

## Clinical Studies



# Intima-media Thickness Measurement of the Carotid Artery in Patients with Primary Hyperparathyroidism. A Prospective Case-control Study and Long-term Follow-up

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**Abstract.** *Background:* The intima-media thickness (IMT) measurement of the common carotid artery is recognized as a reliable marker of systemic atherosclerosis and may be useful in predicting the likelihood of cardiovascular events, since it is related to the extent and severity of coronary artery disease. The aims of this study were to analyze whether correlations exist between the IMT of the common carotid artery and the main clinical and biochemical parameters in patients with primary hyperparathyroidism (PHPT), and to evaluate the possible improvement of the IMT values following parathyroidectomy at long-term follow-up. *Patients and Methods:* Twenty-seven patients (5 men, 22 women; median age 59 years, range 36-82 years) with biochemically confirmed PHPT (Group A, cases), and 27 gender- and age-matched healthy volunteers (Group B, controls) were prospectively enrolled in the study. All patients underwent ultrasound examination and the IMT of each carotid artery were recorded, averaging all values. The measurements were repeated 18-22 months (median 20) later in all patients. *Results:* A significant ( $p<0.05$ ) correlation between age and both systolic BP and IMT, and between IMT and fasting glycaemia was found in each Group. There was an inverse relationship between IMT and serum parathyroid hormone ( $R=-0.56$ ,  $p<0.01$ ), but no correlation ( $p=NS$ ) was found between IMT and serum calcium ( $R=-0.14$ ) or serum phosphate ( $R=0.07$ ). At follow-up a slight (10.4%) improvement in the mean IMT was observed among Group A

patients ( $0.86\pm0.18$  vs.  $0.77\pm0.24$ ;  $p=0.12$ ), but the difference was not significant. *Conclusion:* At long term follow-up, the IMT values did not improve significantly and no correlation was found between serum calcium and IMT. These results suggest that hypercalcemia does not represent a reliable risk of carotid atherosclerosis in patients with PHPT.

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia and more than 100,000 new cases of PHPT are detected each year in the USA alone (1). A Swedish population-based screening suggested that 2% of the post-menopausal women may have PHPT (2). Chronic hypercalcemia is associated with several cardiovascular abnormalities and an increased risk of death in patients with PHPT has long been reported (3-5). The intima-media thickness (IMT) measurement of the common carotid artery (CA) is recognized as a reliable marker of systemic atherosclerosis, and may be useful in predicting likelihood of cardiovascular events, since it is related to the extent and severity of coronary artery disease (6-7). The aims of this study were to analyze whether correlations exist between the IMT of the common CA and the main clinical and biochemical parameters in patients with PHPT, and to evaluate the possible improvement of the IMT values following parathyroidectomy at long-term follow-up.

## Patients and Methods

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*Key Words:* Intima-media thickness, carotid artery, hyperparathyroidism.

*Study population.* Twenty-seven patients (5 men, 22 women; median age 59 years, range 36-82 years) with biochemically confirmed PHPT (Group A, cases), and 27 gender- and age-matched healthy volunteers (Group B, controls) were prospectively enrolled in the study. The main clinical (i.e., age, body mass index [BMI], systolic and diastolic arterial blood pressure [BP]) and biochemical data (i.e., calcium, phosphate, glucose, total cholesterol, triglycerides, PTH serum levels) of the two Groups are reported in Table I. All

**Table I.** Main clinical and biochemical parameters of the two Groups.

Parameter	Group A	Group B	<i>p</i>
Age (years)	61.0±12	56.0±14	0.16
BMI (kg/m <sup>2</sup> )	22.4±4.6	23.6±3.8	0.30
Systolic BP (mm Hg)	136.7±13.9	133.5±10.7	0.34
Diastolic BP (mm Hg)	83.2±7.1	82.7±4.1	0.75
Glycaemia (mmol/L)	5.3±0.5	5.6±0.9	0.14
Cholesterol (mmol/L)	3.8±0.8	3.9±0.9	0.66
Triglycerides (mmol/L)	1.1±0.5	1.7±1.6	0.07
Ca (mmol/L)	2.8±0.2	2.2±0.1	<0.001
P (mmol/L)	0.7±0.3	1.0±0.6	0.024
PTH (ng/L)	183.0±167	52.0±12	<0.001
IMT (mm)	0.86±0.18	0.82±0.18	0.41

Group A=cases, Group B=controls, *p*=*p*-value, BMI=body mass index, BP=arterial blood pressure, PTH=parathyroid hormone, IMT=intima-media thickness of the common carotid artery.

Group A patients underwent successful parathyroidectomy and were followed-up for at least 18 months after surgery.

**Carotid artery ultrasonography.** Once the patients had given informed consent they underwent CA ultrasound (US) examination. High-resolution B-mode US (Esaote AU4, Genova, Italy) was performed using a 7.5 MHz linear probe with an axial resolution of less than 0.2 mm. All subjects were examined in the supine position. US scans of the right and left last distal centimetre of the common CA and bifurcation, and the first proximal centimetre of the internal CA in 3 different projections (anterior, lateral and posterior) were obtained. All measurements were made at the time of scanning on unfrozen images of longitudinal scans. Three measurements of IMT (distance between the lumen-intima and the media-interfaces) and lumen diameter of each CA were recorded, averaging all values. The maximal IMT value of each segment was measured. The single procedure was performed in 25–30 minutes and six carotid segments for each projection (near and far walls of bulb and internal and common carotid arteries) were examined. The US examination was repeated 18–22 months (median 20) later in all patients.

**Statistical analysis.** The reported data are expressed as mean±standard deviation (SD). Comparisons between different groups were performed using the two-tailed Student's *t*-test for means. Spearman's correlation (*R*) coefficient was also calculated to evaluate the linear relationship between pairs of clinical and biochemical parameters and *versus* IMT. A value of *p*<0.05 was considered to be statistically significant.

## Results

The final pathology showed a solitary parathyroid adenoma in all cases. Age, BMI, systolic and diastolic blood pressure (BP), mean IMT and biochemical parameters, except serum calcium and PTH, did not differ significantly between groups (Table I).

There was a significant relationship between age and both systolic BP (Group A: *R*=0.54, *p*=0.02; Group B: *R*=0.47, *p*=0.04) and IMT (Group A: *R*=0.51, *p*=0.02; Group B: *R*=0.44, *p*=0.04), and between IMT and fasting glycaemia (Group A: *R*=0.71, *p*<0.01; Group B: *R*=0.57, *p*=0.02) in each group. As expected, in Group A patients, serum calcium levels significantly correlated with both serum phosphate (*R*=−0.45, *p*=0.04) and PTH (*R*=0.63, *p*<0.01). There was an inverse relationship between IMT and serum PTH (*R*=−0.56, *p*<0.01), but no correlation (*p*=NS) was found between IMT and serum calcium (*R*=−0.14) or serum phosphate (*R*=0.07) (Table II).

At follow-up a slight (10.4%) improvement of the mean IMT was observed among Group A patients (0.86±0.18 vs. 0.77±0.24; *p*=0.12), but the difference was not significant. The IMT of control Group did not change (0.82±0.18 vs. 0.80±0.21; *p*=0.71).

## Discussion

Several cardiovascular risk factors have been reported in patients with PHPT since both calcium and PTH are related to heart function (8). Moreover, elevated levels of PTH are associated with increased cardiovascular morbidity, and an increase in the incidence of acute myocardial infarction in patients with PHPT, who did not undergo surgery, has been demonstrated (9, 10).

Cardiovascular abnormalities are common in patients with PHPT, and endothelium-dependent vasodilatation is impaired in hyperparathyroid patients despite normal IMT (9, 11). However, in a previous study, we did not find any relationship between blood arterial pressure and both serum calcium and PTH levels in a cohort of patients with PHPT (12). Smith *et al.* found significantly higher indices of vessel stiffness in PHPT patients independently of their systolic BP values (13). The inefficacy of surgery on hypertension may indicate the lack of a relationship between BP and both hypercalcemia and high PTH serum levels (14). Nuzzo *et al.* showed that an increase in carotid IMT was the only alteration suggesting a higher risk of cardiovascular abnormalities (15). However, in a previous study, we found that only patients with major cardiovascular risk factors (*i.e.*, diabetes mellitus, hyperlipidemia, hypertension, obesity, smoking habit) may have a significant increase in carotid IMT, compared to healthy subjects and hyperparathyroid patients without risk factors (11).

PTH may play a role in the development of hypertension, but the relationship between PTH and the structure of the artery wall is unclear (16). Increased vessel stiffness may be the initial vascular change in patients with PHPT, due to a combination of changes occurring as a result of hypercalcemia and direct action of PTH on vascular smooth muscle and endothelial cells (17). Although PTH has been

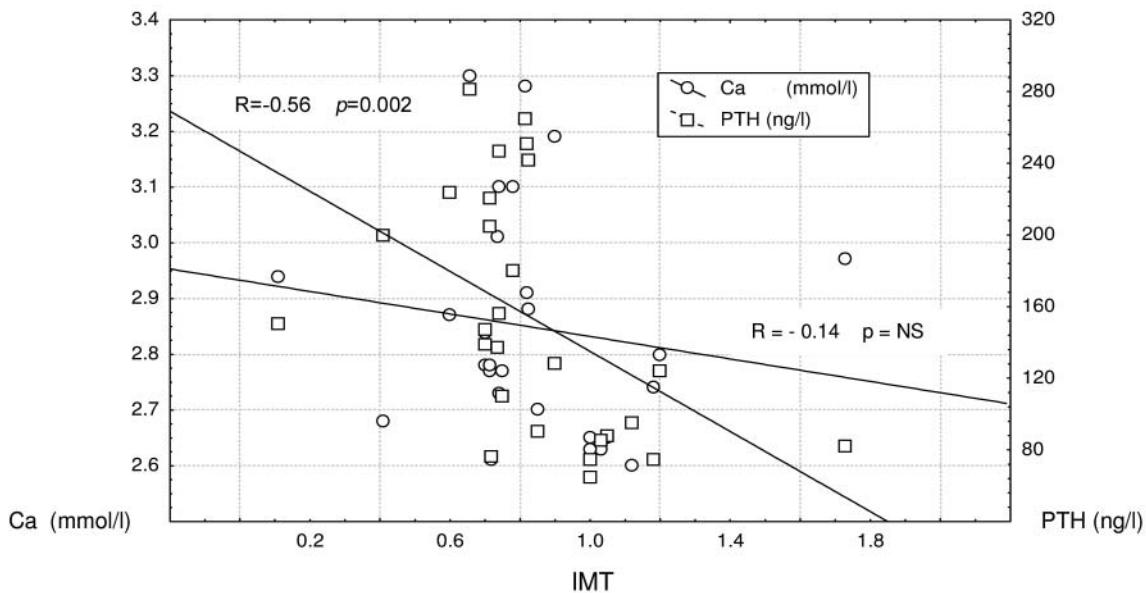


Figure 1. Relationship between intima-media thickness (IMT) of the common carotid artery and PTH or calcium serum levels in a group of patients with primary hyperparathyroidism. There was a significant ( $p < 0.01$ ) inverse relationship between IMT and serum PTH.

Table II. Correlation coefficient ( $R$ ) and the respective  $p$ -value between different clinical and biochemical parameters in patients with primary hyperparathyroidism (Group A, cases).

Variables	Age	Syst BP	Diast BP	Glyc	Chol	Trigl	Ca	P	PTH	IMT
Age	-	0.54 $p=0.02$	0.36 $p=NS$	0.43 $p=0.02$	-0.04 $p=NS$	0.23 $p=NS$	-0.05 $p=NS$	-0.16 $p=NS$	-0.21 $p=NS$	0.51 $p=0.02$
Syst BP	0.54 $p=0.02$	-	0.58 $p<0.01$	0.28 $p=NS$	0.07 $p=NS$	0.09 $p=NS$	0.044 $p=NS$	-0.11 $p=NS$	-0.06 $p=NS$	0.30 $p=NS$
Diast BP	0.36 $p=NS$	0.58 $p<0.01$	-	0.01 $p=NS$	-0.08 $p=NS$	0.23 $p=NS$	0.31 $p=NS$	-0.24 $p=NS$	0.05 $p=NS$	0.14 $p=NS$
Glyc	0.43 $p=0.02$	0.28 $p=NS$	0.01 $p=NS$	- $p=NS$	-0.03 $p=NS$	0.15 $p=NS$	-0.19 $p=NS$	0.11 $p=NS$	-0.32 $p=NS$	0.71 $p<0.01$
Chol	-0.04 $p=NS$	0.07 $p=NS$	-0.08 $p=NS$	-0.03 $p=NS$	- $p=NS$	0.49 $p=0.02$	-0.29 $p=NS$	0.27 $p=NS$	-0.13 $p=NS$	-0.16 $p=NS$
Trigl	0.23 $p=NS$	0.09 $p=NS$	0.23 $p=NS$	0.15 $p=NS$	0.49 $p=0.02$	- $p=NS$	-0.02 $p=NS$	0.27 $p=NS$	-0.07 $p=NS$	0.33 $p=NS$
Ca	-0.05 $p=NS$	-0.05 $p=NS$	0.31 $p=NS$	-0.19 $p=NS$	-0.29 $p=NS$	-0.02 $p=NS$	- $p=NS$	-0.45 $p=0.04$	0.63 $p<0.01$	-0.14 $p=NS$
P	-0.16 $p=NS$	-0.11 $p=NS$	-0.24 $p=NS$	0.11 $p=NS$	0.27 $p=NS$	0.27 $p=0.04$	-0.45 $p=0.04$	- $p=NS$	-0.05 $p=NS$	0.07 $p=NS$
PTH	-0.21 $p=NS$	-0.06 $p=NS$	0.05 $p=NS$	-0.32 $p=NS$	-0.13 $p=NS$	-0.07 $p=NS$	0.63 $p<0.01$	-0.05 $p=NS$	- $p=NS$	-0.56 $p<0.01$
IMT	0.40 $p=0.04$	0.40 $p=0.04$	0.14 $p=NS$	0.71 $p<0.01$	-0.16 $p=NS$	0.33 $p=NS$	-0.14 $p=NS$	0.07 $p=NS$	-0.56 $p<0.01$	- $p=NS$

Syst BP=systolic blood pressure, Diast BP=diastolic blood pressure, Glyc=glycaemia, Chol=serum cholesterol, Trigl=serum triglycerides, Ca=serum calcium,  $p$ =serum phosphate, PTH=serum parathyroid hormone, IMT=intima-media thickness of the common carotid artery.

implicated in hypertension, experimental PTH infusion results in vasodilatation, and the expression of the PTH/PTH-related protein receptor in vascular endothelial cells suggests that the endothelium represents a target tissue for PTH (17, 18).

We found a significant inverse relationship between serum PTH levels and IMT in patients with PHPT (Figure 1), but the mean BP values did not differ significantly between patients with PHPT and controls, although both the PTH and calcium serum levels were normal in Group B patients.

In conclusion, the endothelium is a recognized target of PTH and, in patients with PHPT, the endothelium function is affected (9). However, at long term follow-up the IMT values did not significantly improve and no correlation was found between serum calcium and IMT. These results suggest that hypercalcemia does not represent a reliable risk of carotid atherosclerosis in patients with PHPT.

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