Int J Cardiovasc Imaging (2007) 23:323–328
DOI 10.1007/s10554-006-9166-8

ORIGINAL PAPER

Impairment of flow mediated vasodilatation of brachial artery in patients with primary hyperparathyroidism

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Received: 27 July 2006 / Accepted: 7 September 2006 / Published online: 12 October 2006
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Abstract
Background Hyperparathyroid condition might influence endothelial cells. The aim of this study was to assess flow mediated dilatation (FMD) in patients with primary hyperparathyroidism (PHPT).
Methods We prospectively evaluated 21 patients with PHPT (9 women, 12 men; aged 50 ± 11 years, serum calcium 11.6 ± 0.7 mg/dl, intact parathyroid hormone (iPTH) 489 ± 495 pg/ml) and 27 healthy control subjects (13 women, 14 men; aged 49 ± 10 years, serum calcium 9.4 ± 0.5 mg/dl, iPTH 28 ± 8.5 pg/ml). Endothelial function, measured as FMD of the brachial artery using ultrasound, was calculated in two groups. To avoid confounding factors, conditions known to affect endothelial function like diabetes mellitus, hypertension, dyslipidemia, smoking, coronary and peripheral artery disease were excluded from both groups.
Results FMD was lower in patients with PHPT than that in those without (10.2 ± 5.8 vs. 19.8 ± 5.8, $P = 0.0001$). FMD negatively correlated with serum calcium ($r = –0.55$, $P = 0.002$).
Conclusion Endothelium-dependent FMD may impair in patients with PHPT compared to controls. Endothelial dysfunction can contribute to the deleterious cardiovascular effects of PTH excess. Therapy to reduce or retard endothelial dysfunction in patients with PHPT may lead to decreased cardiovascular morbidity and mortality.

Keywords Primary hyperparathyroidism · Flow mediated dilatation

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1 Introduction

Primary hyperparathyroidism (PHPT) is associated with increased mortality and morbidity due to cardiovascular disease [1, 2]. Myocardial infarction, heart failure and stroke may cause death in patients with PHPT [2–5] and parathyroid hormone (PTH) may cause left ventricular hypertrophy (LVH) [6, 7]. Moreover, increased serum calcium and PTH levels are known to be correlated with the risk of premature death [5, 8]. Diabetes mellitus, insulin resistance, hypertension and hyperlipidemia are found in higher frequency in patients with PHPT [9–12]. PHPT is caused by solitary parathyroid adenomas in 85% of

cases and by diffuse hyperplasia in most of the remaining cases [13].

Endothelial dysfunction is an early phase of atherosclerosis [14] and can be measured non-invasively using high-resolution ultrasonography to measure post-ischemic flow mediated dilatation (FMD) of conduit arteries [15]. Impaired FMD is an early marker of atherosclerotic degeneration and has been shown to be correlated with coronary endothelial dysfunction [16].

Primary hyperparathyroidism may lead to impairment of vascular tone and proliferation of vascular smooth muscle cells and cardiomyocytes [17, 18]. PTH can influence functional and structural properties of large arteries [17]. Some studies show endothelium as a target organ of PTH [19]. However, it is not clear whether endothelial function is impaired in patients with PHPT. The aim of this study was to investigate FMD of the brachial artery in patients with PHPT free of hypertension, diabetes mellitus, coronary artery disease, and smoking.

2 Methods

2.1 Patients

We prospectively evaluated 21 patients with PHPT (9 women, 12 men; aged 50 ± 11 years) and 27 healthy control group (13 women, 14 men; aged 49 ± 10 years). We excluded patients with diabetes mellitus, hypertension, coronary heart disease, bundle branch block, atrial fibrillation, paced rhythm, atrioventricular block, moderate–severe valvular heart disease, restrictive, hypertrophic or dilate cardiomyopathies, congenital heart disease, hyperthyroidism and hypothyroidism. We included patients with no history of angina pectoris, myocardial infarction, or congestive heart failure. In addition, the patients had no complaints or physical signs of congestive heart failure or coronary heart disease. Electrocardiography showed sinus rhythm without any signs of ischemia in all of the patients. Patients who had received any medication such as angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, calcium channel blocker, beta blocker or statin were excluded from the study.

The study was approved by the local scientific ethical committee.

2.2 Flow mediated dilatation

A standard protocol was used to assess endothelial function, as previously reported, according to recommendation [20]. For the FMD of brachial artery, patients fasted ≥8 h before the study. Patients were studied in a quiet, temperature-controlled room. Caffeine intake and cigarette smoking were prohibited for at least 4–6 h before the study. The right arm was immobilized using 2 cushions supporting the elbow and the wrist. A sphygmomanometric cuff was placed on the forearm. After 10–15 min of rest, the brachial artery was visualized longitudinally with the ultrasonic scanner operating B mode. After an optimal image of the artery was obtained, the ultrasonic transducer was fixed in this position with a custom-built probe holder. Brachial arter diameter was determined in end-diastole, indicated by the *R* wave of the electrocardiogram. After 3 baseline measurements were obtained, ischemia was induced by the inflation of the cuff to 100 mm Hg greater than the systolic arteriel pressure to occlude arterial flow for 5 min. After the deflation of the cuff, diameter measurements were performed 30 s, 1 min, 2 min, 3 min, and 4 min, consecutively. Since the arterial dilatation most-likely related to nitric oxide release occurs at 1 min after ischemia, we used FMD at 1 min postischemia to represent the spontaneous endothelial function. Maximal obtained diameter during ischemia-induced hyperemia was used for the calculation of the percentage of FMD (maximum diameter-baseline diameter)/baseline diameter × 100.

2.3 Biochemical assays

Biochemical variables were estimated after an overnight fast by anaerobic sampling. Clinical routine methods were used to estimate values in blood for total serum calcium, serum creatinine, total alkaline phosphatase, fasting blood glucose, total cholesterol and triglycerides (Roche Modular Analytics P-D, Roche Diagnostics GmbH, D-68298 Mannheim-Germany).

Serum concentration of intact PTH (iPTH) was analyzed with the Immulite 2000 (DPC Immulite kit, DPC Biermann GmbH 61231 Bad Nauheim, Germany).

2.3.1 *Statistical analysis*

All the results are expressed as mean ± standard deviations. Baseline and echocardiographic variables were compared by χ^2 test for categoric variables and Student t test for continuous variables. A value of $P < 0.05$ was considered statistically significant. Pearson correlation coefficient was used for calculation.

3 Results

The baseline characteristics of the patients and healthy subjects are listed in Table 1. There were no significant differences between PHPT-patients and controls regarding age, gender, hypertension, smoking, serum lipid profile, serum creatinine levels and body mass index. Plasma iPTH, serum calcium, and alkaline phosphatase levels were significantly higher in patients with PHPT when compared to healthy controls. Serum phosphate level was significantly lower in patients with PHPT when compared to healthy controls. Results of ultrasound measurements in the brachial artery are summarized in Table 2. FMD was lower in patients with PHPT than that in those without (10.2 ± 5.8 vs. 19.8 ± 5.8, P = 0.0001) (Fig. 1).

FMD negatively correlated with serum calcium ($r = -0.55$, $P = 0.002$).

4 Discussion

Primary hyperparathroidism contributes to increased risk of cardiovascular morbidity and mortality [1, 2]. However, the etiopathogenic mechanisms underlying this association and the exact role of PHPT in the development of cardiovascular disease are not fully understood [21]. Some studies show a positive correlation between PTH levels and blood pressure in patients with normotensive, healthy subjects and hypertension [22, 23].

There is some evidence that impairment of endothelium-dependent vasodilatation is an early phenomenon of atherogenesis and it is present before the anatomic evidence of atherosclerosis [24, 25]. Endothelial dysfunction predisposes to thrombosis, leukocyte adhesion and proliferation of smooth muscle cells in the arterial wall [26], which is associated with abnormal nitric oxide physiology [14]. Impaired FMD is an early marker of atherosclerotic degeneration and has been shown to be correlated with extent and severity of coronary artery disease [27]. Endothelial dysfunction can be measured non-invasively by ultrasound and Doppler techniques to detect post-ischemic FMD of the brachial artery [20]. Conduit artery endothelial dysfunction is associated with abnormal vasomotor responses of the coronary circulation [27, 28]. Endothelial function is impaired in the systemic arteries of asymptomatic

Table 1 Clinical and laboratory characteristics of study population

	Patients (n = 21)	Controls (n = 27)	P
Age (years)	50 ± 11	49 ± 10	NS
Sex (men/women)	12/9	14/13	NS
Body mass index (kg/m^2)	28 ± 2.3	27 ± 2.7	NS
SBP/DBP (mm Hg)	123 ± 3/75 ± 2	126 ± 4/74 ± 3	NS
Total cholesterol (mg/dl)	197 ± 45	191 ± 49	NS
Triglycerides (mg/dl)	147 ± 99	146 ± 81	NS
HDL-C (mg/dl)	45 ± 13	46 ± 11	NS
LDL-C (mg/dl)	142 ± 31	138 ± 29	NS
Serum creatinine (mg/dl)	0.8 ± 0.33	0.7 ± 0.19	NS
iPTH (pg/ml)	489 ± 495	28 ± 8.5	0.006
Serum calcium (mg/dl)	11.6 ± 0.7	9.4 ± 0.5	0.0001
Serum phosphate (mg/dl)	2.7 ± 0.8	3.8 ± 0.3	0.0001
Alkaline phosphatase (U/l)	387 ± 38	161 ± 43	0.02

NS, $p > 0.05$; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; iPTH: intact serum parathyroid hormone

Table 2 Results of ultrasound measurements in the brachial artery

	Patients (n = 21)	Controls (n = 27)	P value
Baseline diameter (mm)	0.33 ± 0.42	0.33 ± 0.59	NS
Hyperemia diameter (mm)	0.36 ± 0.92	0.39 ± 0.63	NS
FMD	10.2 ± 5.8	19.8 ± 5.8	0.0001

FMD, Flow mediated dilatation; NS, $P > 0.05$

patients with dyslipidemia, smokers, and coronary artery disease [29, 30].

The precise mechanism of endothelial dysfunction in PHPT is not well understood. There is some evidence that endothelium is a target organ of PTH [31]. PTH may influence vascular tone [32] and stimulate structural alterations like proliferation of smooth muscle cells and cardiomyocytes [33]. PTH stimulates the vascular smooth muscle cell by binding to the PTH/PTH-related peptide receptor and reduces the influx of calcium [34]. In this study, we found FMD of the brachial artery as reduced in patients with PHPT. Our finding related that FMD was also similar to that of Kosch et al. [35]. In addition, Kosch et al. [36] show that FMD improved significantly after successful parathyroidectomy.

Morphologic and functional alterations of vascular smooth muscle cells may lead to impaired vasoreactivity of the brachial artery in the PHPT-patients. In addition, hypercalcemia affects vascular smooth muscle contractility directly and increases vascular tone; as a result of this calcium overload myocytes may get damaged [37]. Barenbrock et al. [38] show that endothelial dysfunction is correlated with PTH levels independent of calcium levels in renal transplant patients and elevated PTH has a deleterious effect on elastic properties of arterial wall [39]. We found a negative correlation between plasma calcium level and FMD of brachial artery in patients with PHPT.

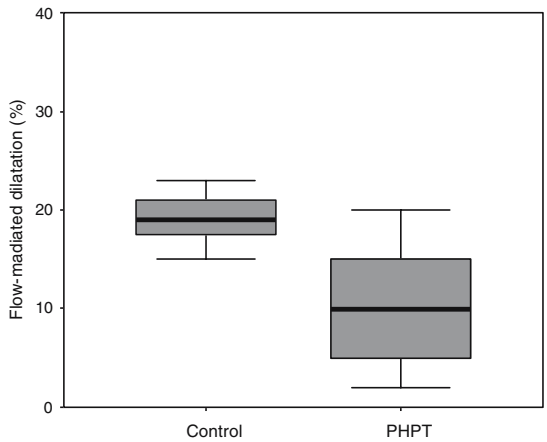

Fig. 1 Flow mediated dilatation (FMD) in 27 patients with primary hyperparathyroidism (PHPT) and 21 healthy control groups (P = 0.0001)

However, in a number of studies, patients with PHPT with concominant systemic hypertension, coronary heart disease or diabetes mellitus were not separately evaluated. In our study, conditions known to affect endothelial function such as hypertension, coronary artery disease, dyslipidemia, smoking or renal failure were excluded to highlight the effect of PTH excess. In contrast to our study, Neunteufl et al. [40] did not find a significantly impaired endothelium-dependent vasodilatation in patients with PHPT. But, smoking, hypertension, and diabetes mellitus were not excluded from the patients and controls in their study, all known to affect endothelial function negatively.

O'Driscoll et al. [41] show that endothelial dysfunction may improve 1 month after initiation of treatment of statins. In addition, endothelial dysfunction may recover after cessation of smoking, during therapy with angiotensin converting enzyme inhibitor, and vitamin C or folic acid supplementation [42–44]. But, smoking and patients who had received any medication such as angiotensin converting enzyme inhibitor, angiotensin II receptor blocker, calcium channel blocker, beta blocker or statin were excluded from our study.

Our control values seem ''super-normal''. But, conditions known to affect endothelial function including coronary artery disease, hypertension, smoking, dyslipidemia, renal failure or patients who had received some medication were excluded from our study.

5 Limitations

The existence of coronary heart disease cannot be ruled out, because non invasive stress test or angiography was not performed. However, there was no clinical, electrocardiographic, and echocardiographic ischemic evidence. Another limitation of this study involves the small number of the patients. Therefore, large prospective studies are needed to establish FMD of brachial artery in patients with PHPT. In addition, lack of assessment of nitrate-induced vasodilatation remains as a limitation of our study.

In conclusion, the results of this study indicate that endothelial dysfunction may develop in the preclinical phase of vascular disease in patients with PHPT. Measurement of endothelial function of the brachial artery could be useful identifying a high-risk of PHPT-patients. Strategies to reduce or retard endothelial dysfunction in patients with PHPT may lead to decreased cardiovascular morbidity and mortality.

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