Atherosclerosis 238 (2015) 420–426

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Parathyroid hormone and calcium are independently associated with subclinical vascular disease in a community-based cohort

Emil Hagström [a, c, *, 1], Tommy Ahlström [b, d, 1], Johan Ärnlöv [a, c], Anders Larsson [a], Håkan Melhus [a], Per Hellman [b], Lars Lind [a]

[a] Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[b] Department of Surgical Sciences, Uppsala University, Uppsala, Sweden
[c] Uppsala Clinical Research Centre, Uppsala University, Uppsala, Sweden
[d] Department of Surgery, Central Hospital, Västerås, Sweden

ARTICLE INFO

Article history:
Received 27 July 2014
Received in revised form
16 November 2014
Accepted 14 December 2014
Available online 20 December 2014

Keywords:
Parathyroid hormone
Calcium
Vascular function
Blood pressure
Vascular stiffness

ABSTRACT

Objective: Diseases with abnormal levels of parathyroid hormone (PTH) and calcium, such as primary and secondary hyperparathyroidism, are associated with an increased risk of cardiovascular morbidity and mortality. However, there is paucity on the association between calcium, PTH and abnormalities in the vascular system in the general population.

Methods: In the PIVUS study (Prospective Investigation of the Vasculature in Uppsala Seniors), a community based cohort of 70-year old men and women (n = 1016), the associations between s-calcium, p-PTH and endothelial function, arterial stiffness and blood pressures were investigated, adjusting for cardiovascular risk factors and mineral metabolism.

Results: In multivariable linear regression models 1 SD increase in calcium was associated with 1.1 units decrease in the stroke volume/pulse pressure ratio and 0.06 decrease in common carotid artery distensibility ($p < 0.001$) indicative of increased arterial stiffness. Further, calcium was associated with increasing calculated central pulse pressure with 1.3 mmHg elevation per 1 SD increase in calcium ($p < 0.05$). 1 SD increase in PTH was associated with 1.9 and 1.0 mmHg increase in intra-arterially measured brachial artery systolic and diastolic blood pressures, respectively ($p < 0.01$), as well as 1.6 and 0.9 mmHg increase in calculated central systolic and diastolic blood pressures ($p < 0.05$). PTH was not associated with arterial stiffness, endothelial function or pulse pressure.

Conclusion: In a large community-based sample of elderly, calcium was independently associated with increased arterial stiffness, and PTH independently to intra-arterial peripheral and calculated central blood pressures. The findings indicate a possible link between the vasculature and mineral metabolism.

1. Introduction

Diseases with a disturbed mineral metabolism, such as primary hyperparathyroidism (pHPT) and chronic kidney disease with secondary hyperparathyroidism (sHPT), are not only associated with mineral metabolism traits such as renal stones, osteoporosis or tissue calcifications, but also with higher risk of cardiovascular morbidity and mortality [1,2]. Multiple lines of evidence from experimental [3–5] and clinical [6,7] studies indicate that levels of both calcium and PTH could be causally involved in the process leading to manifest cardiovascular diseases via development of vascular dysfunction, atherosclerosis and inflammation. Furthermore, a few previous epidemiological studies have shown that both PTH and calcium are associated with high blood pressure [8,9], cardiovascular diseases [10–12] and with increased risk of mortality [13], risks that seem to be present also below the current clinical thresholds for elevated PTH and calcium. Still, there is only limited data on the vascular function, in relation to PTH and calcium in the general population [14].

Since both pathological and normal PTH, and calcium seem to be related to, or predispose to, overt vascular disease and death, we hypothesized that these variables were involved also in

* Corresponding author. Dept of Cardiology, Uppsala Clinical Research Centre, Department of Medical Sciences, Uppsala University, Dag Hammarskjölds väg 14B, Level 1 MTC-building, Science Park, 752 37 Uppsala, Sweden.
E-mail address: emil.hagstrom@ucr.uu.se (E. Hagström).
[1] Contributed equally.

http://dx.doi.org/10.1016/j.atherosclerosis.2014.12.027
0021-9150/

development of subclinical vascular abnormalities. Thus, the aim of the present study was to explore the potential role for PTH and calcium in the development of subclinical cardiovascular morbidity by measuring endothelial function, arterial compliance, as well as intra-arterial and calculated central blood pressure in a large, community based cohort of 70-year old men and women.

2. Patients and methods

2.1. Study sample

The PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study was initiated in 2001 with the primary aim to investigate vascular function in the general population [15]. All men and women aged 70 living in Uppsala, Sweden, were eligible for inclusion and 1016 subjects accepted (participant rate 50.1%, 507 males and 509 females). All participants gave written informed consent, and the Ethics Committee of the Uppsala University, Uppsala, Sweden, approved the study. None of the included individuals had previously been diagnosed with primary or secondary HPT, and none was taking calcium or vitamin D supplementation [15].

2.2. Clinical and biochemical evaluation

Venous blood for biochemical analyses was drawn after an overnight fast and stored at −70 °C until analysis. S-calcium (normal range 2.20–2.50 mmol/L) and s-albumin (normal range 37–48 g/L) were measured spectrophotometrically and s-albumin corrected s-calcium (below only denoted s-calcium) was calculated: (0.019 * [46 − s-albumin] + s-calcium). P-parathyroid hormone (PTH) (normal range 1.3–6.9 pmol/L) was analyzed using the Immulite 2000 Intact PTH Assay (Diagnostic Products Corporation, Los Angeles, CA, USA). Serum creatinine and phosphate measurements were performed on an Architect Ci8200 analyzer (Abbott Laboratories, Abbott Park, IL, USA). Glomerular filtration rate was estimated with the CKD-EPI formula. P-25-OH vitamin D was analyzed with a Liason 25(OH)D_3 assay in a Liason analyzer (DiaSorin Inc., Saluggia, Italy). Vitamin D insufficiency was defined as a 25-OH vitamin D < 37.5 nmol/L [13]. C-reactive protein and NT pro-B type natriuretic peptide were measured as previously described [16]. Fasting P-glucose was measured by routine laboratory analysis. Height, weight, body mass index (weight [kg]/height^2 [m], BMI), and supine systolic and diastolic blood pressures were measured under standardized conditions. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication (53% used beta-blockers, 32% used calcium antagonists, 31% used diuretics, 19% angiotensin-converting enzyme inhibitors, and 25% used angiotensin receptor blockers, in monotheraphy or in combinations). Diabetes mellitus was defined as fasting P-glucose ≥7.0 mmol/L or use of oral hypoglycemic agents or insulin. Hypercholesterolemia was defined as total S-cholesterol >5 mmol/L, LDL-cholesterol >3 mmol/L or use of lipid-lowering treatment. Possible hypercalcemic pHPT was defined as an albumin corrected s-calcium >2.5 mmol/L, a p-PTH >6.9 pmol/L and a glomerular filtration rate of >60 mL/min/1.73 m^2. Impaired renal function was defined as glomerular filtration rate <60 mL/min/1.73 m^2, i.e. chronic kidney disease stages 3–5. Medical history, medication and smoking status were collected from questionnaires.

2.3. Invasive forearm investigation

Forearm blood flow (FBF) was measured by venous occlusion plethysmography (Elektromedicin, Kullavik, Sweden) [15]. A mercury strain gauge was placed at the upper third of the forearm, which rested slightly above the level of the heart. The strain gauge was connected to a calibrated plethysmograph. Venous occlusion was achieved by a blood pressure cuff applied proximal to the elbow which was inflated to 50 mmHg by a rapid cuff inflator. An arterial cannula was placed in the brachial artery for blood sampling and later regional infusions of vasodilators. Resting FBF was measured 30 min after cannulation. After evaluation of resting FBF, local intra-arterial drug infusions were given during 5 min for each dose with a 20 min washout period between the drugs.

The infused dosages were 25 and 50 mg/min for acetylcholine (Clin-Alpha, Laufelfingen, Switzerland) to evaluate endothelium-dependent vasodilation (EDV) and 5 and 10 mg/min for sodium nitroprusside (SNP, Nitropress, Abbot, UK) to evaluate endothelium-independent vasodilation (EIDV). The drugs were given in a random order at a maximal rate of 1 mL/min. EDV was defined as FBF during infusion of 50 mg/min of acetylcholine minus resting FBF divided by resting FBF. EIDV was defined as FBF during infusion of 10 mg/min of SNP minus resting FBF divided by resting FBF [15]. EDV and EIDV were evaluated in 87% of the participants of this study. Cannulation of the artery was not performed in the 3% of the patients who were on regular treatment with warfarin and in another 10% cannulation failed.

2.4. Carotid artery investigations

The diameter of the common carotid artery (CCA) of the right-side 1–2 cm proximal of the bifurcation was measured at its maximal diameter in systole and the minimal diameter in diastole by an Acuson XP124 cardiac ultrasound unit (Acuson, Los Angeles, CA, USA) with a 7.5-MHz transducer. The CCA distensibility was calculated as the percentage change in the diameter maximum to minimum in relation to the minimal diameter in diastole divided by the central pulse pressure obtained by pulse wave analysis [17]. Coefficient of variation for carotid artery distensibility has previously been estimated to 20% in this cohort [17].

2.5. Echocardiography and doppler

A two-dimensional doppler echocardiography was performed with an Acuson XP124 cardiac ultrasound unit (Acuson, Los Angeles, CA, USA) A 2.5-MHz transducer was used for the majority of the two-dimensional, M-mode and doppler examinations. This investigation was carried out in 97% of the participants. The presence of stenosis or regurgitations in the mitral and aortic valves was recorded by use of color and continuous doppler. Left ventricular dimensions were measured with the M-mode online from the parasternal projections, using the leading-edge to leading-edge convention. Measurements included left ventricular diameters in end-diastole and end-systole. The left ventricular volumes in end-diastole and end-systole were calculated according to the Teichholz formula ($7\times D^3/[2.4 + D]$) and from that the ejection fraction and stroke volume (SV) were calculated. The SV/PP ratio was calculated as the SV divided by the central pulse pressure (PP, achieved by pulse wave analysis, see below) [17].

2.6. Intra-arterial blood pressure analysis

Invasive blood pressure was measured intra-arterially by a standard pressure transducer in the brachial artery with the arm placed at the heart level. The pressure given was the mean of all continuous sampled recordings during 5 min of controlled breathing (12 breaths/min). The intra-arterial blood pressure recordings were obtained by a catheter (20 G/1·10 × 45 mm) connected to a pressure tube (150 mm) and a transducer (DTX Plus