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ORIGINAL ARTICLE

Correlation between plasma calcium, parathyroid hormone (PTH) and the metabolic syndrome (MetS) in a community-based cohort of men and women

Tommy Ahlström*,‡, Emil Hagström*, Anders Larsson†, Claes Rudberg*,‡, Lars Lind† and Per Hellman*

*Department of Surgical Sciences, †Department of Medical Sciences, University Hospital, Uppsala and ‡Department of Surgery, Central Hospital, Västerås, Sweden

Summary

Context In recent years, an association has been noted between several abnormalities that characterize the metabolic syndrome (MetS) and primary hyperparathyroidism (pHPT). These abnormalities include dyslipidaemia, obesity, insulin resistance and hypertension. The correlations between plasma calcium, parathyroid hormone (PTH) and the variables in the MetS in a normal population are still unclear.

Objective To describe correlations between plasma calcium and PTH and the various abnormalities present in the MetS in a healthy population.

Design We studied 1016 healthy individuals from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) population of 70 years old, by means of plasma analyses of calcium, PTH, creatinine, lipids, insulin and glucose, as well as by standardized blood pressure measurements. Further, body mass index (BMI) and waist circumference were determined.

Results The more National Cholesterol Education Program (NCEP) criteria for the MetS that were met, the higher the s-PTH and albumin-corrected s-calcium. Further, positive correlations between plasma calcium and BMI ($P = 0{\cdot}0003$), waist circumference ($P = 0{\cdot}0009$) and insulin resistance ($P = 0{\cdot}079$) were found. PTH and BMI ($P < 0{\cdot}0001$), waist circumference ($P < 0{\cdot}0001$), systolic blood pressure ($P = 0{\cdot}0034$), diastolic blood pressure ($P = 0{\cdot}0008$), serum triglycerides ($P = 0{\cdot}0003$) and insulin resistance ($P = 0{\cdot}0003$) were positively correlated, whereas serum high density lipoproteins (HDL) ($P = 0{\cdot}036$) and PTH were negatively correlated.

Conclusions We conclude that PTH correlates with several of the metabolic factors included in the MetS within a normocalcaemic population. In addition, individuals with mild pHPT present significantly more NCEP criteria for MetS. We postulate that increased levels of PTH in pHPT may be associated with the increased cardiovascular morbidity and mortality seen in pHPT.

Correspondence: Per Hellman, Department of Surgery, University Hospital, SE-751 85 Uppsala, Sweden. Fax: +46 18 504414; Tel: +46 18 6114617; E-mail: per.hellman@surgsci.uu.se

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Introduction

Primary hyperparathyroidism (pHPT) is a common disease prevalent in approximately 1–2% of the population and is the highest in postmenopausal women.[1,2] Investigations in recent years have noted the presence of so-called nonclassical features of this disease, some of them possibly related to the higher morbidity and mortality in cardiovascular diseases documented previously.[3–5] These abnormalities include dyslipidaemia, obesity, hypertension and insulin resistance,[6,7] which are also present in the metabolic syndrome (MetS). MetS is characterized by a clustering of cardiovascular risk factors such as abdominal obesity, elevated blood pressure, atherogenic dyslipidaemia, insulin resistance and glucose intolerance. MetS is most often diagnosed using criteria from the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP), and the presence of MetS is associated with an increased risk of cardiovascular morbidity and mortality.[8] Previous reports of pHPT have suggested that common mechanisms are responsible for the development of cardiovascular disease in pHPT and the MetS, but no studies have scrutinized these variables in detail, or the eventual association between the two entities. We postulate that MetS is associated with disturbances in plasma calcium and parathyroid hormone (PTH), and that increased levels of these substances are found in conjunction with NCEP criteria. For this purpose, we utilized a thoroughly characterized, healthy population of 70-year old men and women with no clinical signs of pHPT, but of an age similar to the approximate peak age of pHPT.

The aim of this study is to investigate correlations between the parameters for MetS and plasma calcium and PTH. As a secondary aim, we also investigated the relationship between plasma calcium and PTH and insulin sensitivity, as measured by homeostasis model assessment (HOMA).

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Patients and methods

Patients

The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study was initiated in 2001, with the primary aim of investigating the predictive power of different measurements of endothelial function and arterial compliance in a random sample of 1000 subjects aged 70, living in the community of Uppsala, Sweden. All men and women aged 70, living in the community of Uppsala, Sweden, were eligible for inclusion. The subjects were chosen from the community register and were invited at random. The subjects received a written invitation within 2 months of their 70th birthday. Subject selection for the study was completed in June 2004, and comprised 1016 subjects (507 males and 509 females). Of the 2025 subjects invited, 1016 subjects accepted, giving a participation rate of 50·1%. The study was approved by the Ethics Committee of the University of Uppsala and the participants gave informed consent. None of the individuals included had been operated on for pHPT, none was on surveillance for nonoperated pHPT and none was taking calcium or vitamin D supplementation for any reason.

Clinical and biochemical investigation

All plasma samples were collected in the morning after an overnight fast. No medication or smoking was allowed after midnight. After recording height, weight and abdominal and hip circumference, an arterial cannula was inserted in the brachial artery for blood sampling. The arterial cannula was also used for investigations of endothelial regulation not included in the present study. The subjects were supine in a quiet room maintained at a constant temperature, and blood pressure was measured by a calibrated mercury sphygmomanometer in the noncannulated arm to the nearest mmHg after at least 30 min of rest. The average of three recordings was used.

Body mass index (BMI) was calculated as body weight/(body height)^2 (kg/m^2). Standing height was measured to the nearest whole 0·5 cm with a Harpender Stadiometer (Holtain Ltd, Crymych, UK) and body weight to the nearest 0·1 kg. Waist circumferences were measured in a standing position midway between the lowest rib and the iliac crest.

Laboratory investigations were performed as follows:

Plasma calcium (normal range 2·20–2·50 mmol/l) was measured spectrophotometrically with a complexiметric method using ortho-cresolphthalein dye binding. Plasma albumin was measured with spectrophotometry using bromine cresol purple (normal range 37–48 g/l). Albumin-corrected plasma calcium was calculated as [plasma calcium + 0·019 × (42 − plasma albumin)]. Intact plasma PTH (normal range 12–65 ng/l) was determined with an immunochemiluminometric assay (Nichol's Institute, San Juan Capistrano, CA, USA). Plasma creatinine was analysed with spectrophotometry using a modified Jaffe's reaction (normal range 60–106 μmol/l). Creatinine clearance (normal range in men 97–137 ml/min and in women 88–128 ml/min) was calculated using the Cockcroft–Gault formula; for men ≥20 years, creatinine clearance = [1·23 × (140 − age) × weight]/S-creatinine, and for women ≥20 years, creatinine clearance = [1·04 × (140 − age) × weight]/S-creatinine.[9] Plasma phosphate was determined with spectrophotometry and a complexiметric method with ammonium molybdenum (normal range 0·74–1·54 mmol/l). Plasma glucose was analysed with the hexokinase method (normal range 3·3–5·7 mmol/l). Plasma insulin was assayed by using chemiluminescence (Roche, Basel, Switzerland). High sensitivity C-reactive protein was measured with a turbidimetric method (normal range <10 mg/l). Fasting total plasma cholesterol (normal range 2·6–7·1 mmol/l), plasma HDL-cholesterol (normal range 0·8–1·9 mmol/l) and plasma triglycerides (normal range 0·23–1·70 mmol/l) were determined in an enzymatic assay. Low density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula. This formula was not applied in the three subjects with serum triglycerides >4·0 mmol/l. The instrument used for biochemical analysis was an Architect (Abbott, Abbot Park, IL, USA) unless otherwise stated.

Diabetes mellitus was defined as a fasting plasma glucose ≥7·0 mmol/l and impaired fasting glucose (IFG) as fasting glucose between 6·1 and 6·9 mmol/l.

MetS was defined if three or more of the following were present: fasting plasma glucose ≥6·1 mmol/l, waist circumference >102 cm in males and >88 cm in females, blood pressure ≥130/85 mmHg, total triglycerides ≥1·7 mmol/l, HDL-cholesterol <1·04 mmol/l in men and <1·3 mmol/l in women, or the presence of pharmacological treatment for hypertension, dyslipidaemia or diabetes mellitus. BMI >25 was regarded as overweight and BMI >30 as obesity.[8]

Insulin sensitivity was determined with the HOMA [fasting glucose] × [fasting insulin]/22·5.[10,11]

Statistical analysis

All statistical analyses were defined *a priori*. Where necessary, logarithmic transformation was done to achieve normal distribution. $P < 0·05$ was regarded as significant and two-tailed 95% confidence intervals (CI) were applied. Odds ratio, multiple linear regression and ANOVA were used, and adjustments for gender and creatinine clearance were also made. The STATVIEW 5.0.1.0 statistical software package (SAS Institute, Cary, NC, USA) was used. Data are presented as mean ± SEM.

Results

The baseline characteristics of the individuals in the study, all of whom were 70 years old, can be seen in Table 1. Out of the 1016 individuals, 116 had albumin-corrected plasma calcium above 2·50 mmol/l and 149 had PTH levels above 65 ng/l. Sixty-one subjects had concomitantly increased plasma calcium (>2·50 mmol/l) and PTH (>40 ng/l), indicating possible signs of mild pHPT. The analyses were performed on all individuals, as well as after excluding those with signs of mild pHPT. The 61 individuals with signs of pHPT had a mean s-calcium of 2·61 ± 0·02 mmol/l (range 2·51–3·27 mmol/l), and a mean PTH of 62·4 ± 3·8 ng/l (range 41·5–206·6 ng/l). Overall, 92 individuals had elevated plasma creatinine, but only 12 of them had signs of hyperparathyroidism. Of all, only

Table 1. Baseline characteristics for mineral metabolism

Variable	Mean ± SD
Age (years)	70 ± 0
C-reactive protein	3·16 ± 4·74
Plasma calcium (mmol/l)	2·36 ± 0·13
Plasma albumin (g/l)	40·34 ± 2·73
Albumin-corrected calcium (mmol/l)	2·39 ± 0·13
Plasma PTH (ng/l)	46·86 ± 21·00
Plasma creatinine (μmol/l)	80 ± 19
Creatinine clearance (ml/min)	80 ± 22
Plasma phosphate (mmol/l)	1·10 ± 0·17
Plasma magnesium (mmol/l)	0·82 ± 0·07

SD, standard deviation.

five individuals had plasma phosphate above 1·54 mmol/l, and none of them had elevated plasma creatinine. Characteristics associated with the MetS are depicted in Table 2. Sixty-two individuals were medicated with oral anti-diabetic drugs, and 15 of them also had insulin treatment. One individual was medicated with insulin only. Altogether, 77 patients were diagnosed with diabetes mellitus (types I and II) and 51 had IFG.

Medication for hypertension was found in 325 individuals, whereas 829 (82%) of the 1016 had an increased systolic blood pressure at or above 130 mmHg, and 276 (27%) had a diastolic blood pressure at or above 85 mmHg. Medication to reduce plasma serum lipids was found in 158 (16%) individuals.

The MetS could be identified in 234 individuals (23%), with three or more of the criteria present. The most prevalent criterion was elevated blood pressure (in 97% of individuals classified with MetS), followed by increased waist circumference (80%). The study revealed a positive, but not statistically significant correlation between plasma PTH levels and the number of variables associated with MetS (Fig. 1). A tendency towards a positive correlation between albumin-corrected plasma calcium and the number of positive NCEP criteria was also demonstrated (Fig. 2). When comparing the 61 individuals with signs of mild pHPT to the remainder

Table 2. Values of parameters involved in the metabolic syndrome in the 1016 individuals from the PIVUS study

Variable	Mean ± SD
Body mass index (kg/m^2)	27·0 ± 4·3
Fasting plasma glucose (mmol/l)	5·34 ± 1·61
Waist circumference (cm)	
Men	94·7 ± 10·5
Women	87·6 ± 11·6
Blood pressure (mmHg)	
Systolic	149 ± 23
Diastolic	79 ± 10
Triglycerides (mmol/l)	1·28 ± 0·60
HDL-cholesterol (mmol/l)	
Men	1·36 ± 0·37
Women	1·66 ± 0·43

SD, standard deviation.

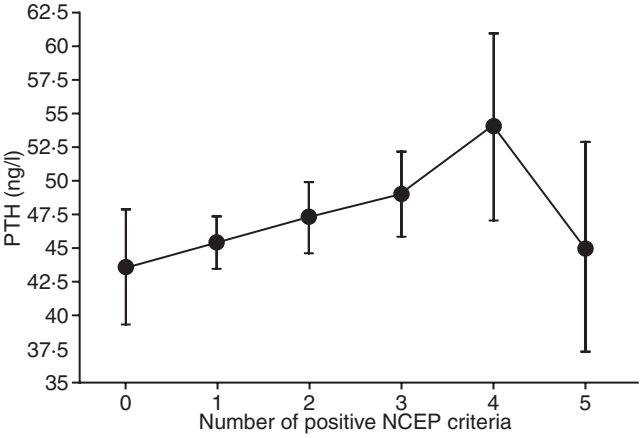

Fig. 1 ANOVA interaction graph with 95% confidence intervals between PTH and NCEP totals. The column showing five NCEP criteria is an anomaly, possibly because of the low number of observations (n = 15).

of the cohort, it was found that the pHPT patients were at a significantly increased risk of expressing three or more NCEP criteria (odds ratio 2·30 ± 0·27; 95% CI limits: 1·34–3·93).

Multivariable linear regression models, adjusted for gender and renal function, revealed significant positive correlations between plasma PTH and signs of overweight such as waist circumference and BMI. Moreover, plasma PTH correlated significantly and positively with several other parameters associated with cardiovascular disease such as systolic and diastolic blood pressure measured manually, plasma triglycerides and HOMA of insulin sensitivity. Excluding the individuals with signs of mild pHPT, as described above, did not alter these significant correlations (Table 3). In addition, there was a negative correlation in all individuals between plasma PTH and plasma HDL-cholesterol, which disappeared when excluding the mild pHPT individuals (Table 3). We also excluded individuals with antihypertensive and/or lipid-lowering agents from additional analyses, but could not detect any significant changes in any of the variables when comparing them with the original cohort. Plasma calcium correlated positively with BMI,

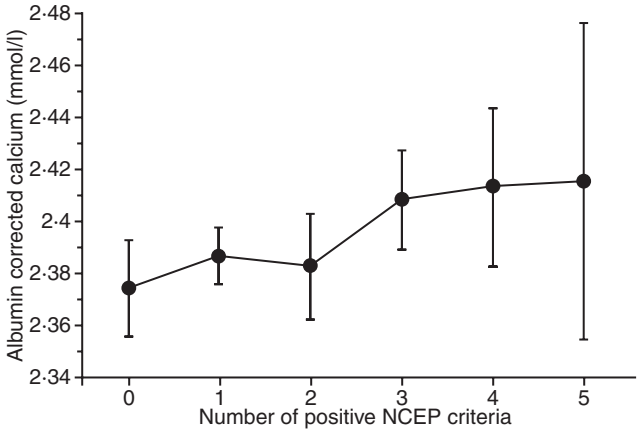

Fig. 2 ANOVA interaction graph with 95% confidence intervals between albumin-corrected plasma calcium and NCEP criteria totals.

Table 3. Multiple linear regression test of albumin-corrected plasma calcium and plasma PTH against factors included in the metabolic syndrome and insulin resistance

	Albumin-corrected plasma calcium		Plasma PTH	
	r	*P*	*r*	*P*
All individuals (n =1016)				
Fasting glucose	0·059	0·069	−0·010	0·753
Waist circumference	0·088	0·0009	0·151	<0·0001
Systolic blood pressure	0·054	0·091	0·093	0·0034
Diastolic blood pressure	0·014	0·672	0·107	0·0008
Triglycerides	0·054	0·0995	0·115	0·0003
HDL	0·024	0·434	−0·062	0·036
BMI	0·102	0·0003	0·152	<0·0001
HOMA of insulin sensitivity	0·079	0·024	0·126	0·0003
Excluding individuals with mild pHPT (n = 955)				
Fasting glucose	0·049	0·154	−0·012	0·725
Waist circumference	0·083	0·0028	0·164	<0·0001
Systolic blood pressure	0·079	0·0184	0·120	0·0003
Diastolic blood pressure	0·041	0·2263	0·132	<0·0001
Triglycerides	0·059	0·0807	0·114	0·0007
HDL	0·070	0·0268	−0·028	0·3604
BMI	0·101	0·0005	0·168	<0·0001
HOMA of insulin sensitivity	0·077	0·0383	0·146	<0·0001

The values are adjusted for gender and creatinine clearance.

waist circumference and HOMA, but not with plasma HDL-cholesterol, plasma triglycerides or blood pressure. However, after excluding patients with mild pHPT, albumin-corrected calcium correlated positively with plasma HDL (Table 3).

Discussion

The aim of this study was to identify potential correlations between calcium and/or PTH and the parameters of the MetS, because these are surrogate variables for the increased risk of cardiovascular disease. The study demonstrates that plasma PTH is associated with several parameters involved in the MetS, and that there is a somewhat weaker association between plasma calcium and these criteria. Our findings support the hypothesis that plasma PTH rather than plasma calcium is an explanation for the association between primary HPT and the increased risk for cardiovascular diseases.[12–15] This study further demonstrates an association between having MetS and having abnormal plasma PTH and calcium levels, although the findings fall short of being statistically significant. On the contrary, patients expressing signs of mild pHPT have a significantly higher risk of meeting at least three of the NCEP criteria for MetS.

Fasting glucose was not associated with plasma calcium or plasma PTH. However, an earlier sign of disturbed glucose-insulin metabolism, namely decreased insulin sensitivity, correlated with both key variables in the calcium homeostasis system. Studies have previously noted associations between plasma PTH, plasma calcium and insulin sensitivity.[16–18] In one of these studies, an earlier study performed in our group, decreasing insulin sensitivity was associated with increasing plasma calcium, when assessed with hyperinsulinaemic euglycaemic clamp[18] in a population of 70-year old men (the Uppsala Longitudinal Study of Adult Men, ULSAM). The mechanisms behind the relationship between PTH, plasma calcium and insulin resistance are unclear. A correlation between intracellular calcium affected by PTH and insulin resistance has been proposed in earlier studies.[19,20]

Plasma PTH was associated with both the systolic and the diastolic blood pressures in our cohort, whereas plasma calcium was not. These results are supported by earlier findings that describe a clear connection between PTH and blood pressure.[12,21]. However, other authors have also documented a correlation between plasma calcium and blood pressure.[22]

The underlying mechanisms explaining the relationship between PTH and blood pressure are not completely understood, but PTH seems to have a proliferative effect on vascular smooth muscle cells,[23] possibly contributing to vessel wall thickening. PTH also activates the renal enzyme 1-α-hydroxylase, which adds a hydroxyl group to the vitamin D precursor 25-OH-cholecalciferol, leading to the formation of active vitamin D, 1·25-dihydroxy cholecalciferol. It has also been suggested that when serum active vitamin D is elevated, this increases vascular smooth muscle intracellular calcium, which results in contraction and increased peripheral vascular resistance.[24,25] Indeed, individuals with pHPT and high plasma PTH may have high levels of active vitamin D in serum.[26]

Plasma PTH also correlated significantly with plasma triglycerides and HDL-cholesterol. This supports earlier findings from our own group based on populations with primary HPT.[27] Thus, correlations between plasma PTH and plasma triglycerides and HDL-cholesterol were seen in both the previous and the current study. As noted above, calcium does not correlate with the serum lipids in this study. Waist circumference and BMI correlated significantly with plasma PTH and plasma calcium in our cohort. This is in

accordance with other studies where being overweight is more prevalent in those with pHPT than in the normal population.[27] The underlying mechanisms of the effects of calcium and PTH on serum lipids and adipose tissue are more or less unknown. However, hypotheses that have been presented include the effect of PTH on lipolysis, either leading to increased secretion of triglycerides or impeding catecholamine-induced lipolysis.[29–32] Some of these suggestions are contradictory.

Thus, we can demonstrate correlations between plasma PTH and several of the variables included in the MetS. Earlier studies have demonstrated a connection between the mineral metabolism abnormalities seen in pHPT, with one variable of MetS at a time.[7,27,28,33] This study now demonstrates that in a 70-year old normocalcaemic population, the same associations are strongly correlated with plasma PTH, but not with plasma calcium. Although not significant at the 95% level, the more MetS criteria that are met, the higher the plasma PTH. It is presumed that plasma calcium is regulated in a variety of ways including mechanisms in the kidney. On the contrary, PTH, which is tightly regulated by plasma calcium and vitamin D, may not be affected as much as plasma calcium because of individual variations in basal PTH secretion. Our results imply that PTH may be one causative factor for the abnormalities seen in the MetS, or may at least be associated with other hitherto unknown changes co-varying with plasma PTH. The fact that the mild pHPT patients have a significantly higher risk of meeting three or more NCEP criteria supports our hypothesis. Indeed, lowering plasma PTH by parathyroidectomy in pHPT normalizes several of the abnormal variables such as serum triglycerides and HDL-cholesterol as well as insulin resistance.[27,34] Abnormalities involved in the MetS have also been seen in normocalcaemic pHPT patients with elevated PTH.[6]

The increased risk of cardiovascular mortality and morbidity in pHPT is well documented in epidemiological studies.[3,16,35–37]

Plausible explanations of the mechanisms behind this risk have been reported previously. These include findings of dyslipidaemia, hypertension and endothelial disturbances. The study of this particular cohort consolidates the hypothesis that there is an association between the metabolic syndrome and plasma parathyroid hormone, and potentially pHPT. Several mechanisms may lead to the metabolic syndrome, where higher concentrations of plasma parathyroid hormone and plasma calcium levels similar to those seen in primary hyperparathyroidism have an increased effect on the mechanisms leading to the abnormalities being studied. The result is a condition similar – or equal – to the metabolic syndrome, which has been well documented in scientific literature to be associated with increased cardiovascular morbidity and mortality.

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Competing interests/financial disclosure

Nothing to declare.

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