertiary care hospital.

Participants

Twenty adults with hypercalcemic PHPT and 25 control subjects without PHPT were enrolled between September 2024 and August 2025. During the study period, all patients with PHPT who met the eligibility criteria were invited to participate. Controls subjects without PHPT were recruited from patients' companions and hospital staff without PHPT.

Eligibility criteria

Eligible participants were adults aged ≥ 18 years with a diagnosis of hypercalcemic PHPT according to current international guidelines (3). Exclusion criteria were pregnancy; active malignancy (except non-melanoma skin cancer); advanced chronic liver disease; personal history of coronary artery disease; ischemic stroke; Paget's disease of bone; chronic corticosteroid use at doses ≥ 5 mg/day of prednisone

or equivalent for more than three months; and an estimated glomerular filtration rate <30 mL/min/1.73 m². The same exclusion criteria were applied to controls, in addition to the absence of PHPT. Family history of coronary artery disease was recorded as a clinical variable and was not an exclusion criterion.

Ethics

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Research Ethics Committees. All participants provided written informed consent.

Clinical and laboratory assessment

Demographic and clinical data were collected through face-to-face interviews. Blood pressure was measured using an Omron HEM-7320 monitor following European Society of Hypertension recommendations [21]. Laboratory tests included fasting plasma glucose, glycated hemoglobin, lipid profile, creatinine, PTH, calcium, albumin, phosphorus, 25-hydroxyvitamin D (25(OH)D), and 24-hour urinary calcium. PTH and 25(OH)D were measured using electrochemiluminescence (Cobas E601, Roche, Switzerland). Peripheral venous blood samples were collected after a 12-hour overnight fast. Serum calcium was albumin-corrected using: $\text{total calcium (mg/dL)} - 0.8 \times [\text{albumin (g/dL)} - 4]$.

Coronary artery calcium score

CACS was assessed by non-contrast cardiac computed tomography and expressed as Agatston units and percentiles. Images were acquired using a 64-slice multidetector scanner (Revolution Maxima, GE Healthcare).

Arterial stiffness assessment

Central hemodynamic measurements and arterial stiffness parameters were obtained using the Arteris AOP® monitor (Cardios, São Paulo, Brazil), an oscillometric device that records the brachial pulse waveform and applies proprietary algorithms to estimate central blood pressure, Alx, and PWV. Data were analyzed using MAPAs® software. The Arteris AOP® is classified among oscillometric devices that estimate PWV based on brachial waveform analysis, a method consistent with current guidelines [22,23]

Statistical analysis

Data were entered into Microsoft Excel and analyzed using SPSS version 27 (IBM Corp., United States). Categorical variables were expressed as counts and percentages and compared using the Pearson chi-square test or, when the assumptions for its use were not met, Fisher's exact test. Continuous variables were presented as mean $\pm$ standard deviation for normally distributed data or median (interquartile range) for non-normally distributed data. Normality was assessed using the Shapiro–Wilk test and homogeneity of variances using Levene's test.

Between-group comparisons were performed using Student's t test or the Mann–Whitney U test, as appropriate. Correlations between continuous variables were assessed using Spearman's rank

correlation coefficient. A two-sided p -value < 0.05 was considered statistically significant.

Results

A total of 45 participants were included, comprising 20 patients with PHPT and 25 control subjects without PHPT. The groups were comparable in age (62.95 vs. 63.56 years; p=0.719) and sex distribution, with a predominance of women. No participant had a personal history of coronary artery disease, as this was an exclusion criterion.

Demographic and clinical characteristics and medication use are summarized in Table 1. Comorbidities were similarly distributed between groups, except for prediabetes, which was more frequent among controls (15% vs. 44%; p=0.037). Vitamin D supplementation was more common in the PHPT group (60% vs. 24%; p=0.014).

Table 1. General characteristics of the study subjects

Variable	PHPT (N = 20)	Controls (N = 25)	P-value
Age (years), mean $\pm$ SD	62.95 $\pm$ 5.77	63.56 $\pm$ 5.50	0.719
Sex, N (%)			1.000
Male	1 (5.0)	1 (4.0)	
Female	19 (95.0)	24 (96.0)	
Comorbidities, N (%)			
Dyslipidemia	18 (90.0)	22 (88.0)	1.000
Arterial hypertension	16 (80.0)	21 (84.0)	1.000
Diabetes mellitus	9 (45.0)	10 (40.0)	0.736
Prediabetes	3 (15.0)	11 (44.0)	0.037*
Family history of CAD	6 (30.0)	2 (8.0)	0.113
Smoking	1 (5.0)	0 (0.0)	0.444
Medication use, N (%)			
Vitamin D supplementation	12 (60.0)	6 (24.0)	0.014*
Calcium supplementation	3 (15.0)	2 (8.0)	0.642
Bisphosphonates	3 (15.0)	1 (4.0)	0.309
Oral hypoglycemic agents	9 (45.0)	12 (48.0)	0.841
Insulin	3 (15.0)	0 (0.0)	0.080
Statins	16 (80.0)	14 (56.0)	0.090
ARBs	12 (60.0)	13 (52.0)	0.592
ACE inhibitors	4 (20.0)	5 (20.0)	1.000
Calcium channel blockers	7 (35.0)	5 (20.0)	0.258
Antiplatelet agents	0 (0.0)	2 (8.0)	0.495

Abbreviations: N: number; SD, standard deviation; PHPT, primary hyperparathyroidism; ARBs, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme; CAD, coronary artery disease.

Categorical variables are presented as N (%). Continuous variables are presented as mean $\pm$ SD. Continuous variables were compared using Student's t test and categorical variables using the Pearson chi-square test or, when the assumptions for its use were not met, Fisher's exact test. *p < 0.05.

Anthropometric measures, blood pressure, and lipid profile did not differ significantly between groups (Table 2). As expected, PHPT patients had higher albumin-corrected calcium, PTH, and 24-hour urinary calcium levels and lower phosphorus levels. Median 25(OH)D levels were lower in the PHPT group (p=0.023).

Table 2. Anthropometric and laboratory data of the study subjects

Variable	PHPT (N = 20)	Controls (N = 25)	P-value
BMI (kg/m ²)	30.32±7.27	29.96±4.46	0.849
Waist circumference (cm)	98.73±13.66	97.20±10.47	0.674
Systolic blood pressure (mmHg)	140.10±19.94	138.08±16.65	0.713
Diastolic blood pressure (mmHg)	84.65±10.13	83.76±7.21	0.742
Fasting glucose (mg/dL)	96.00 (85.25–139.25)	106.00 (97.50–113.00)	0.299
Glycated hemoglobin (%)	5.55 (5.33–7.23)	6.20 (5.65–6.85)	0.217
Total cholesterol (mg/dL)	198.45±44.68	204.16±50.54	0.694
HDL cholesterol (mg/dL)	55.00±16.32	49.64±10.97	0.196
LDL cholesterol (mg/dL)	108.36±39.63	126.74±44.71	0.157
Triglycerides (mg/dL)	152.00 (101.50–215.25)	128.00 (96.50–185.50)	0.350
Creatinine (mg/dL)	0.73±0.18	0.67±0.08	0.123
CKD-EPI (mL/min/1.73 m ²)	95.00 (85.00–100.75)	98.00 (94.00–101.00)	0.229
Albumin-corrected calcium (mg/dL)	10.91±0.97	9.02±0.31	<0.001*
PTH (pg/mL)	137.00 (107.63–162.50)	35.00 (29.35–48.40)	<0.001*
25(OH)D (ng/mL)	32.15 (24.05–37.30)	35.20 (29.10–46.60)	0.023*
Phosphorus (mg/dL)	3.15 (2.53–3.30)	3.60 (3.45–3.90)	<0.001*
24-hour urinary calcium (mg/24 h)	187.50 (129.25–312.50)	106.50 (47.40–158.75)	<0.001*

Abbreviations: N: number; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

Normally distributed variables are presented as mean ± SD; non-normally distributed variables as median (interquartile range). Student's t test or Mann–Whitney U test was used as appropriate. *p < 0.05.

Cardiovascular parameters are shown in Table 3. No significant differences were observed between groups in CACS, CACS percentile, central blood pressure, heart rate, Alx, or PWV. The proportion of participants with CACS = 0 was similar in PHPT and control groups (48.0% vs. 55.0%; $p=0.641$).

Table 3. Coronary calcifications, central blood pressure and arterial stiffness in patients and controls

Variable	PHPT (N = 20)	Controls (N = 25)	P-value
CACS (Agatston units)	0.00 (0.00–52.00)	7.00 (0.00–256.50)	0.443
CACS percentile	0.00 (0.00–79.25)	70.00 (0.00–92.00)	0.418
Central systolic pressure (mmHg)	120.80±17.54	116.80±15.93	0.428
Central diastolic pressure (mmHg)	80.65±13.96	79.32±9.42	0.705
Central pulse pressure (mmHg)	39.00 (27.25–49.75)	35.00 (27.50–43.50)	0.790
Heart rate (bpm)	70.00 (63.50–78.50)	71.00 (61.00–77.00)	0.950
Alx, (%)	24.55±11.26	26.72±10.73	0.513
PWV (m/s)	9.13±1.22	9.07±1.10	0.868

Abbreviations: N: number; CACS, coronary artery calcium score; PHPT, primary hyperparathyroidism; Alx, augmentation index; PWV, pulse wave velocity.

Normally distributed variables are presented as mean $\pm$ SD; non-normally distributed variables as median (interquartile range). Student's t test or Mann–Whitney U test was used as appropriate.

Among participants with CACS > 0, mean Agatston scores did not differ significantly between groups (302.44 vs. 292.00; $p=0.357$), and CACS percentiles were similarly elevated (77.78 vs. 89.15; $p=0.299$).

In correlation analyses (Table 4), CACS was not associated with serum PTH or albumin-corrected calcium in either group. Alx and PWV were also not correlated with these biochemical parameters. Notably, a positive correlation between CACS and Alx was observed exclusively in PHPT patients ($r = 0.472$; $p=0.035$), whereas no such association was identified in controls ($r = -0.012$; $p=0.956$).

Table 4. Correlations between serum PTH and serum calcium with coronary artery calcium score and arterial stiffness in PHPT patients and controls

Dependent variable	Correlated variable	PHPT patients	Controls
CACS (Agatston units)	PTH	0.153 (p=0.519)	0.197 (p=0.344)
	Albumin-corrected calcium	0.146 (p=0.538)	0.137 (p=0.512)
Alx (%)	PTH	0.072 (p=0.764)	-0.005 (p=0.980)
	Albumin-corrected calcium	0.353 (p=0.127)	0.034 (p=0.870)
PWV (m/s)	PTH	-0.100 (p=0.675)	0.071 (p=0.738)
	Albumin-corrected calcium	0.171 (p=0.471)	-0.021 (p=0.921)
CACS (Agatston units)	Alx	0.472 (p=0.035*)	-0.012 (p =0.956)
	PWV	0.342 (p=0.140)	0.265 (p=0.200)

Abbreviations: CACS, coronary artery calcium score; Alx, augmentation index; PWV, pulse wave velocity; PTH, parathyroid hormone; PHPT, primary hyperparathyroidism.

*Spearman's rank correlation

Discussion

In this cross-sectional study, we evaluated CACS and arterial stiffness parameters in patients with PHPT and control subjects. The principal finding was a positive correlation between CACS and Alx exclusively in PHPT patients, despite the absence of significant between-group differences in either marker when assessed independently.

Overall CACS values did not differ between PHPT and controls, consistent with prior reports in hypercalcemic and normocalcemic PHPT [18,24]. Koubaity et al. reported comparable proportions of CACS > 0 among patients with PHPT and MESA controls (53% versus 50%). In line with these findings, a similar proportion was observed in our sample between patients and controls (48.9% versus 52%; p=0.641). However, when comparing their patients with the MESA reference population, those authors observed greater severity of coronary calcification, as evidenced by the positioning of individuals with PHPT at the 67th percentile of the population distribution [19]. In our study, the percentile among patients with CACS > 0 was also elevated (77,78 ± 19,27), even higher than that reported by Koubaity et al.; however, unlike that study, we used a control group composed of individuals without PHPT. In this direct comparison between patients and controls, no statistically significant difference in CAC percentiles was observed (77,78 ± 19,27 vs 89,15 ± 8,56; p=0.299). These results may have been influenced by the higher prevalence of prediabetes in the control group, given current evidence indicating that prediabetes is associated with increased cardiovascular risk [25,26].

A recent retrospective study that evaluated patients undergoing computed tomography for CACS identified a similar proportion of individuals with CACS > 0 among those with and without PHPT.

However, among patients with positive CACS, those with PHPT exhibited a higher proportion of moderate to severe coronary calcification, defined as CACS ≥ 100 (67% versus 50%). In that study, patients with PHPT were slightly older and had a higher prevalence of arterial hypertension and chronic kidney disease, as well as a higher estimated cardiovascular risk according to the Framingham and PREVENT risk scores, factors that may have contributed to the greater calcification burden observed in this group [27].

In the present study, no significant differences were observed in mean PWV values between the groups evaluated. These findings contrast with the results of the meta-analysis conducted by Bernardi et al., which included ten studies and demonstrated that patients with PHPT, even in mild forms, exhibit significantly higher PWV compared with control individuals, with a mean difference of 1.18 m/s (95% CI 0.67–1.68; $p < 0.0001$) [16]. The studies included were predominantly observational, small in size (with sample sizes ranging from 14 to 83 participants), and employed different methodologies for carotid–femoral PWV assessment, including applanation tonometry, doppler ultrasound, and oscillometric devices based on brachial waveform analysis, which corroborates the substantial methodological heterogeneity reported in the literature.

In 2022, Grillo et al., in a systematic review encompassing 16 studies involving PHPT and hypoparathyroidism, reported increased arterial stiffness markers in PHPT, but explicitly highlighted methodological heterogeneity as one of the main barriers to direct comparison across studies [28].

With regard to Alx, our findings differ from those reported by Rubin et al., who, using radial applanation tonometry with derivation of the central aortic waveform, identified significantly higher Alx values in patients with PHPT [17]. These results may have been influenced by the higher prevalence of prediabetes in our control group.

Moreover, there is a paucity of studies that have simultaneously evaluated arterial stiffness and coronary artery calcification in patients with PHPT. The pilot study by Dural et al. included 21 individuals and assessed the impact of parathyroidectomy on both outcomes. In the preoperative period, most patients exhibited a CACS of 0 (67%), whereas the remaining 33% showed CAC percentiles ranging from 39 to 99; notably, no control group was included for comparison of CACS. In our study, a higher prevalence of CACS > 0 was observed (52%). Regarding arterial stiffness parameters, the authors identified higher central systolic pressure and Alx values in patients with PHPT compared with healthy controls derived from a cohort of kidney donors [29]. Although both outcomes were evaluated, no correlation analysis between arterial stiffness and coronary calcification was performed, precluding conclusions regarding their potential interrelationship.

The positive correlation between CACS and Alx, observed exclusively in the PHPT group, may suggest a potential interaction between central hemodynamic alterations and subclinical atherosclerosis within the pathophysiological context of PHPT [30]. A population-based study has shown that measures of arterial stiffness and wave reflection are associated with vascular calcification across different vascular beds, indicating that calcification and arterial hemodynamics share common and potentially bidirectional

mechanisms. Notably, the study population was predominantly composed of current and former smokers. [31]. In patients with chronic kidney disease, a study demonstrated that PTH impairs vascular reactivity, possibly through interference with endothelial function, whereas large-artery distension appears to be more closely related to disturbances in mineral metabolism, particularly the calcium–phosphate product, than to PTH levels per se. These findings suggest the existence of a dual mechanism of vascular injury, involving a functional endothelial component that may be mediated by PTH and a structural impairment of the medial and adventitial layers that may be associated with disturbances in calcium homeostasis[30]. In addition, a study in animal models indicates that PTH plays a direct role in the induction of vascular, including coronary, calcification, further supporting its involvement in arterial wall mineralization [32]. Accordingly, it is possible that, in patients with PHPT, a greater burden of coronary calcification reflects not only structural atherosclerosis but also a stiffer vascular phenotype with enhanced wave reflection, resulting in the observed positive correlation between CACS and Alx. The absence of this correlation in the control group reinforces the hypothesis that PHPT creates a specific vascular milieu in which functional and structural markers of arterial damage become interdependent.

This study has some limitations, including its cross-sectional design, which does not allow causality to be established. The relatively small sample size may have limited the statistical power to detect modest differences or associations. Therefore, these findings should be considered hypothesis-generating and warrant confirmation in larger studies. Strengths include the strict exclusion of established CAD, the inclusion of a control group for direct comparison, and the integrated assessment of structural and functional vascular markers.

In conclusion, our data demonstrated a positive correlation between CACS and Alx in patients with PHPT but not in controls. This finding may suggest a potential disease-specific interplay between central hemodynamics and subclinical atherosclerosis in the context of primary hyperparathyroidism.

Abbreviations

ACE: Angiotensin-converting enzyme;

Alx: Augmentation index;

ARBs: Angiotensin II receptor blockers;

BMI: Body mass index;

CACS: Coronary artery calcium score;

CAD: Coronary artery disease;

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration;

HUOC: Hospital Universitário Oswaldo Cruz (Oswaldo Cruz University Hospital);

PHPT: Primary hyperparathyroidism;

PROCAPE: Pronto-Socorro Cardiológico Universitário de Pernambuco Professor Luiz Tavares (Professor Luiz Tavares University Cardiology Emergency Hospital of Pernambuco);

PTH: Parathyroid hormone;

PWV: Pulse wave velocity;

25(OH)D: 25-hydroxyvitamin D.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Research Ethics Committees of the HUOC/PROCAPE Hospital Complex, University of Pernambuco (CEP-HUOC/PROCAPE; approval no. 6.826.396; CAAE 79413224.0.0000.5192). All participants provided written informed consent prior to enrollment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RS contributed to the conceptualization and methodology of the study, data curation, and writing of the original draft. VK contributed to the investigation, data curation, and review and editing of the manuscript. BA contributed to the investigation, data curation, interpretation of imaging data, and review

and editing of the manuscript. AL contributed to the investigation, provision of resources, and review and editing of the manuscript. FB contributed to the conceptualization of the study, supervision, project administration, and review and editing of the manuscript. All authors read and approved the final manuscript.

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