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ORIGINAL PAPER

Evaluation of subclinical coronary atherosclerosis in mild asymptomatic primary hyperparathyroidism patients

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Abstract *Objective* Although there is sufficient data supporting the increased cardiovascular risk in patients with advanced stage of primary hyperparathyroidism (pHPT), it is not clear whether same is valid for patients with subclinical forms of this disease. In this study we aimed to evaluate coronary atherosclerosis burden of asymptomatic pHPT patients by using tomographic coronary calcification scoring. *Patients and methods* Thirty-one mild asymptomatic pHPT patients (28 female, 3 male; mean age: 54.4 ± 12.1 years) and 19 gender- and age-matched normotensive healthy controls (17 female, 2 male; mean age: 50.6 ± 5.8) constituted our study population. Asymptomatic pHPT patients were subdivided according to presence of hypertension (19 hypertensive and 12 non-hypertensive patients). All subjects in study population underwent tomographic coronary calcification scoring by using 16-multidetector computed tomography (16-MDCT). *Results* Median tomographic coronary calcification score was comparable between the whole group of pHPT patients [0.0 (Interquartile Range, IQR:18.70] and the controls [0.0 (IQR: 0.90). Median tomographic coronary calcification scores of pHPT patients with hypertension was 0.90 (IQR: 75.0) HU, whereas no calcification was noted in coronary arteries of normotensive pHPT patients. Calcification scores of hypertensive pHPT patients were significantly higher than both normotensive pHPT patients ($P = 0.014$) and controls ($P = 0.046$). There was no significant difference regarding calcification scores of normotensive pHPT patients versus controls. In the binary logistic regression model, only the presence of hyperlipidemia was found to be independently associated with presence of calcification on coronary arteries (relative risk 6.56, 95% CI 1.18–36.56, $P = 0.032$). *Conclusion* These results suggest that mild asymptomatic pHPT with serum calcium levels in the high-normal range does not constitute an independent risk factor for coronary atherosclerosis. The combined presence of classic cardiovascular risk factors determines the severity of coronary atherosclerosis in these patients.

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Introduction

Primary hyperparathyroidism (pHPT) is characterized by disturbances in calcium homeostasis in which calcium is mobilized excessively to the blood stream with resultant complications as renal stones, osteoporosis and symptoms of hypercalcemia such as constipation, weakness and fatigue [1]. Patients with complicated pHPT have been reported to suffer from increased cardiovascular mortality [2, 3]. Apart from associated cardiovascular risk factors as systemic hypertension, impaired renal functions and associated metabolic abnormalities; direct effects of parathyroid hormone (PTH) and excess calcium on vasculature have also been implicated in the increased vascular risk [4].

Once a symptomatic disorder characterized by significant hypercalcemia, pHPT today is most commonly seen in asymptomatic individuals with milder hypercalcemia due to the large availability of routine serum calcium measurements and developments in assay systems [5]. However, there are still limited data on the incidence of cardiovascular abnormalities in the mild pHPT. A number of studies designed on these patients to evaluate potential damages of increased levels of parathyroid hormone and associated hypercalcemia on cardiovascular system yielded controversial results, either suggesting an increased vascular risk or not [6–13]. The reasons for these controversial results are not clear, however, heterogeneity of patient groups and differences in methods used in these studies may have contributed to observed discrepancies.

Coronary atherosclerosis constitutes the single most important contributor to cardiovascular morbidity and mortality. Arterial calcium development is intimately associated with vascular injury and atherosclerotic plaque [14]. Coronary artery calcification is an active process and can be seen at all stages of atherosclerotic plaque development. Various tomographic techniques permit quantification of coronary artery calcification which reflects amount of coronary atherosclerosis burden [14].

The aim of this study is to directly evaluate the effects of uncomplicated primary pHPT on coronary calcification, hence coronary atherosclerosis by using tomographic coronary calcium scoring.

Patients and methods

Patients

Thirty-one consecutive patients with mild asymptomatic primary hyperparathyroidism (28 female, 3 male; mean age: 54.4 ± 12.1 years) were recruited to study. Nineteen gender- and age-matched normotensive healthy subjects with serum PTH and calcium levels within normal range constituted our control group (17 female, 2 male; mean age: 50.63 ± 5.84).

A detailed medical story, physical examination, chest X-ray, 12 lead electrocardiography, complete blood count and serum biochemistry were obtained from all patients. Presence of classic cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, obesity and smoking habitus were assessed. Patients with a history of any kind of heart disease, evidence of ischemia on electrocardiograms and the ones with evidence of pHPT complications as nephrolitiasis and high turnover bone disease (osteoporosis, osteitis fibrosa cystica) were excluded from the study.

To exclude patients with marked hypercalcemia, we limited pHPT patients to those with serum calcium levels within 0.25 mmol/l of the upper limits of normal. Patients above this limit is thought to be at greater risk for symptomatic hyperparathyroidism and for complications of disease and surgery is recommended for these patients [15]. Other exclusion criteria were a history of premature menopause, diabetes, hyper- or hypothyroidism, chronic liver or renal disease, malignancy and receiving medications that could affect serum calcium and phosphorus (such as supplemental calcium and biphosphonates).

Mild asymptomatic pHPT patients were subdivided into 2 groups according to the presence of hypertension. The first group included 19 (61%) hypertensive asymptomatic pHPT patients (16 female, 3 male; age: 59.10 ± 10.3 years) and second group included 12 (39%) asymptomatic pHPT patients without hypertension (all female, age: 47.0 ± 11.3 years).

The study was approved by the local ethics committee and written informed consent was obtained from all patients.

Risk factors

Based on the criteria used previously in a similar study on asymptomatic primary hyperparathyroidism [8], we defined hyperlipidemia as fasting total serum cholesterol more than 5.6 mmol/l and/or serum tryglicerides more than 1.75 mmol/l or when patients were taking an oral lipid-lowering agent. Subjects currently taking antihypertensive drugs or showing a systolic blood pressure of 140 mm Hg or more and/or a diastolic blood pressure of 90 mm Hg or more, based on the average of two or more readings taken in the sitting position at different days before investigation, were defined as hypertensive. Patients smoking at least one cigarette daily for 1 yr within the last 5 yr were considered smokers.

Tomographic coronary calcification scoring

All subjects in the study population underwent non-enhanced multi-slice computed tomography (MSCT) with retrospective ECG-gating. All subjects were in sinus rhythm throughout the scan. All of the examinations were performed with a 16-MDCT scanner (Sensation 16, Siemens Medical Solutions, Erlangen, Germany). The area between carina to apex of the heart was scanned in craniocaudal direction. Calcium scoring parameters were tube voltage 120 kV, an effective tube current-time product of 133 mAseff, a collimation of 12 $\times$ 0.75 mm, a table feed of 2.8 mm per rotation, and a tube rotation time of 420 ms. No tube current modulation has been applied. In each patient, 60% of the R–R reconstruction was prepared at 512 $\times$ 512 reconstruction matrix and a medium smooth convolution kernel (B35f). All reconstructed images were transferred to an external workstation (Leonardo, Siemens Medical Solutions, Erlangen, Germany) for coronary calcium scoring (Syngo Calcium Scoring CT, Siemens, Germany). Coronary calcium score was determined by applying the method described by Agatston et al. [16], using a threshold of 130 HU. All examinations were analyzed by an experienced radiologist. Data analysis included calcium volume, calcium mass, Agatston score and number of lesions.

Laboratory studies

Serum calcium (normal, 2.2–2.7 mmol/l) and phosphate (normal, 0.9–1.5 mmol/l) levels were determined with standard methods. Intact parathormone levels (normal range, 12–72 pg/ml) were determined by the chemiluminescence method (Immulite, Bio-DPC, Los Angeles, CA). The intra-assay variance for this method was 5.4%, and inter-assay reproducibility was 5.5%. The sensitivity was 1.0 pg/ml.

Statistical analysis

Ordinal parameters displaying normal distribution were expressed as mean $\pm$ SD and ordinal parameters not displaying normal distribution were expressed as median (interquartile range). Nominal parameters were expressed as %. Statistical analysis was performed using the SPSS for WINDOWS (version 12.0; SPSS Inc., Chicago, Illinois, USA). Significance of differences between normotensive pHPT, hypertensive pHPT and control groups was assessed by using one-way ANOVA, followed by Sheffe post-hoc test for ordinal parameters displaying normal distribution and Kruskal–Wallis test followed by Bonferroni corrected Mann–Whitney U post-hoc test for ordinal parameters not displaying normal distribution. Significance of differences between groups for nominal parameters was assessed by using Chi-square test. Bivariate correlation analyses were done by Spearman rank correlation test. Binary logistic regression was used to test independent contribution of following potential predictors for the presence of coronary calcification (atherosclerosis): age, presence of hypertension, presence of hyperlipidemia, presence of smoking habitus, serum PTH levels and body-mass index. Statistical significance was accepted as P value less than 0.05.

Results

Considered as a whole group, PTH ranged between 68.9–398 ng/l and total serum calcium ranged between 2.2–2.8 mmol/l in the pHPT group. PTH levels were always inappropriately high in the patient group even if calcium levels lay within normal limits. In the controls, PTH ranged between 17.6–65.2 ng/l and total calcium levels ranged between

Table 1 Cardiovascular risk factor profile of asymptomatic primary hyperparathyroidism (pHPT) patients and controls

	Asymptomatic pHPT patients ($n = 31$)	Controls ($n = 19$)	P value
Age (years)	54.4 ± 12.1	50.6 ± 5.8	NS
Sex (male/female)	3 M, 28 F	2 M, 17 F	NS
BMI (kg/m^2)	30.2 ± 3.8	26.5 ± 2.6	0.001
Hyperlipidemia, n (%)	11 (35.5)	8 (42.1)	NS
Smoking habit, n (%)	6 (19.4)	7 (36.8)	NS
Hypertension, n (%)	19 (61.3)	0	<0.001

NS: Not significant
BMI: Body mass index

2.2–2.7 mmol/l, all being within normal limits. There were no significant differences between asymptomatic pHPT patients and controls with respect to age, presence of hyperlipidemia and smoking habitus (Table 1). However, body-mass indices (BMI) of asymptomatic pHPT patients were significantly higher compared to those of controls (Table 1). Tomographic coronary calcification scores were comparable between the pHPT patients (whole group) and the controls (0.0 (IQR: 18.70) vs 0.0 (IQR: 0.90) respectively; $P = 0.39$, Fig. 1a). Tomographic coronary calcium scores of 6 out of 31 (19.4%) asymptomatic pHPT patients and 3 out of 19 (15.8%) control subjects were found to be over 50th percentile according age-and gender- stratified coronary calcium scoring distribution designed by Hoff et al. [17], revealing no statistically significant difference as well.

Clinical and biochemical data of mild asymptomatic hyperparathyroidism patients with/without hypertension and controls are given in Table 2. The groups were comparable with regard to prevalence of hyperlipidemia and smoking status. Hypertensive pHPT patients were older than the other two groups, and had higher BMIs than the controls (Table 2).

Median tomographic coronary calcification score of pHPT patients with hypertension was 0.90(IQR: 75.0) HU, whereas it was 0.0 (IQR: 0.90) HU for control subjects (Fig. 1b). No calcification was noted in the coronary arteries of normotensive pHPT patients. Since the difference among the three groups was significant ($P = 0.003$), we performed post-hoc tests that revealed significant differences between calcification scores of hypertensive pHPT patients versus normotensive pHPT patients and controls ($P = 0.014$ and $P = 0.046$, respectively, Fig. 1b). There was no significant difference regarding median calcification score of normotensive pHPT patients versus controls. While ten out of 19 (52.6%) patients

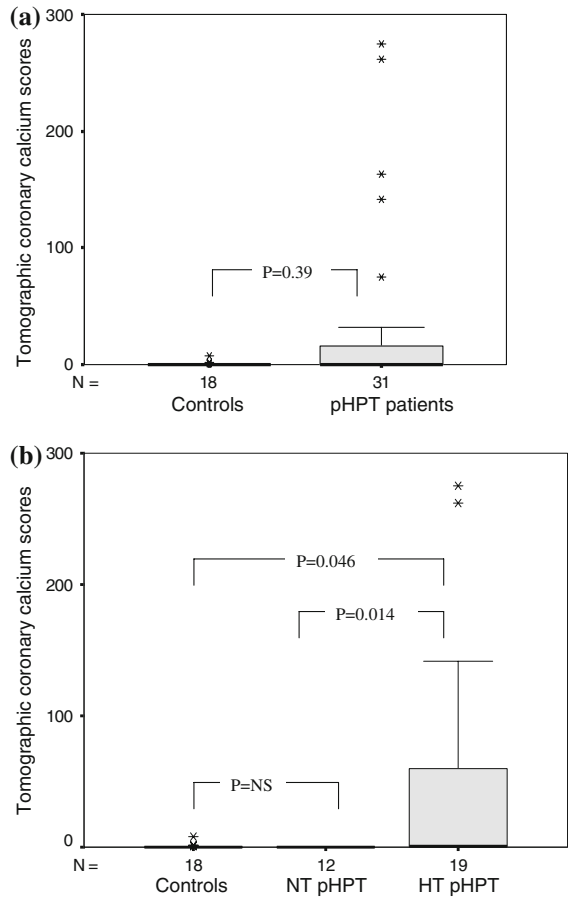

Fig. 1 Boxplots of tomographic coronary calcification scores of pHPT patient group versus controls (**a**), and tomographic calcification scores of pHPT patients subdivided as hypertensive or normotensive versus controls (**b**). (Data are expressed as median, interquartile range and extremes; Post-hoc P values calculated by Mann–Whitney U test. $P = 0.003$ for the differences among hypertensive pHPT, normotensive pHPT and control groups in graph B by Kruskal–Wallis test). NT pHPT: Normotensive primary hyperparathyroidism. HT pHPT: Hypertensive primary hyperparathyroidism

Table 2 Clinical and biochemical data of asymptomatic primary hyperparathyroidism (pHPT) patients with and without hypertension, and controls

	PHPT patients with hypertension ($n = 19$)	PHPT patients without hypertension ($n = 12$)	Controls ($n = 19$)
Age (years)	59.1 ± 10.3*	47.0 ± 11.3	50.6 ± 5.8
Sex (male/female)	3 M, 16 F	12 F	2 M, 17 F
BMI (kg/m^2)	31.12 ± 3.55**	28.56 ± 3.84	26.57 ± 2.64
Serum PTH (ng/l)	88.8 (27.6)[a]***	94.4 (21.5)***	33.2 (17.8)
Serum calcium (mmol/l)	2.47 ± 0.18	2.51 ± 0.16	2.40 ± 0.08
Serum phosphate (mmol/l)	1.17 ± 0.21	1.13 ± 0.19	1.26 ± 0.20
Hyperlipidemia, *n* (%)	9 (47.4)	2 (16.7)	8 (42.1)
Smoking habit, *n* (%)	5 (26.3)	2 (16.5)	7 (36.8)

[a] Ordinal parameters displaying normal distribution were expressed as 'mean ± SD' and ordinal parameters not displaying normal distribution were expressed as 'median (interquartile range)'

* $P < 0.05$, asymptomatic PHPT patients with hypertension vs asymptomatic PHPT patients without hypertension and controls

** $P = 0.001$, asymptomatic PHPT patients with hypertension vs controls

*** $P < 0.001$, asymptomatic PHPT patients (with and without hypertension) vs controls

BMI: Body mass index

in hypertensive hyperparathyroidism group had coronary calcium scores above the median value, only five out of 19 control subjects (26.3%) had scores above the median value ($P = 0.007$). No correlations were found between the tomographic calcification scores and PTH (r value: 0.016) and serum calcium levels (r value: 0.133) in the pHPT patients.

In the binary logistic regression model presence of hyperlipidemia was the only significant independent explanatory variable for the presence of calcification on coronary arteries among other variables included in the model (relative risk 6.56, 95% CI 1.18–36.56, $P = 0.032$).

Discussion

We observed that mild asymptomatic hyperparathyroidism patients without hypertension do not have any calcification in their coronary arteries. Our results suggest that asymptomatic pHPT without overt hypercalcemia does not constitute a risk factor for development of coronary atherosclerosis. Excess coronary calcification observed in hypertensive asymptomatic pHPT patients may be, in part, a reflection of presence of co-existing cardiovascular risk factors as these patients are older, have higher incidence of hyperlipidemia and obesity besides all being hypertensive. In our logistic regression analysis only hyperlipidemia turned out to be independent predictor of presence of calcification on coronary arteries which is in agreement with the notion that high PTH level is not independently associated with coronary atherosclerosis. There is still ongoing discussion regarding the optimal treatment modality (surgery vs medical follow-up) for patients with mild asymptomatic pHPT. Our observations support medical follow-up of these patients without surgical intervention.

Parathormone (PTH) has been suggested to exert a variety of effects on heart, vascular smooth muscle cells and endothelial cells. pHPT patients often show cardiovascular abnormalities, such as hypertension, LV hypertrophy, valvular and myocardial calcification and cardiac arrhythmias (reviewed in 1). So far, the high incidence of hypertension in pHPT patients have complicated the decision making about the any pathogenetic role of high PTH levels on cardiovascular abnormalities observed in these patients. High prevalence of hypertension in our pHPT patients is in agreement with previous studies which point to the association between pHPT and systemic hypertension [18]. We subdivided pHPT patients into 2 groups based on the presence of hypertension to examine the confounding effect of this common risk factor for development and progression of coronary atherosclerosis in these patients.

Previous studies had shown an increased cardiovascular mortality in pHPT patients with gradually

reducing risk after surgery [19]. Both elevated parathyroid hormone levels and hypercalcemia were suggested to be independent risk factors for premature death [20–22]. In an autopsy study, increased calcium deposition in intima and media of the coronary arteries of hyperparathyroidism patients were observed suggesting a possible link between hyperparathyroidism and associated chronic hypercalcemic state with coronary calcification [23]. However, most of these patients had advanced disease with higher serum calcium concentrations.

There are still limited data on the incidence of cardiovascular abnormalities in the mild pHPT. In the population-based, cross-sectional Tromso study, serum PTH level was found to be one of the independent predictors for coronary heart disease [6]. However, presence of coronary artery disease was assessed using a questionnaire without objective quantification of atherosclerosis. Rubin et al. [9] reported increased arterial stiffness in mild pHPT patients by using a non-invasive device as the 'augmentation index'. Most studies evaluating the association between PHPT and atherosclerosis have used carotid artery intima-media thickness as a marker of systemic atherosclerosis. In one of those studies, Nuzzo et al. [7] observed markedly increased carotid intima-media thickness in pHPT patients compared with controls. However this could not be confirmed in populations in which the serum calcium did not extend to the abnormal range. In one of these studies, however, Kosch et al. [10] found impaired endothelium-dependent flow-mediated vasodilation in pHPT patients compared to controls suggesting increased prevelance of endothelial dysfunction in these patients. In a study evaluating novel plasma risk markers of cardiovascular disease in pHPT patients, Ogard et al. [24] reported no significant correlation between PTH or calcium and risk markers of cardiovascular disease.

The reasons for these different results are not clear but differences in the methods for excluding the confounding effects of co-existing cardiovascular risk factors and differences in patient characteristics with varying degrees of hypercalcemia may have contributed to these discrepancies. In our study, we used tomographic coronary calcification scoring for direct evaluation of coronary atherosclerosis burden. In a similar study, Watson et al. [25] evaluated the associations between vascular calcification and serum levels of osteoregulatory molecules and found no correlation between serum PTH levels and coronary calcification quantified by electron beam computed tomography. In addition, in agreement with our results, Kosch et al. [13] could not find any association between increased PTH levels and mechanical arterial wall properties in pHPT patients devoid of hypertension and renal disease.

In conclusion, the present study suggests that asymptomatic primary hyperparathyroidism does not constitute an independent risk factor for coronary calcification, as such for coronary atherosclerosis. Our results are in agreement with results of other studies performed on pHPT patients without overt hypercalcemia.

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