



HAL
open science

Coronary artery disease is more severe in patients with primary hyperparathyroidism

Omar Koubaity, Damien Mandry, Phi-Linh Nguyen-Thi, Florence Bihain, Claire Nomine-Criqui, Léa Demarquet, Valérie Croise-Laurent, Laurent Brunaud

► To cite this version:

Omar Koubaity, Damien Mandry, Phi-Linh Nguyen-Thi, Florence Bihain, Claire Nomine-Criqui, et al.. Coronary artery disease is more severe in patients with primary hyperparathyroidism. *Surgery*, 2020, 167 (1), pp.149-154. 10.1016/j.surg.2019.05.094 . hal-03254728

HAL Id: hal-03254728

<https://hal.univ-lorraine.fr/hal-03254728>

Submitted on 21 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial| 4.0 International License

Coronary artery disease is more severe in patients with primary hyperparathyroidism.

Authors: Omar KOUBAITY ¹, Damien MANDRY ¹, Phi-Linh NGUYEN-THI ², Florence BIHAIN ³, Claire NOMINE-CRIQUI ³, Léa DEMARQUET ⁴, Valérie CROISE-LAURENT ¹, Laurent BRUNAUD ^{3,5}

1: University of Lorraine, CHU Nancy, Brabois Hospital, Department of Radiology, Nancy, France

2: University of Lorraine, CHU Nancy, Medical Evaluation Departement, Department of Clinical Research Support PARC, Nancy, France

3 : University of Lorraine, CHU Nancy, Brabois Hospital, Department of Surgery, Section of Endocrine, Thyroid and Metabolic Surgery, Nancy, France

4: University of Lorraine, CHU Nancy, Department of Endocrinology, Diabetology and Nutrition, Nancy, France

5: University of Lorraine, INSERM U1256, « Nutrition, Genetics, Environmental Risks », Faculty of Medicine, Nancy, France

40th Annual Meeting of the American Association of Endocrine Surgeons in Los Angeles, California from April 7-9, 2019

Corresponding author: Laurent BRUNAUD, Department of Surgery, CHU Nancy (Brabois 3^{ème} étage), Université de Lorraine, 11 allée du morvan, 54511 Vandoeuvre-les-Nancy, FRANCE, Tel: (33)-383153120; Fax: (33)-383153121 Email: l.brunaud@chu-nancy.fr and l.brunaud@gmail.com

Background: Primary hyperparathyroidism (PHPT) is associated with an increased cardiovascular mortality, but mechanisms underlying this association are unclear. The goal of this study was to evaluate coronary artery calcifications via the coronary calcification score (CAC score) in PHPT patients, to compare with control subjects, and to identify risk factors for high to intermediate risk CAC scores (CAC score > 100).

Method: Cross-sectional study of PHPT patients without a history of coronary artery disease, diabetes, or severe chronic kidney disease. CAC scores were compared with a cohort of population-based control subjects.

Results: The mean CAC score was 120 ± 344 in 130 PHPT patients. The CAC score was > 100 in 27 patients (21%). When compared with control subjects, the percentage of positive CAC scores was similar in PHPT patients (53 versus 50%); however, positive CAC scores were at the 67th percentile of the control subjects cohort ($p < 0.001$). In multivariable regression, patient age (1.1; 1.1-1.2; $p < 0.001$), patients in the mild normocalcemic PHPT group (5.1; 1.1 – 22.6 ; $p = 0.037$), and the need for antihypertensive medications (6.1; 1.8 – 20.9; $p < 0.001$) remained independent predictors for a CAC score > 100.

Conclusion: Positive CAC scores were greater in PHPT patients than in population-based control subjects. These study data may provide new criteria for parathyroidectomy in patients with PHPT.

INTRODUCTION

Primary hyperparathyroidism (PHPT) has been associated with an increased cardiovascular mortality, but the mechanisms underlying this association have not been elucidated (1-4). Moreover, in asymptomatic and/or mild PHPT, there is a lack of consensus about cardiac risk with some but not all studies reporting an increase in incidence of cardiovascular events (1-5).

Coronary artery calcification (CAC) is a marker of atherosclerosis, which is proportional to the extent and severity of coronary artery disease and can be easily evaluated with unenhanced cardiac computed tomography (2, 6). The coronary calcium score (CAC score) is a strong and independent risk predictor for a 10-year coronary event in the general population: there is a 22-28% when the CAC is > 400 (high risk), 12-16% when the CAC is 101-400 (intermediate risk), 2-6% when the CAC is 1-100 (low risk), and 1-2% when the CAC = 0 (very low risk)(7-9). Available data about CAC scores are very limited in patients with PHPT with most available studies including less than 50 patients (1-3, 10, 11). Furthermore, the Multi-Ethnic Study of Atherosclerosis (MESA) provides a unique opportunity to examine and compare the distribution of CAC on the basis of age, sex, and race/ethnicity in a cohort free of clinical cardiovascular disease and treated diabetes (12).

The goal of this study was to evaluate the CAC score in a large number of PHPT patients compared with control subjects from the MESA cohort, and to identify independent risk factors for high-intermediate risk CAC scores (CAC score > 100).

METHODS

We performed a cross-sectional study of consecutive, sporadic PHPT patients who underwent a parathyroidectomy (PTX) (**ELSEVIER LEAVE THIS ABBREVIATION IN PLEASE IT IS VERY COMMON IN THIS FIELD**) from April 2015 to September 2016. Exclusion criteria included history of coronary artery disease (angina, coronary syndrome, myocardial infarction), diabetes mellitus (any patient with antidiabetic medications or insulin), and severe chronic kidney disease (GFR < 30 mL/min/1.73m²). These exclusion criteria were selected, because they should be applied when using the MESA public data and are independent risk factors for coronary calcium in the general population (8, 9, 12). Also excluded were patients diagnosed with benign familial hypocalciuric hypercalcaemia, multiple endocrine neoplasia, and patients taking lithium or thiazide diuretics. All included patients consented to participate (CNIL n°DC2014-2114). This study was approved by our institutional review board and registered at clinicaltrials.gov (NCT03410394).

All PHPT patients were included at the preoperative clinical visit and were evaluated (biologic workup, cardiac computed tomography [CT]) during the interval before PTX (about 6 weeks). The diagnosis of PHPT was made based on the presence of hypercalcemia with an inappropriately normal or increased parathyroid hormone level (4, 5, 13). PHPT patients were classified according to the 4th International Workshop Guidelines and the guidelines of the American Association of Endocrine Surgeons (AAES) for PTX: serum calcium > 1mg/dL above the upper normal limit, bone density T score < -2.5 at any site, creatinine clearance < 60mL/min, 24-h urine calcium > 400 mg/day, presence of kidney stones, and age less than 50 (4, 5). Patients were also classified according to PHPT clinical phenotypes (14, 15). The mild

normocalcemic group comprised of patients with a serum calcium concentration at the upper limit of normal (<104 mg/L or 2.60 mmol/L) with an inappropriately high level of PTH (> 35 ng/L). The mildly hypercalcemic group comprised of patients with a serum calcium concentration ranging from 104 to 114 mg/L (2.60 and 2.85 mmol/L) with an inappropriately high level of PTH (15). The classic hypercalcemic group comprised of patients with a serum calcium concentration >114 mg/L (> 1 mg/dL above the upper normal limit) with an inappropriately high level of PTH (15). All patients underwent a PTX and final pathology confirmed one or more abnormal gland(s) in all of them (adenoma or hyperplasia).

Data from patients were collected on patient age, sex, BMI, antihypertensive medication, lipid-lowering medication, smoking status (currently smoking or quit smoking within the last year before parathyroidectomy), systolic blood pressure (SBP in mmHg), diastolic blood pressure (DBP in mmHg), and mean arterial pressure (MAP in mmHg)(1). Blood tests included total serum calcium] ($85-104$ mg/L or $8.5-10.4$ mg/dL), phosphate ($25-45$ mg/L or $2.5-4.5$ mg/dL), serum parathormone ($15-65$ ng/L or pg/mL), serum 25-OH-vitamin D (≥ 30 ng/mL), glomerular filtration rate (MDRD in ml/min/1.73m²), fasting serum glycemia ($0.75-1.1$ g/L), fasting serum insulin ($18-173$ pmol/L), HOMA-IR (Homeostatic model assessment of insulin resistance defined as $\text{glucose} \times \text{insulin} / 22.5$), serum osteocalcin ($15-46$ ng/mL), serum bone alkaline phosphatase ($5.2-24.4$ microgr/L), and serum aldosterone in supine position (normal range $30-280$ ng/L). 24-h urinary calcium (normal range < 400 mg/24h), pathology type (uniglandular / multiglandular disease), and specimen weight (mg), were also collected.

Measurement of coronary artery calcium -Coronary artery calcium score (CAC score) representing coronary artery deposition of calcium was measured via a multidetector row, noncontrast CT of the coronary arteries (Revolution CT, General Electric Healthcare, Milwaukee, WI, USA). CAC was quantified by using the Agatston method, which incorporates both density (Hounsfield units) and area (surface)(6). The presence of calcification was defined as a density >130 Hounsfield units (HU) in more than 3 contiguous pixels (> 1mm²). The Agatston method uses the weighted sum of lesions with a density >130 HU and multiplying the area of calcium by a factor related to maximum plaque attenuation. The sum of the scores in the left main, left anterior descending, circumflex, and right coronary arteries was considered the CAC score. The presence of CAC was defined as a positive CAC score (> 0) and high-intermediate risk CAC scores as a CAC score > 100 (6-9, 12).

Population-based control subjects from the multi-ethnic study of atherosclerosis (MESA) - MESA was a prospective, observational, cohort study designed to investigate subclinical cardiovascular disease in a multi-ethnic cohort without clinical cardiovascular disease or treated diabetes (12). This study included 6110 community-dwelling participants from 6 study sites throughout the United States. In those individuals, the mean age was 62 years, 68% had a BMI > 25 kg/m², 42% had a history of hypertension (use of antihypertensive medications), 32% had dyslipidemia (taking a lipid-lowering medication), and 13% were current smokers (12). At the MESA public website (<http://www.mesa-nhlbi.org>), an interactive form allows one to enter an age, sex, race/ethnicity, and CAC score value. Consequently, for each PHPT patient in this study, the MESA website provided the estimated probability for

a non-zero calcium score (positive CAC score) and the estimated percentile of the observed CAC score in comparison with control subjects. This information was used to examine whether a PHPT patient had a greater or lesser CAC score relative to control subjects with adjustments for patient age, sex, and ethnicity (8, 9, 12).

Statistical analysis - Patient characteristics were described as numbers and proportions for categorical variables and means +/- standard deviation for continuous variables. Bivariate analysis was performed between groups using the χ^2 -test or Fisher's exact test for categorical variables and the independent samples t-test or Wilcoxon's test for continuous variables. Logistic regression analysis was performed to identify independent factors associated with CAC score > 100. Statistical analyses were performed using Statview® (version 5.0.1) and SPSS® software (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 153 consecutive patients underwent PTX for PHPT during this study period; 23 (15%) were excluded due to exclusion criteria. Thus, 130 patients were included (109 women) with a mean age of 62.7 ± 13 years. Mean BMI was 27.8 ± 6 kg/m² (63% had a BMI > 25 kg/m²), and 114 patients (87%) had uniglandular disease (**Table 1**). Among the 130 included patients, 57 (44%) took at least one antihypertensive medication, 23 (18%) took one lipid-lowering medication, and 14 (11%) were smokers (**Table 2**). According to the 4th International Workshop Guidelines and guidelines of the AAES for PTX, 98 of our 130 patients (75%) met at least one of the criteria for PTX(4,

5). According to PHPT phenotypes, 94 patients (72%) had mild PHPT (normo- and hypercalcemic), and 36 (28%) had classic hypercalcemic PHPT (5, 15). The mean preoperative CAC score was 120 ± 344 (range 0-2587) in 130 patients. This corresponded to a mean number of calcifications per patient of 4.4 ± 9.6 (range 0-65) with a mean volume of $87 \pm 236 \text{ mm}^3$ (range 0-1699). Mean CAC scores in the left main, left anterior descending, left circumflex, and right coronary arteries were 18 ± 54 , 43 ± 127 , 18 ± 113 , and 41 ± 135 , respectively. Distribution of CAC scores and corresponding risk for a 10-year coronary event were detailed in **Figure 1**. Overall, 21% of patients among all PHPT patients (n=27/130) had either high or intermediate risk CAC scores (CAC score > 100). When CAC scores in PHPT patients were compared with control subjects, we observed that the percentage of positive CAC scores was similar in both groups (53 % versus 50%, p=ns). The mean CAC score values in patients with positive CAC scores (n=69), however, was greater and at the 67th percentile of control subjects from the MESA cohort (p<0.001)(**Table 3**).

In PHPT patients, the CAC score was positively correlated with patient age (OR 0.34; 0.18 - 0.48; p<0.001), number of antihypertensive medications (OR 0.21; 0.04 - 0.37; p=0.018), and the 25-OH vitamin D level (OR 0.19; 0.02 - 0.35; p=0.029), and was negatively correlated with the GFR (OR -0.21 ; -0.37 - -0.04 ; p=0.015) and the 24h-urinary calcium (OR -0.19 ; -0.36 - -0.01 ; p=0.035)(**Table 4**). The mean CAC score was greater in patients (n=57) taking at least one antihypertensive medication (231 ± 484 versus 33 ± 111 ; p=0.001), but no difference was observed between patients who did or did not take lipid-lowering medication (141 ± 336 versus 115 ± 347 ; p=ns) or between smokers versus non-smokers (61 ± 177 versus 127 ± 359 ; p=ns).

The 32 patients in our cohort who did not meet at least one of the criteria for PTX (4th International Workshop Guidelines and AAES guidelines) had a greater mean CAC score in comparison with patients who met at least one of the criteria for PTX (206 ± 555 versus 91 ± 236 ; $p=0.035$). We also observed that mean CAC score was greater in patients with mild normocalcemic PHPT compared to xxxxx (**ELSEVIER PLEASE HAVE THE AUTHORS FILL IN THE UNDERLINED PART I SUSPECT IT IS IN COMPARISON TO THE CONTROL PATIENTS BUT THEY NEED TO CLARIFY THIS**) ($p=0.025$) (**Figure 2**) (5, 15). Mean values for age, GFR, number of antihypertensive medications, and 24-h urinary calcium were similar between the 3 different PHPT phenotype groups (**Table 5**). In contrast, the mean values for serum levels of phosphorus and 25-OH vitamin D were greater in patients with mild normocalcemic PHPT.

In multivariate analysis, patient age (OR 1.1 ; 1.1-1.2 ; $p<0.001$), patients with mild normocalcemic PHPT (OR 5.1 ; 1.1-22.6; $p=0.037$), and the need for antihypertensive medications (OR 6.1; 1.8-20.9; $p<0.001$) remained independent risk factors for preoperative high or intermediate risk CAC scores (CAC score > 100) (**Table 6**).

DISCUSSION

This cross-sectional study provides insight into CAC scores in patients with sporadic PHPT. This study, similar to prior studies, indicated the greatest CAC scores observed in the left anterior descending artery (2). This study also confirmed that about 20% of PHPT patients have high or intermediate risk CAC scores (CAC > 100) with a corresponding risk for 10-year coronary

event > 12% (1-3, 7-11). Characteristics of PHPT patients in this study were similar to previous reports (4, 5, 13, 14, 16-18).

This study showed that positive CAC scores were significantly more severe in PHPT patients than in control subjects, corresponding to a greater burden of atherosclerosis. This observation may provide a rationale as to why PHPT patients have a greater incidence of cardiac disease compared with age-matched controls (4, 13, 14). We acknowledge that this comparison could be potentially biased, however, exclusion criteria in both groups of patients were similar as requested when using data from the MESA cohort (12). Furthermore, both groups were matched for demographics and clinical features, including BMI > 25 kg/m², smoking, and patients taking antihypertensive medications (12). Patients taking lipid-lowering medications were more frequent in control subjects (32 versus 11%), which could be considered to favor the conclusions of our study. In addition, all PHPT patients with a GFR < 30 mL/min (CKD stages 4 and 5) were excluded to avoid potential bias (19). Lastly, each comparison was performed with adjustments for patient's age, sex, and ethnicity (12).

In 2008, Streeten et al. published the only available comparative study using the MESA cohort data and found no difference in _____ (ELSEVIER HAVE THE AUTHORS FILL THIS IN) (1); however, only 20 PHPT patients were included in their study, and most of them (95%) were considered asymptomatic (1). Other previous studies were either non-comparative or used their own control groups without adjustments leading to potential bias (2, 3, 10, 11). This study showed that PHPT patients classified as asymptomatic and those with mild normocalcemic PHPT had significantly

greater mean CAC score values than _xxxx_____ **(ELSEVIER HAVE THE AUTHORS FILL THIS IN)** . These data give evidence to the fact that patients labelled as “asymptomatic” using current guidelines actually have substantial enough symptoms or effects related to the hyperparathyroidism. These data provide new insight into the correlation between PHPT and cardiac disease and with further studies may help guide future guidelines and criteria for PTX(4, 13, 14).

This study also provided new knowledge in patients with mild normocalcemic PHPT showing a strong association with greater CAC scores in multivariate analysis. Mild normocalcemic PHPT is a recent entity that could represent the very early stages of PHPT, PHPT with concomitant vitamin D deficiency, or partial resistance of PTH target-tissues (5, 14, 16). This PHPT variant is also associated with an increased risk of fatal and non-fatal cardiovascular disease (16, 18, 20). Our study showed that coronary calcium could be one mechanism explaining this association, but we acknowledge that underlying mechanism(s) remain to be elucidated. Vitamin D deficiency does not explain our findings, because serum vitamin D levels were greater in this subgroup of patients. Similarly, renal function was similar between PHPT phenotype groups. Mean serum phosphorus levels were greater in patients with mild normocalcemic and could explain why those patients had greater CAC scores (1). We also acknowledge that the definition of mild normocalcemic PHPT used in this study did not include a normal ionized calcium blood level and could lead to potential biases (5, 14); however, this definition has been published previously with similar distribution of patients with mild normocalcemic PHPT (15, 18).

This study identified risk factors for high or intermediate risk CAC scores in PHPT patients. Our study showed that serum markers for bone remodelling, glucose metabolism, BMI, blood pressure values, and gland weight were not correlated with CAC score values. Although PHPT patients with antihypertensive medications were not excluded, the study data do not support the aldosterone hypothesis as a key mediator of coronary artery disease in PHPT patients (21). In contrast to a prior study, our study showed that serum calcium and parathormone levels were not correlated with CAC score values (11). Not surprisingly, patient age remained a statistically significant criterion in the multivariate analysis, because CAC score is heavily influenced by age (8, 12). Finally, the need for antihypertensive medications was an independent risk factor for CAC > 100. This finding corroborates the relationship between hypertension and CAC score observed in the general population (22). We believe that this new simple criterion could be used as an to recommend PTX in patients with PHPT (17).

This study has several limitations. We compared PHPT patients from Europe with US control subjects with potential unaccounted biases. The number of patients with positive CAC scores was limited, and larger studies are needed for confirmation. Patients with low serum vitamin D levels were not excluded, but recent data showed insufficient evidence to support a consistent association between this group of patients and the CAC score (23). Smokers and patients with a GFR between 30 and 60 ml/min/1.73m² (stage 3 CKD) were not excluded, because those conditions were compatible with the use of the MESA cohort public data. Furthermore, PHPT patients with stage 3 CKD do not have biochemical or clinical evidence of more severe

hyperparathyroidism compared with those without CKD (24) and were also included, because we aimed to evaluate CAC scores in all patients with PHPT including those patients with end-organ effects of PHPT(25). Lastly, lipid blood levels were not evaluated in this study.

In conclusion, our study showed that positive CAC scores were significantly more severe in PHPT patients than in control subjects. PHPT patients classified as asymptomatic and those with mild normocalcemic PHPT had significantly greater mean CAC score values. These data provide new insight into the correlation between PHPT and cardiac disease, bringing new perspectives on normocalcemic PHPT patients and may provide new criteria for PTXin patients with PHPT. The impact of PTXon CAC score progression in patients with PHPT 2illhave to be addressed in future studies.

Conflicts of interest/Disclosure: All authors certify that they have no conflict of interest associated with this manuscript.

Funding/Support: none to disclose

TABLES and FIGURES (6 tables and 2 figures)

Table 1 – Patient characteristics in all patients with PHPT (n=130).

Parameter	Value
Age (y)	62.7 ± 13
Sex (female / male) (%)	109 / 21 (84 / 16%)
BMI (kg/m ²)	27.8 ± 6.3
Calcium (mg/L)	109.8 ± 10.1
Calcium (mg/dL)	10.9 ± 1.0
Phosphorus (mg/L)	25.7 ± 4.9
Phosphorus (mg/dL)	2.6 ± 0.5
Parathormone (ng/L)(pg/mL)(normal range 15-65)	147 ± 116
Vitamin D 25-OH (ng/mL)	20.7 ± 8.4
Glomerular filtration rate (MDRD in ml/min/1.73m ²)	86 ± 18
Glomerular filtration rate (n)	
Stage 1 – normal or high GFR (GFR ≥ 90 mL/min)	64 (49%)
Stage 2 – mild CKD (GFR = 60-89 mL/min)	52 (40%)
Stage 3 – moderate CKD (GFR = 30-59 mL/min)	14 (11%)
Fasting serum glycemia (g/L)	0.97 ± 0.13
Fasting serum insulin (pmol/L)	92.6 ± 89
24-h urinary calcium (mg/24h)	317 ± 166
HOMA-IR	3.2 ± 2.9
Serum osteocalcin (ng/mL)	41.8 ± 23.4
Serum bone alkaline phosphatase (microgr/L)	25.8 ± 26.6
Serum aldosterone (ng/L)	137 ± 112
Systolic blood pressure (mmHg)	142 ± 19
Diastolic blood pressure (mmHg)	81 ± 12
Mean arterial blood pressure (mmHg)	102 ± 12
Pathology	
Uniglandular disease	114 (87%)
Multiglandular disease	16 (13%)

HOMA-IR : Homeostatic model assessment of β-cell function and insulin resistance ; MDRD : modification in diet in renal disease ; GFR : glomerular filtration rate ; CKD : chronic kidney disease ;

Table 2 – Clinical phenotypes and criteria for parathyroidectomy (4th International Workshop Guidelines and AAES guidelines) in all patients with PHPT (n=130).

Parameter	Value
<u>Clinical phenotypes</u> (5, 15)	
Patients with mild PHPT	94 (72%)
- mild normocalcemic	37 (28%)
- mild hypercalcemic	57 (44%)
Patients with classical hypercalcemic HPT1	36 (28%)
<u>Criteria for parathyroidectomy</u> (4, 5)	
Age < 50 years	20 (15%)
Calcium level greater than 1mg/dL above normal	36 (28%)
DEXA with T score < -2.5 SD	27 (21%)
Renal involvement	
- Stone	37 (28%)
- Hypercalciuria > 400 mg/24h	33 (25%)
- GFR < 60 mL/min	14 (11%)
Patients with at least one criterion for parathyroidectomy	98 (75%)
<u>Patients taking antihypertensive medications</u> (%)	57 (44%)
No antihypertensive medication	73
One antihypertensive medication	41
Two or more antihypertensive medications	16
Mean number of antihypertensive medications	0.56 ± 0.7
<u>Patients with lipid-lowering medication</u> (%)	23 (18%)
<u>Smoker patients</u>	14 (11%)

DEXA : dual-energy x-ray absorptiometry ; SD : standard deviation ; GFR : glomerular filtration rate

Table 3 – Comparison between PHPT patients and control subjects from the MESA cohort with adjustment based on patient age, sex, and ethnicity (<http://www.mesa-nhlbi.org>)(12)

	PHPT patients	Control subjects (MESA)	P value
Percentage of positive CAC score (%)	53%	50% *	ns
CAC score values in patients with positive CAC scores	67th percentile **	- reference	p<0.001

* : *estimated percentage of positive CAC scores in control subjects from the MESA cohort (when entering patient's age, sex, ethnicity on MESA website);*
 **: *estimated percentile of the observed CAC score in comparison with control subjects with the same age, sex, and race/ethnicity (when entering patient's age, sex, ethnicity, and observed CAC score on MESA website)*

Table 4 - Correlation matrix for CAC score values in patients with PHPT

Criteria	Coefficient	CI 95%	P value
Age (y)	0.34	0.18 - 0.48	<0.001
25-OH Vitamin D (ng/mL)	0.19	0.02 - 0.35	0.029
number of antihypertensive medications (n)	0.21	0.04 – 0.37	0.018
GFR (MDRD in ml/min/1.73m ²)	- 0.21	- 0.37 - -0.04	0.015
24-h urinary calcium (mg/24h)	- 0.19	- 0.36 - - 0.01	0.035
Serum Calcium (mg/L)(mg/dL)	-0.15	-0.32 – 0.02	0.081
Serum Phosphorus (mg/L)(mg/dL)	0.04	-0.13 – 0.21	0.650
Erum Parathormone (ng/L)(pg/mL)	-0.13	-0.28 – 0.04	0.135
BMI (kg/m ²)	0.05	-0.16 – 0.17	0.955
Fasting serum glycemia (g/L)	0.04	-0.17 – 0.18	0.967
Fasting serum insulin (pmol/L)	-0.06	-0.24 – 0.12	0.540
HOMA-IR	-0.06	-0.24 – 0.12	0.525
Serum Osteocalcin (ng/mL)	-0.07	-0.24 – 0.11	0.456
Serum Bone alkaline phosphatase (microgr/L)	-0.17	-0.35 – 0.02	0.075
Serum Aldosterone (ng/L)	-0.05	-0.22 – 0.12	0.537
Systolic blood pressure (mmHg)	0.14	-0.03 – 0.30	0.117
Diastolic blood pressure (mmHg)	0.07	-0.11 – 0.24	0.448
Mean arterial pressure (mmHg)	0.12	-0.06 – 0.28	0.184
Pathology, gland weight (mg)	-0.04	-0.21 – 0.14	0.665

Table 5 – Patient characteristics according to PHPT clinical phenotypes

(5).

ELSEVIER SEE THE CRITERIA PHOSPHORUS IN THE TABLE THERE ARE TWO LINES THE FIRST OF WHICH IS NOT CORRECT THE ONE THAT SAYS THE SERUM PHOSP[HORIS IS 28=?- 4; I DO NOT KNOW HOW TO DELTE IT SORRY

Criteria *	Mild N n=37	Mild H n=57	Classical H n=36	P value
Age (y)	65 ± 11	61 ± 13	63 ± 14	0.269
GFR (MDRD in ml/min/1.73m ²)	84 ± 22	86 ± 17	86 ± 15	0.514
Antihypertensive medications (n)	0.67 ± 0.71	0.59 ± 0.75	0.39 ± 0.59	0.269
24-h urinary calcium (mg/24h)	301 ± 222	306 ± 146	351 ± 125	0.096
Serum Vitamin D 25-OH (ng/mL)	24 ± 9	21 ± 8	17 ± 6	0.003
Serum Calcium (mg/L)	101 ± 4	109 ± 3	121 ± 12	0.001
Serum Calcium (mg/dL)	10.1 ± 0.4	10.9 ± 0.3	12.1 ± 0.1	0.001
Serum Phosphorus (mg/L) THIS IS WRONG DELETE IT	28 ± 4	26 ± 4	23 ± 5	0.001
serumPhosphorus (mg/dL)	2.8 ± 0.4	2.6 ± 0.4	2.3 ± 0.5	0.001
Parathormone (ng/L)(pg/mL)	119 ± 129	116 ± 56	225 ± 136	0.001

** : These criteria were used because they had a significant correlation with CAC score values (correlation matrix) or defined the PHPT patients population (calcium, phosphorus, parathormone); Mild N : mild normocalcemic group patients ; Mild H. : mild hypercalcemic group patients ; Classic H : classic hypercalcemic PHPT group patients*

**Table 6 – Multivariate analysis (logistic regression) for CAC score > 100
(dependent variable)**

Criteria	n	Bivariate regression		P value	Multivariate regression	
		OR	CI 95%		OR	CI 95%
Age (y)	130	1.1	1.1 – 1.2	< 0.001	1.1	1.1 – 1.2
Antihypertensive Medications						
No	73	1			1	
Yes	57	11.7	3.7 – 36.4	< 0.001	6.1	1.8 – 20.9
Clinical phenotypes						
Classical H	36	1			1	
Mild H	57	1.7	0.5 – 5.9		2.3	0.5 – 10.4
Mild N	37	4.3	1.3 - 15	0.037	5.1	1.1 – 22.6

Mild N : mild normocalcemic group patients ; Mild H. : mild hypercalcemic group patients ; Classic H : classic hypercalcemic PHPT group patients

Figure 1 – CAC scores in 130 patients with PHPT according to the risk for 10-year coronary event (American College of Cardiology)(7-9). CAC scores were > 400 in 13 patients (10%)(high risk for 10-year coronary event: 22-28%), between 101 and 400 in 14 patients (11%)(intermediate risk for 10-year coronary event: 12-16%), between 1 and 100 in 42 patients (32%)(low risk for 10-year coronary event: 2-6%), and null in 61 patients (47%)(very low risk for 10-year coronary event: 1-2%).

Figure 2 – Mean CAC scores in 130 PHPT patients according to clinical phenotypes (5, 15). Mean CAC score was significantly higher in mild normocalcemic PHPT patients, followed by mild hypercalcemic PHPT patients, and lower in patients with classical hypercalcemic PHPT (241 ± 536 versus 91 ± 257 versus 41 ± 103 ; $p=0.025$), respectively.

REFERENCES (25 max)

1. Streeten EA, Munir K, Hines S, Mohamed A, Mangano C, Ryan KA, et al. Coronary artery calcification in patients with primary hyperparathyroidism in comparison with control subjects from the multi-ethnic study of atherosclerosis. *Endocr Pract.* 2008;14:155-61.
2. Dural C, Okoh AK, Seicean A, Yigitbas H, Thomas G, Yazici P, et al. A pilot study investigating the effect of parathyroidectomy on arterial stiffness and coronary artery calcification in patients with primary hyperparathyroidism. *Surgery.* 2016;159:218-24.
3. Mesquita PN, Dornelas Leão Leite AP, Chagas Crisóstomo SD, Veras Filho E, da Cunha Xavier L, Bandeira F. Evaluation of coronary calcium score in patients with normocalcemic primary hyperparathyroidism. *Vasc Health Risk Manag.* 2017;13:225-9.
4. Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. *JAMA Surg.* 2016;151:959-68.
5. Silverberg SJ, Clarke BL, Peacock M, Bandeira F, Boutroy S, Cusano NE, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab* 2014;99:3580-94.
6. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990;15:827-32.
7. Arnon Y, Rozanski A, Gransar H, Friedman JD, Hayes SW, Thomson LE, et al. Comparison of the Coronary Artery Calcium Score and Number of Calcified Coronary Plaques for Predicting Patient Mortality Risk. *Am J Cardiol.* 2017;120:2154-9.
8. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med.* 2008;358:1336-45.
9. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary Calcium Score and Cardiovascular Risk. *J Am Coll Cardiol.* 2018;72:434-47.
10. Kepez A, Harmanci A, Hazirolan T, Isildak M, Kocabas U, Ates A, et al. Evaluation of subclinical coronary atherosclerosis in mild asymptomatic primary hyperparathyroidism patients. *Int J Cardiovasc Imaging.* 2009;25:187-93.
11. Wu G, Xu B, Wu T, Wang XY, Wang T, Zhang X, et al. Correlation between serum parathyroid hormone levels and coronary artery calcification in patients without renal failure. *Biomedical reports.* 2016;5:601-6.
12. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation.* 2006;113:30-7.
13. McDow AD, Sippel RS. Should Symptoms Be Considered an Indication for Parathyroidectomy in Primary Hyperparathyroidism? *Clin Med Insights Endocrinol Diabetes.* 2018;Jun 27;doi: 10.1177/1179551418785135.
14. Bilezikian JP. Primary Hyperparathyroidism. *J Clin Endocrinol Metab.* 2018;103:3993-4004.

15. Bannani S, Christou N, Guérin C, Hamy A, Sebag F, Mathonnet M, et al. Effect of parathyroidectomy on quality of life and non-specific symptoms in normocalcaemic primary hyperparathyroidism. *Br J Surg*. 2018;105:223-9.
16. Anastasilakis DA, Makras P, Polyzos SA, Anastasilakis AD, COMBO ENDO team 2017. Asymptomatic and normocalcemic hyperparathyroidism, the silent attack: a combo-endocrinology overview. *Hormones*. 2018;doi: 10.1007/s42000-018-0069-6.
17. Heylinger A, Tangpricha V, Weber C, J. S. Parathyroidectomy decreases systolic and diastolic blood pressure in hypertensive patients with primary hyperparathyroidism. *Surgery*. 2009;146:1042-7.
18. Yan H, Calcaterra N, Moo-Young TA, Prinz RA, Winchester DJ. Degree of hypercalcemia correlates with parathyroidectomy but not with symptoms. *Am J Surg*. 2019;217:437-40.
19. Daniel WT, Weber C, Bailey JA, Raggi P, Sharma Y. Prospective analysis of coronary calcium in patients on dialysis undergoing a near-total parathyroidectomy. *Surgery*. 2013;154:1315-22.
20. Yu N, Donnan PT, Leese GP. A record linkage study of outcomes in patients with mild primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study (PEARS). *Clin Endocrinol*. 2011;75:169-76.
21. Brunaud I, Germain A, Zarnegar R, Rancier M, Alrasheedi S, Caillard C, et al. Serum aldosterone is correlated positively to parathyroid hormone (PTH) levels in patients with primary hyperparathyroidism. *Surgery*. 2009;146:1035-41.
22. Aladin AI, Al Rifai M, Rasool SH, Dardari Z, Yeboah J, Nasir K, et al. Relation of Coronary Artery Calcium and Extra-Coronary Aortic Calcium to Incident Hypertension (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol*. 2018;121:210-6.
23. Malik R, Aneni EC, Roberson L, Ogunmoroti O, Ali SS, Shaharyar S, et al. Measuring coronary artery calcification: is serum vitamin D relevant? *Atherosclerosis*. 2014;237:734-8.
24. Walker MD, Nickolas T, Kepley A, Lee JA, Zhang C, McMahan DJ, et al. Predictors of renal function in primary hyperparathyroidism. *J Clin Endocrinol Metab*. 2014;99:1885-92.
25. Assadipour Y, Zhou H, Kuo EJ, Haigh PI, Adams AL, Yeh MW. End-organ effects of primary hyperparathyroidism: A population-based study. *Surgery*. 2018;165:99-104.

Figure 1

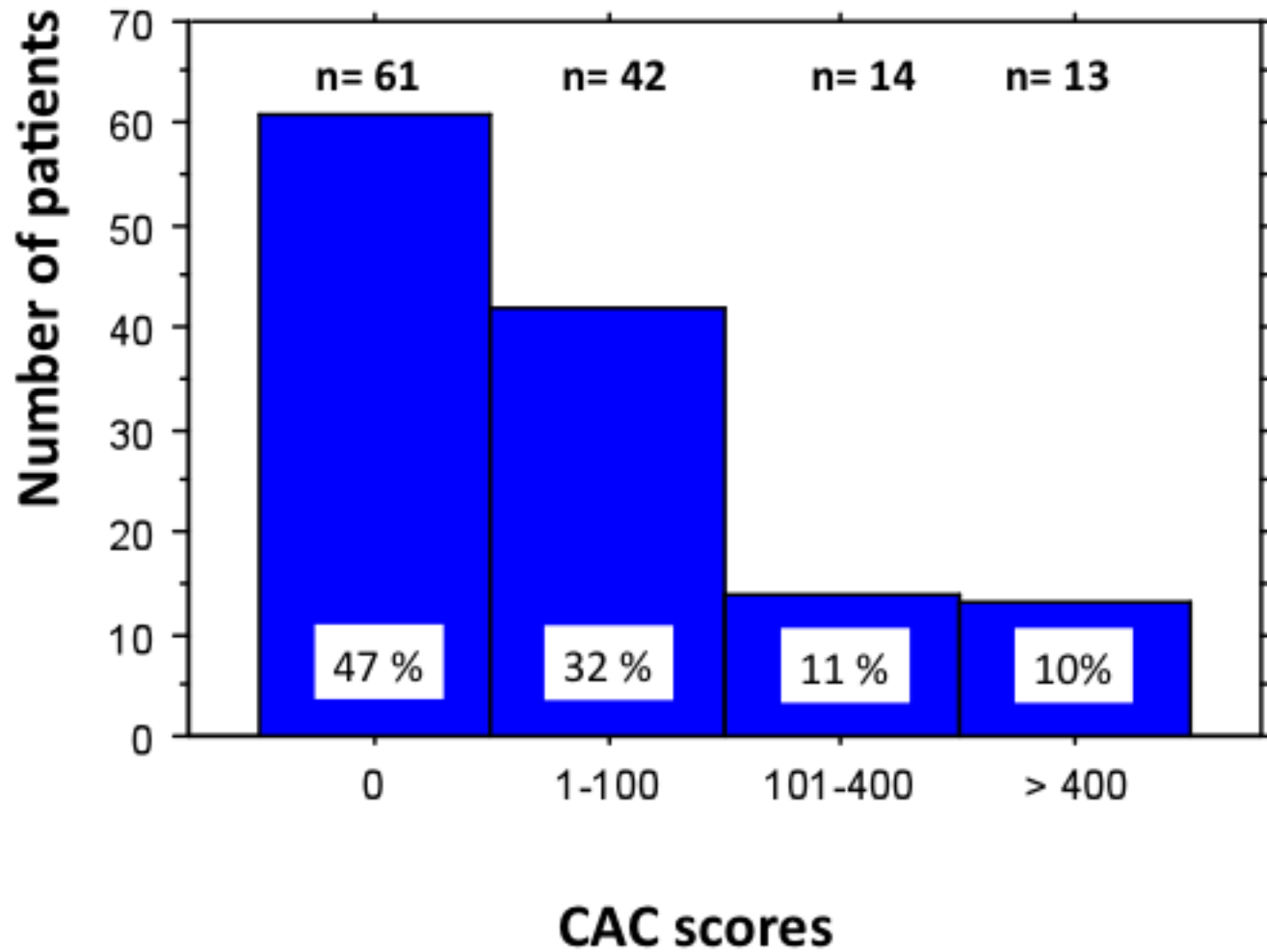


Figure 2

