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Ultrasound Evaluation of Carotid Artery in Primary Hyperparathyroidism

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Patients with primary hyperparathyroidism (PHPT) have an increased cardiovascular morbidity and mortality. Elevated serum calcium and/or PTH may directly contribute to vascular tissue damage, but the role of classic factors for atherosclerosis has not fully been evaluated in this disease. The aim of our study was to dissect the potential effect of hypercalcemia and/or high PTH from that of major cardiovascular risk factors (*i.e.* diabetes mellitus, hyperlipidemia, hypertension, obesity, smoking habit) on the carotid artery structure of patients with PHPT. Twenty-six consecutive patients with PHPT [subdivided into two groups according to the absence (n = 10) or the presence (n = 16) of one or more risk factors] and 15 normocalcemic healthy subjects as controls were studied. At ultrasonography, a significant increase ($P < 0.001$) of carotid mean and maximum intima-media thickness, as well as a significant reduction of lumen diameter ($P < 0.05$) were found in the PHPT group with risk factors, compared with the other two groups. This suggests that hypercalcemia and/or PTH elevation *per se* are not determinant of carotid atherosclerosis in PHPT, and that increased cardiovascular mortality and morbility in this disease is attributable to the combined presence of classic cardiovascular risk factors. (*J Clin Endocrinol Metab* 88: 2096–2099, 2003)

PRIMARY HYPERPARATHYROIDISM (PHPT) is a common disease, especially in the elderly, and is reported to be associated with increased morbidity and mortality from cardiovascular disease (1–3). However, most reports on this issue include patients with symptomatic disease and serum calcium concentrations greater than 3.0 mM, and the contribution of otherwise established cardiovascular risk factors has not been fully evaluated. The development of noninvasive ultrasound techniques has opened up the field for *in vivo* studies of arterial structure and function in humans. In this regard, an increased intima-media thickness (IMT) of the common carotid artery correlates significantly with traditional cardiovascular risk factors (4), predicts the likelihood of cardiovascular and cerebrovascular events in population groups (5), and is related to the severity and extent of coronary artery disease (6). To our knowledge, only two recent studies, so far, have reported measurements of carotid IMT in patients with PHPT, giving controversial results. PHPT has not been found by Kosch *et al.* (7) to be associated with carotid structural changes, whereas an association with an increased carotid IMT has been observed by Nuzzo *et al.* (8). The aim of our study was to dissect the potential effect of hypercalcemia and/or high PTH levels from that of major cardiovascular risk factors on the carotid wall of patients with PHPT.

Patients and Methods

Patients

Twenty-six patients (20 women and 6 men, 32–76 yr old), admitted in the last 2 yr to our Institutions for PHPT because of solitary parathyroid adenoma, were consecutively enrolled into the study. Three patients were symptomatic, *i.e.* had nephrolitiasis. The patients were subdivided into 2 groups. The first group included 10 PHPT patients (8 women and 2 men, 32–73 yr old) without classic cardiovascular risk factors, *i.e.* diabetes mellitus, hyperlipidemia, hypertension, obesity, smoking habit. No patients of this group had evidence of coronary or peripheral artery disease, history of cardiovascular and cerebrovascular events, or impaired renal function, defined as serum creatinine more than 1.2 mg/dl (>106 μM). The second group included 16 PHPT patients (12 women and 4 men, 41–76 yr old) with one or more cardiovascular risk factors. Two of these patients also had signs of coronary heart disease at electrocardiogram, 1 patient had mild renal impairment, and 1 patient had a history of cerebrovascular events. No patients of either group had heart failure. The proportion of patients with mild hyperparathyroidism, *i.e.* serum calcium ≤ 12 mg/dl (≤3.0 mM), was similar in PHPT patients without (4 of 10 patients) and with (7 of 16 patients) risk factors.

Fifteen normal subjects, consecutively evaluated for dizziness and/or cervical bruits and/or headache, and sex- and age (range, 32–73 yr)-matched to PHPT patients with risk factors, served as controls. Control subjects were also statistically comparable [in terms of age, sex, and body mass index (BMI)] with PHPT patients without risk factors.

The study had approval by the local Ethics Committee, and all subjects gave their informed consent to participate. None of the PHPT patients who were recruited and eligible for the study declined to participate in vascular ultrasound evaluation.

Risk factors

Diabetes mellitus was diagnosed when patients were taking hypoglycemic medications or when, in the absence of treatment, fasting blood glucose levels were higher than 126 mg/dl (7.0 mM) in two consecutive determinations (9). Hyperlipidemia was defined as fasting total serum cholesterol more than 220 mg/dl (5.7 mM) and/or serum tryglicerides more than 1.56 mg/dl (1.8 mM), 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. In all hypertensive patients, secondary hypertension was excluded on the basis of standard bio-

Abbreviations: CI, Confidence intervals; BMI, body mass index; IMT, intima-media thickness; M-IMT, maximum IMT; m-IMT, mean IMT; NS, not significant; PHPT, primary hyperparathyroidism.

chemical, hormonal, and instrumental tests. A BMI of 30 kg/m^2 or more was considered as an index of obesity (10). Patients smoking at least one cigarette daily for 1 yr within the last 5 yr were considered smokers.

Carotid ultrasonography measurement

Carotid artery ultrasound imaging was performed in all subjects by high-resolution B-mode ultrasonography (Sonos 5000; Hewlett-Packard Co., Palo Alto, CA), using a 7.5-MHz probe with an axial resolution of less than 0.20 mm. Common carotid arteries were scanned, and longitudinal images of the distal 20 mm of each common carotid artery, proximal to the dilation of the bulb, were recorded at the end-diastole. Three measurements for IMT and lumen diameter at each carotid artery were taken, averaging all values. Carotid IMT (defined as the distance between the lumen-intima and the media-interfaces) and the lumen diameter (defined as the distance between the lumen-intimal edges) were measured in the far wall of the common carotid artery (11). Mean IMT (m-IMT) and maximum IMT (M-IMT) were assessed (12). m-IMT represents the mean value of all measurements at each common carotid artery, averaging the left and right sides. M-IMT represents the mean value of the single highest IMT measurements at each common carotid artery, averaging the left and right sides. The intimal-media far wall thickness of 1.3 mm or more at any segment in carotid arteries was defined as plaques (13). All readings were performed by a trained physician (G. Camporese), who was blinded, with respect to patients or controls. The intraobserver coefficient of variation of carotid IMT and lumen diameter measurement was less than 5%.

Laboratory studies

In all subjects, biochemical data were obtained during routine blood testing at the time of ultrasound evaluation of carotid arteries. PTH measurement was not available in the control population.

Serum intact (1–84) PTH concentrations were determined using a two-site chemiluminescent immunometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA); reference range, 10–65 pg/ml (1.0–6.8 pM).

Statistical analysis

All values are expressed as mean ± SD. Differences between means were assessed by one-way ANOVA, followed by Newman-Keuls *post hoc* test. Differences in prevalence rates among groups were analyzed by the χ^2 test. Relationships were assessed by the Pearson's correlation coefficients and linear regression analysis. Statistical significance was accepted as P value less than 0.05. For ultrasound vascular parameters, differences between means with associated 95% confidence intervals (CI) were also calculated.

Results

Clinical and biochemical data for PHPT without and with cardiovascular risk factors, in comparison with controls, are reported in Table 1. No difference in serum calcium, serum phosphate, and PTH levels were observed between the 2 groups of PHPT patients. All 16 PHPT patients with risk factors had at least 1 risk factor, 5 patients had 1 additional risk factor, 3 patients had 2 additional risk factors, and 1 patient had 3 additional risk factors. Distribution of risk factors among PHPT patients is shown in Table 1. Three of the 16 PHPT patients with risk factors (1 with hypertension, 2 with hypertension and diabetes) had atherosclerotic plaques.

The ultrasonography carotid characteristics of PHPT patients, without and with risk, and of normal controls are reported in Table 2. Carotid m-IMT and M-IMT were significantly higher in PHPT patients with risk factors than in PHPT patients without risk factors (difference between means = 0.27 mm, 95% CI = 0.16–0.38 mm, $P < 0.001$; and difference between means = 0.27 mm, CI = 0.18–0.36 mm, $P < 0.001$, respectively) and in controls (difference = 0.30 mm, CI = 0.21–0.38 mm, $P < 0.001$; and difference = 0.30 mm, CI = 0.20–0.40 mm, $P < 0.001$, respectively). Carotid lumen diameter was significantly lower in PHPT patients with risk factors than in PHPT patients without risk factors (difference = 0.67 mm, CI = 0.17–1.16 mm, $P < 0.05$) and controls (difference = 0.76 mm, CI = 0.31–1.20 mm, $P < 0.05$). No significant difference for any ultrasonographic parameter was found between PHPT without risk factors and normocalcemic healthy controls. Individual data of carotid m-IMT in PHPT patients, without and with risk factors, and in controls are reported in Fig. 1. Only 3 of the 10 (30%) PHPT patients without risk factors had m-IMT values above the mean for the controls. In contrast, all 16 patients (100%) in the PHPT group with risk factors were above this value in controls ($P < 0.005$).

No correlation was found between carotid m-IMT or M-IMT and serum calcium [r = −0.048, P = NS (not significant), and r = −0.069, P = NS, respectively] as well as between m-IMT or M-IMT and PTH (r = −0.192, P = NS; and r =

TABLE 1. Clinical and biochemical data of PHPT patients without cardiovascular risk factors, PHPT patients with cardiovascular risk factors, and controls

	PHPT patients without risk factors (n = 10)	PHPT patients with risk factors (n = 16)	Controls (n = 15)
Age (yr)	54 ± 13	58 ± 8	59 ± 9
Sex (M/F)	2/8	4/12	4/11
BMI (kg/m^2)	22 ± 3	28 ± 6[a]	24 ± 2
Serum calcium (mM)	2.91 ± 0.26[b]	3.05 ± 0.16[b]	2.31 ± 0.22
Serum phosphate (mM)	0.70 ± 0.13[b]	0.62 ± 0.14[b]	1.23 ± 0.17
PTH (pM)	20.1 ± 11.1	18.5 ± 14.5	NA
Diabetes mellitus	0	4/16[c]	0
Hyperlipidemia	0	10/16[c]	0
Hypertension	0	12/16[c]	0
Obesity	0	7/16[c]	0
Smoking habit	0	6/16[c]	0

Several PHPT patients had two or more risk factors. NA, Not available.
[a] $P < 0.05$.
[b] $P < 0.001$, PHPT group without cardiovascular risk factors and PHPT group with risk factors *vs.* controls.
[c] $P < 0.001$ PHPT group with risk factors *vs.* PHPT group without risk factors and controls.

TABLE 2. Ultrasound parameters of carotid artery in PHPT patients without cardiovascular risk factors, PHPT patients with cardiovascular risk factors, and controls

	PHPT patients without risk factors (n = 10)	PHPT patients with risk factors (n = 16)	Controls (n = 15)
m-IMT (mm)	0.74 ± 0.10	1.01 ± 0.17[a]	0.71 ± 0.14
M-IMT (mm)	0.77 ± 0.10	1.04 ± 0.12[a]	0.74 ± 0.12
Lumen diameter (mm)	6.37 ± 0.54	5.70 ± 0.64[b]	6.46 ± 0.60
Carotid plaques	0	3[a]	0

[a] $P < 0.001$ PHPT group with cardiovascular risk factors *vs.* controls and PHPT group without risk factors.
[b] $P < 0.05$.

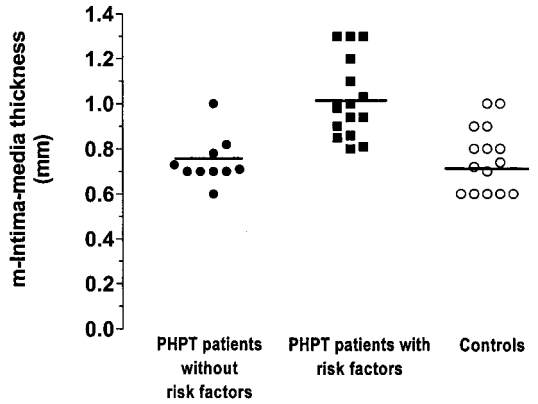

FIG. 1. Individual data of carotid mean m-IMT of PHPT patients without cardiovascular risk factors (●), PHPT patients with cardiovascular risk factors (■), and controls (○). The *line* for each group represents mean value.

−0.194, P = NS, respectively) within PHPT patients with cardiovascular risk factors.

Discussion

The present study shows that PHPT patients without the classically established cardiovascular risk factors (*e.g.* diabetes, hyperlipidemia, hypertension, obesity, smoking habit) do not have structural changes of the carotid artery wall, whereas the PHPT patients with risk factors have an increased carotid IMT. These results are only apparently surprising. In fact, there is evidence that hypercalcemia and/or high PTH levels may exert negative effects on the cardiovascular system and influence vascular tone and blood pressure (14). However, the pathophysiology of cardiovascular damage in PHPT is not clear (15). Chronic hypercalcemia is associated with increased deposition of calcium in the fibrous skeleton of the heart and valvular cups, as well as in coronary arteries and in myocardial fibers (1), and has been reported to be a risk for accelerated coronary atherosclerosis (16). Cardiac myocytes and vascular smooth muscle cells are also direct targets for PTH. PTH binds to specific receptors in the heart, leading to increased entry of calcium into cells, as well as mobilization of calcium from the sarcoplasmatic reticulum by a calcium-induced calcium release mechanism, and the increased accumulation of calcium causes damage of myocytes (17). On the other hand, PTH is known as a vasodilator in different species (18). The vasodilatory action on blood vessels does not require an intact endothelium, indicating a direct relaxant mechanism for PTH on vascular smooth muscle cells (19). In PHPT patients, the prevalence of hypertension has been reported to vary between 28 and 73% (20) and is particularly high in older age, where different causes of hypertension frequently occur. Moreover, large population studies, including that of one of ours, suggest that there is no simple cause-and-effect relationship accounting for hypertension in PHPT (21). In patients with PHPT, no independent correlation, using univariate or multiple-regression analysis, has been found between serum calcium levels and carotid IMT (7) or clinical arteriosclerotic disease (22), as well as between calcium or PTH levels and impairment of endothelium-independent vasodilation at the brachial artery (23). At variance, an independent positive correlation was found by Kosch *et al.* (7) between calcium levels, but not PTH levels, and the reduction in endothelium-dependent vasodilation at the brachial artery. A positive correlation between PTH levels, but not serum calcium levels, and carotid IMT was found by Suwelack *et al.* (24) only in renal transplant recipients with secondary elevation of PTH. Therefore, the role of calcium as well of PTH, as independent cardiovascular risk factors when using carotid IMT as marker for systemic atherosclerosis, is not demonstrated on clinical ground so far. The presence of other risk factors as confounders in assessing the importance of calcium and PTH in the pathogenesis of cardiovascular damage has been indirectly considered. In fact, several studies have shown, in PHPT patients with an otherwise cardiovascular risk profile disease, the lack of benefit from parathyroidectomy in terms of metabolic cardiovascular risk factors, hypertension, and renal function (22). Our study seems indeed to exclude, in the absence of otherwise confounding cardiovascular risk factors, an effect of elevated levels of calcium or PTH on vascular structure. These data are in accordance with the results by Kosch *et al.* (7), who used criteria of exclusion, for their series of PHPT patients, similar to those used for our PHPT patients without risk factors, though not in agreement with the results by Nuzzo *et al.* (8). These latter authors excluded patients with PHPT who had hypertension, hyperlipidemia, and diabetes mellitus but included patients who were smokers and obese; also, their series of patients had higher prevalence of males (40%), compared with our series (23%). Moreover, it is possible that duration of the disease in our PHPT patients with risk factors may have been longer than in the PHPT group without risk factors, so that it may have been a confounder for the carotid parameters measured. Indeed, the age of patients in the PHPT group with risk factors was slightly higher, although not significantly, than in PHPT patients without risk factors.

Potential limitations of our study have to be considered. These include the small sample size of our groups of patients with PHPT, as well as the marked prevalence in our groups of old age and female gender. However, our patients were

consecutive and were compared with consecutive patients recruited at our Institutions, thus avoiding the bias of choosing normal controls within a preselected population; and age-sex prevalence was similar in patients and in normal controls. At variance with other studies (25), BMI was also similar in the whole group of 26 PHPT patients and in controls (25 ± 4 *vs.* 24 ± 2 kg/m^2, P = NS). However, BMI values of 30 or more was present in 7 of 26 (27%) of our PHPT patients, whereas the general population in Italy shows 14–19% prevalence of obesity (26). This suggests that BMI may not be an independent variable in increasing cardiovascular risk in PHPT. Another limitation could have been the low sensitivity of carotid ultrasound methodology in detecting functional vascular wall abnormalities. We recognize that other techniques can identify endothelium dysfunctions or altered vascular compliance in peripheral arteries before ultrasound parameters measuring carotid structure become pathologic, and that endothelium dysfunctions can be predictors of vascular atherosclerotic damage (27). In fact, the presence of abnormal function in the brachial artery (7), as well as the augmentation index of aortic pressure measured by arterial pulse wave analysis (28), have been shown in patients with PHPT.

In conclusion, our study suggests that hypercalcemia and/or PTH elevation *per se* are not determinant of carotid atherosclerosis in PHPT. Although prospective studies are needed before definitive conclusions can be drawn, increased cardiovascular mortality and morbility in PHPT reported by epidemiological studies may be attributable to the combined presence of classic cardiovascular risk factors.

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