High prevalence of abdominal aortic calcification in patients with primary hyperparathyroidism as evaluated by Kauppila score

Jessica Pepe1, Daniele Diacinti2, Emanuela Fratini2, Italo Nofroni2, Antonella D’Angelo1, Roberta Pilotto1, Claudio Savoriti1, Luciano Colangelo1, Orlando Raimo1, Mirella Cilli1, Cristiana Cipriani1 and Salvatore Minisola1

Departments of 1Internal Medicine and Medical Disciplines, 2Radiological Sciences, Oncology and Pathology and 3Public Health and Infectious Diseases, ‘Sapienza’ University, Rome, Italy

Abstract

Objective: The prevalence of abdominal aortic calcification (AAC) in primary hyperparathyroidism (PHPT) is unknown. We assessed both prevalence and severity of AAC in PHPT postmenopausal women.

Methods: In this study 70 PHPT postmenopausal women and 70 age- and sex-matched controls were enrolled. Each participant underwent biochemical evaluation, lateral spine radiograph, bone mineral density (BMD) measurement (lumbar, femoral, radial sites), and kidney ultrasound. Lateral lumbar films were analyzed in the region of L1–L4 vertebrae and the Kauppila score (a semi-quantitative grading system) was used to assess the severity of AAC.

Results: There were no differences regarding demographic and cardiovascular risk factors in the two groups. PHPT patients had higher prevalence of kidney stones (30% vs 7%, P=0.0008) and lower radial BMD values (0.558±0.071 vs 0.588±0.082 g/cm2, P<0.05) compared with controls. PHPT patients showed higher prevalence of AAC (31 vs 18, P=0.03), with more severe calcifications (Kauppila score 7.35±6.1 vs 5.05±3.5, P=0.007). PHPT patients with AAC were older and had been suffering from the disease for a longer period compared with those without ACC. Moreover, PHPT patients with severe AAC had mean higher serum parathyroid hormone levels compared with patients with moderate or mild calcifications. In PHPT patients with AAC, multiple regression analysis, adjusted for age and years since diagnosis, showed that only parathyroid hormone significantly correlated with Kauppila score.

Conclusion: We found a higher prevalence and severity of AAC in PHPT related to parathyroid hormone effect.

Introduction

Several lines of evidence, from both experimental and clinical studies, suggest that parathyroid hormone (PTH) has a direct influence on atherogenesis via both vascular remodeling and calcification (1, 2). Furthermore, hyperparathyroidism per se may have an indirect effect that accelerates atherogenesis due to its presumed positive relation with hypertension, endothelial dysfunction, and dyslipidemia, which are well-known contributors to the development of atherosclerosis (3, 4, 5). Accordingly, some studies demonstrate that patients with primary hyperparathyroidism (PHPT) have an increased mortality, mainly related to cardiovascular diseases (CVD) (6, 7, 8). Surprisingly, studies on the prevalence of cardiovascular risk factors, such as atherosclerosis, in PHPT patients, are few reporting subclinical carotid and coronary artery vascular involvement (9, 10).
To the best of our knowledge, there have been no studies in PHPT patients on the prevalence of aortic atherosclerosis, particularly abdominal aortic calcification (AAC), which is considered a relevant and independent predictor of future cardiovascular events in the general population (11). AAC is easily detected on a lateral lumbar spine radiograph, an imaging procedure usually performed in PHPT patients for the detection of vertebral fractures, according to the latest guidelines on PHPT management (12). Kauppila score (13) is a validated scoring system used to assess the severity of AAC; it has been demonstrated that both the presence and the degrees of calcification are predictive of higher relative cardiovascular risk in the general population (11).

The aim of this study was to assess the prevalence and severity of AAC in PHPT postmenopausal women by evaluating the Kauppila score, from X-rays of lateral lumbar spine.

Subjects and methods

Between January 2012 and December 2014, we consecutively enrolled 70 Caucasian postmenopausal women (age range 45–85 years) diagnosed as having PHPT at the Mineral Metabolism Centre of the University of Rome ‘Sapienza’ (Italy). They were recruited on the basis of their willingness to participate in the study and to conduct biochemical and imaging studies at our Institution. The diagnosis of PHPT was made following the finding of hypercalcemia together with raised or unsuppressed serum levels of PTH (14). During the same period of time, 70 age-matched volunteer postmenopausal Caucasian women, attending the same center mostly for a screening visit for osteoporosis, were enrolled as a control group. Exclusion criteria for participation in the study were the following: BMI >30 kg/m², hypo- and hyperthyroidism, previous CVD, previous recognized medical history of dyslipidemia and/or use of statins, and creatinine clearance (CrCl) <60 mL/min. The history of CVD was assessed employing a questionnaire on self-reported chronic diseases. When a subject reported to have a chronic disease, a further questionnaire concerning the specific disease was offered. We used the information on heart diseases and peripheral arterial diseases. To be classified as having CVD, suffering from either one was taken as sufficient condition in the analyses.

After informed consent was obtained, patients and control subjects with 25(OH)D levels <20 ng/mL were treated with 50 000 IU weekly of cholecalciferol for 1 month; calcium supplements (1000 mg p.o. daily) were given to those on a calcium poor diet after completing a validate questionnaire (15). From a biochemical point of view, both PHPT patients and control subjects were studied after 1 month of such a calcium and vitamin D regimen.

Body weight was measured without clothes and without shoes, using a calibrated bathroom scale. Height was measured using a stadiometer. BMI was calculated as weight (kg) divided by the square of height (m²). Alcohol consumption, current smoking status, and the presence of chronic diseases like diabetes were assessed in a face-to-face medical interview. To obtain information on medication use, the respondent had to show all medication she used at the moment of interview. Blood pressure (BP) (mm of mercury) was measured after 5 min of rest at the upper left arm with subjects in a lying position, using an oscillometric BP monitor.

Serum ionized calcium was determined using an ion-specific electrode (Nova 8; Nova Biochemical, Waltham, MA, USA); serum total 25(OH)D concentrations were measured by RIA (DiaSorin Inc, Stillwater, MN, USA); the intra- and interassay coefficients of variation values (CV values) were 8.1 and 10.2%, respectively (16). Serum PTH levels were assessed by immunoradiometric assay (N-tact PTH SP; DiaSorin Inc, Stillwater, MN, USA); the intra- and interassay CV values were 3 and 5.5%, respectively (17). Serum calcium, phosphorus, creatinine, and alkaline phosphatase levels were assessed as described previously (18). CrCl was calculated using the formula of Cockcroft and Gault (Cockcroft). Total cholesterol, HDL, and triglycerides (TC) were measured using enzymatic methods; the intra- and interassay CV values were 3.8 and 5.0%, respectively (Hitachi 911 analyzer, Roche Diagnostics). LDL was calculated with the Friedewald formula: LDL = TC – HDL – TG/5.0 (mg/dL).

Bone mineral density (BMD) of the lumbar spine (L1–L4) in the anterior–posterior projection, of the femur (neck and total hip) and nondominant distal one-third radius was measured in each patient by dual-energy X-ray absorptiometry (Hologic QDR 4500, Hologic Inc, Waltham, MA, USA). The precision error of lumbar spine and total hip measurements was 1.3 and 1.7%, respectively and 1.3% at the distal 1/3 radius (19). Fractured lumbar vertebrae were excluded from BMD measurement.

Each patient and control subject underwent standardized lateral radiographs of the thoracic and lumbar spine, centered at T8 and L3, respectively, at a film focus distance of 105 cm. After visual inspection of these radiographs by two independent experienced observers, vertebral deformity was defined when anterior, middle, or posterior height loss was more than 20% with respect to the adjacent vertebra, according
to Genant’s method (20). All patients had abdominal ultrasound performed by a skilled radiologist to detect renal calculi. Each ultrasonogram was performed with a low–medium frequency (3.5–5 MHz, depending on the physical characteristics of the subject) convex probe and the ultrasound scanner (Esaote MyLab 70 x Vision; Genoa, Italy), as previously described (21). The protocol was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the ‘Sapienza’ University of Rome Ethics Committee.

**Abdominal aortic calcification**

The extent of AAC was assessed by a semi-quantitative grading system developed by Kauppila et al. (13). Briefly, calcium deposits in both the anterior and posterior wall of the aorta parallel to vertebra L1 up to L4 on lateral abdominal radiographs are visualized as scattered or linear areas of high density. These calcium lesions are scored on a 0–3 scale for each area parallel to the mentioned vertebra and separately for both the anterior and posterior walls. The calcium lesions are graded as follows: 0 = no aortic calcium deposits; 1 = small scattered calcium deposits filling less than one-third of the longitudinal wall of the aorta; 2 = one-third to two-thirds of the longitudinal wall of the aorta calcified; 3 = greater than two-thirds of the longitudinal wall of the aorta calcified. This gives eight wall- and segment-specific scores, which are then summed to yield a posterior–anterior score between 0 and 24 for each subject. All radiographs were assessed by an expert radiologist without knowing the clinical status of participants.

**Statistical analysis**

The data are presented as mean ± S.D. Differences between groups were assessed with χ²-test for categorical variables and comparison of continuous variables were made using unpaired t-test. Pearson’s correlation coefficient was used to assess the relationship between continuous variables. A multiple regression analysis was performed to determine the correlation between all the variables considered and Kauppila score. We considered potential confounders: sex, age, BMI, diabetes mellitus (self-reported and/or use of antidiabetic medicine), hypertension (diastolic >90 mmHg, systolic >140 mmHg, and/or use of antihypertensive drugs), HDL cholesterol, total cholesterol, glomerular filtration rate (GFR), smoking (yes, no), and alcohol use (yes, no). Outcomes were considered statistically significant when two-tailed values for P were <0.5. Analyses were performed using SPSS 18.0 for Windows (SPSS).

**Results**

Baseline demographic and biochemical values of postmenopausal PHPT and control subjects are reported in Table 1. The PHPT group (mean ± S.D. years since biochemical diagnosis: 2.4 ± 1.5) included only four patients with mild PHPT (patients with serum calcium levels <1 mg/dL above the normal range, without evidence of bone and/or renal disease). There were no statistical differences in mean demographic and biochemical values between PHPT patients and controls, except for higher serum total and ionized calcium, 24h urinary calcium (normal range 4 mg/kg/24h) and lower mean serum phosphate levels.

**Table 1** Anthropometric and biochemical parameters in patients with primary hyperparathyroidism and controls. Results are presented as mean ± S.D.

<table>
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<tr>
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<th>PHPT (n = 70)</th>
<th>Controls (n = 70)</th>
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<tr>
<td>Age (years)</td>
<td>67.4 ± 8.9</td>
<td>69.1 ± 8.5</td>
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<tr>
<td>Years since menopause</td>
<td>17.7 ± 9.5</td>
<td>19.7 ± 7.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 3.5</td>
<td>24.3 ± 2.5</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min/1.73 m²)</td>
<td>87.1 ± 24.4</td>
<td>82.1 ± 13.1</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>11.1 ± 0.7</td>
<td>9.4 ± 0.4**</td>
</tr>
<tr>
<td>Ionized calcium (mmol/L)</td>
<td>1.45 ± 0.12</td>
<td>1.23 ± 0.03**</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>3.0 ± 0.6 mg/</td>
<td>3.7 ± 0.6**</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/mL)</td>
<td>108.9 ± 73.2</td>
<td>38.0 ± 13.5**</td>
</tr>
<tr>
<td>25(OH)D (ng/mL)</td>
<td>25.3 ± 10.2</td>
<td>27.1 ± 12.8</td>
</tr>
<tr>
<td>Urinary calcium (mg/24h)</td>
<td>297.3 ± 97.8</td>
<td>221.7 ± 56.9**</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>87.7 ± 24.4</td>
<td>75.5 ± 24.6*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>204.8 ± 39.1</td>
<td>215.5 ± 29.8</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>63.9 ± 23.6</td>
<td>59.7 ± 13.4</td>
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<tr>
<td>LDL (mg/dL)</td>
<td>124.0 ± 34.6</td>
<td>130.7 ± 20.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>123.7 ± 49.4</td>
<td>109.7 ± 35.1</td>
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*P ≤ 0.05; **P ≤ 0.001.
Also mean PTH (normal range 13–54 pg/mL) and alkaline phosphatase values (normal range 35–129 IU/L) were higher in PHPT patients compared with controls.

Regarding traditional organ involvement, we found that PHPT patients had a higher prevalence of kidney stones, detected by ultrasound examination, compared with controls (30% vs 7%, \( P = 0.0008 \)). We found no differences in BMD values as well as in morphometric vertebral fractures in PHPT patients compared with controls, with the exception of lower BMD at radial site in PHPT compared with controls (Supplementary Table 1, see section on supplementary data given at the end of this article).

Supplementary Table 2 gives the prevalence of traditional risk factors for CVD as well as current medications taken by PHPT patients and controls; we found no significant statistical differences between the PHPT patients and controls.

Concerning atherosclerotic aortic involvement evaluated by Kauppila score, we found that 31 PHPT patients had AAC compared with 18 controls (\( P = 0.03 \)). Considering the severity of the score, PHPT patients showed a significantly higher mean Kauppila score compared with controls (7.35 ± 6.1 vs 5.05 ± 3.5, \( P = 0.007 \)). In particular, 7 PHPT patients had severe Kauppila score (>12) vs only 1 among control subjects; 12 patients had moderate score (5–12) and 12 had mild score (1–4) vs 7 and 10 respectively, in controls.

Mean duration of years since diagnosis (3.3 ± 1.3 vs 1.7 ± 1.4 years, \( P < 0.0001 \)), age (71.8 ± 8.0 vs 63.9 ± 8.1 years, \( P < 0.0001 \)), and years since menopause (21.9 ± 9.4 vs 14.3 ± 8.0 years, \( P = 0.001 \)) were significantly different between the PHPT patients with and without AAC.

PHPT patients with severe aortic calcifications had higher mean PTH values compared with both patients with moderate (PTH: 160.0 ± 118.6 vs 84.3 ± 31.9 pg/mL, \( P = 0.04 \)) and mild calcifications (82.0 ± 41.6 pg/mL, \( P = 0.05 \)) (Fig. 1). There were no other differences regarding biochemical parameters, traditional cardiovascular risk factors, as well as BMD and vertebral fractures between PHPT patients with different degrees of severity scores.

Multiple regression analysis showed that in the PHPT patients with AAC, PTH remained significantly correlated with Kauppila score (\( B = 0.035, P = 0.024 \)) after adjusting for age and years since diagnosis.

**Discussion**

This is the first study showing higher prevalence and greater severity of AAC in postmenopausal PHPT women compared with weight, age-, and sex-matched controls. To this end, we used the Kauppila score, a validated tool for the detection of AAC. This measurement adds no additional cost to the management of PHPT patients, because the Kauppila score has the advantage of being a fast and low-cost estimation of location and severity of aortic atherosclerosis through a simple lateral lumbar spine X-ray; the last is routinely prescribed in PHPT patients for the detection of vertebral fractures (22).

Our study shows that the differences between PHPT patients with and without AAC are older age, years since menopause, and time since diagnosis, suggesting that atherosclerotic process is a function not only of aging and estrogen failure, but also of long-standing hyperfunction of the parathyroid glands. However, considering the severity of AAC, the only significant difference between PHPT patients with severe atherosclerosis score (i.e., Kauppila score >12) and patients with moderate and mild scores was higher PTH levels, independently of other risk factors. Among the cardiovascular risk factors, we did not find any difference in serum lipid profile levels between patients and controls, probably because we excluded patients with obesity and previous CVD (to avoid potential confounding), highlighting the role of PTH in the development of atherosclerosis.
Interestingly, according to this last finding, AAC are related to PTH levels in the general population, thus indicating a possible association between PTH and atherosclerosis even in the general population (23). This observation is strengthened by two independent community-based cohort studies, where PTH levels are associated with the degree of atherosclerosis and risk of clinically overt atherosclerotic disease, respectively (24).

In patients with PHPT, an increased vessel stiffness may be the initial vascular event, due to a combination of changes occurring as a result of hypercalcemia and direct action of PTH on vascular smooth muscle and endothelial cells (25, 26). In addition, it has been shown that in patients with PHPT, aldosterone levels were elevated and positively correlated with PTH values, possibly causing atherosclerosis because of proinflammatory, prothrombotic, and profibrotic effects (27, 28). However, in our sample, there were no differences in the prevalence of hypertension in patients with or without AAC.

Considering other vascular districts, such as the carotid artery, a significant inverse relationship between serum PTH levels and intima-media thickness was found (29). Also in the coronary artery district, the coronary functional reserve, which represents the first marker of the atherosclerotic process, was associated in a multivariable linear regression analysis with PTH, age, and heart rate. However in multiple logistic regression analysis, only PTH increased the probability of an impaired coronary functional reserve (10). Therefore, in line with these reports, our findings point to the abdominal aortic vasculature as a novel putative PTH target.

This study has some limitations. We enrolled only postmenopausal women, while men could have a different prevalence of cardiovascular risk factors. However, it is well known from epidemiological surveys that women are more affected by PHPT than men (14); furthermore, a negative effect of PTH levels on cardiovascular mortality has been demonstrated also in men (30). We did not measure serum levels of osteoprotegerin, receptor activator of nuclear factor kappa-B ligand (RANKL), Dickkopf-1 (DKK1), and sclerostin, which are probably involved in vascular calcification; these markers might have a role due to altered serum levels in PHPT patients compared with controls, as well as in osteoporotic patients under PTH therapy (31, 32, 33). However, the roles of these pathways in vascular calcification pathogenesis are still under debate (32).

In conclusion, our study for the first time shows a higher prevalence and severity of AAC in PHPT compared with controls directly related to PTH values. The Kauppila score provides a simple method to assess AAC without additional cost. This finding together with previous studies on cardiovascular risk factors in PHPT patients, including data on valve and cardiac calcifications, cardiomyopathy, and arrhythmia (5, 10, 28, 34, 35), suggests the need of a cardiovascular assessment in PHPT patients. Stratification according to CV risk category, as a result of AAC scoring, may improve patient care, with a more aggressive prevention strategy targeting patients with higher risk profiles. Further longitudinal studies are needed to determine the temporal relationship between the development of AAC and incident cardiovascular events in PHPT patients, as well as the effect of surgical treatment.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-15-1152.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References
Clinical Study

J Pepe and others

Aortic calcification in PHPT


