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PTH: A NEW TARGET IN ARTERIOSCLEROSIS?

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Context: Growing evidence demonstrates that hyperparathyroidism is associated with an increased risk of cardiovascular morbidity and mortality. However, little is known about the relation between serum PTH levels within the normal range and cardiovascular diseases (CVD).

Objective: In this study the relation of serum PTH levels within the normal range with CVD and abdominal aortic calcifications (AAC) was investigated.

Design: A cross-sectional population-based study was performed using data of the Longitudinal Aging Study Amsterdam (LASA), including 558 men and 537 women, aged 65–88 years. Models were controlled for sex, age, body mass index, hypertension, diabetes mellitus, high-density lipoprotein cholesterol, total cholesterol, smoking, physical activity, alcohol consumption, glomerular filtration rate, season of blood collection, calcium or diuretic use, serum 25-hydroxyvitamin D and osteocalcin when these variables were found to be relevant confounders.

Results: Multivariate models showed that subjects in the highest quintile of serum PTH had a significantly higher risk of CVD as compared to subjects in the lowest quintile (OR = 2.22, CI = 1.39–3.56). The relation between PTH and AAC was observed only in men, which remained significant after adjusting for confounding (OR = 4.03, CI= 1.50–10.83).

Conclusions: This study demonstrated that in older persons the presence of serum PTH levels within the upper normal range is highly related to CVD. In men, this association may partly be explained by calcifications of the abdominal aorta. Since CVD poses an important health risk, further elucidation of the role of serum PTH in CVD and arteriosclerosis is relevant.

Parathyroid hormone (PTH) is known to be one of the key regulatory hormones of mineral homeostasis and bone metabolism. In addition, hyperparathyroidism has been reported to be associated with cardiovascular mortality and cardiovascular morbidity (1). Besides atherosclerosis (2), valve and cardiac calcifications, hyperparathyroidism has been linked with cardiomyopathy, arrhythmia and myocardial hypertrophy (3). It is suggested that PTH has a direct influence on atherogenesis via vascular remodelling and vascular calcification (4), which is supported by an in vitro study that demonstrated a prosclerotic effect of PTH on vascular smooth muscle cells (VSM) (5). In addition to this direct involvement, hyperparathyroidism may have an indirect effect on CVD, due to its presumed positive relation with hypertension (6–8). However, not all studies were conclusive (9). Although less likely an acute increase in PTH may be characterized by vasodilatation at first which could have contributed to this conflicting results (10).

Currently, little is known about the relation between serum PTH and CVD when levels of serum PTH are within the normal range. Interestingly, two observational studies

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suggest a possible adverse effect on CVD (11, 12). However, not all confounders were taken into account and one study included only men. Moreover, three studies about the relation between serum PTH and atherosclerosis showed conflicting results while not all serum PTH levels were within the normal range (9, 13, 14).

Our hypothesis is that not only hyperparathyroidism but also serum PTH in the upper normal range may promote arteriosclerosis and thereby the risk of CVD, which may partly be explained by a direct relation of PTH to aortic calcifications. Therefore, the aim of this study was to investigate the relationship between serum PTH levels within the normal range and CVD, as well as abdominal aortic calcifications (AAC), taking into account several important confounders of CVD. An increasing amount of studies suggest that vitamin D deficiency may be directly involved in the pathogenesis of CVD (15), although some of the results are contradictory. Due to the close relationship between PTH and serum 25(OH)D, the question remains whether in this studied group, serum 25(OH)D has an additional PTH dependent or independent relation to CVD. Therefore, the relation of serum 25(OH)D with CVD, as well as AAC, was investigated separately. The study was performed in a representative sample of the Dutch older population with serum PTH levels within the normal range.

Materials and Methods

Subjects

Data for this study were collected within the Longitudinal Aging Study Amsterdam (LASA).

LASA is an ongoing cohort study on predictors and consequences in physical, cognitive, emotional and social functioning in older persons in the Netherlands (predominantly Causasian). A sample of older men and women (aged 55–84 y), stratified for age, sex, and expected 5 y mortality, was drawn from the population registry of 11 municipalities in areas in the west, northeast, and south of the Netherlands. The sample represents the older Dutch population with respect to geographic region and degree of urbanization. The sampling and data collection procedures have been described elsewhere (16). In total, 3107 persons took part in the baseline examination (1992/1993). Nonresponse was related to age ($P < .001$), the oldest persons being less likely to participate.

In the present study analyses were performed in the group of participants who took part in the medical interview in the first follow-up (1995–1996) and who were born in 1930 or earlier (n = 1509). Blood samples were available for 1352 persons. We excluded participants with hyperparathyroidism (PTH > 7) (n = 59), using vitamin D supplements (n = 18), bisphosphonates (n = 18), estrogens (n = 15), statins (n = 68) and participants with missing data (serum PTH, serum 25(OH)D and/or CVD) (n = 236). As a result, our study sample consisted of 1095 participants.

Additional analyses on the relationship between serum PTH and AAC were performed in a subgroup (1995/1996), which consisted of participants from Amsterdam and vicinity, who participated in a study on the consequences of vertebral deformities in older men and women (n = 535). Valid lateral radiographs of the lumbar spine were obtained in 527 of these participants, from which the presence and severity of the AAC was assessed. Due to overor under exposure or not showing the complete aorta between the vertebrae L1 up to L4, we excluded 132 participants. The posterior-anterior scores were analyzed by two persons. In this subgroup exclusion criteria were hyperparathyroidism (PTH > 7.0) (n = 13), the use of vitamin D supplements (n = 4), bisphosphonates (n = 5), estrogens (n = 3), statins (n = 24) and participants with missing data (serum PTH, serum 25(OH)D, CVD and/or AAC) (n = 32). As a result, this subgroup consisted of 314 participants.

Informed consent was obtained from all respondents. The study was approved by the medical Ethics Committee (VU University Medical Center) and conducted according to the principles of the Helsinki declaration.

Measurements

Parathyroid Hormone (PTH). Blood samples were collected in 1995 and 1996 after an overnight fast. The participants were allowed to have tea and toast, but no dairy products. The serum samples were centrifuged and stored at –20°C. Serum PTH concentrations were determined in 1997 and 1998 using an immunoradiometric assay (IRMA) (Incstar Corp., Stillwater, MN, USA). Interassay variation was < 12% at all levels.

25(OH) vitamin D. Serum 25(OH)D was measured using a competitive protein binding assay in 1997/1998 (Nichols Diagnostics, San Juan Capistrano, CA, USA). The interassay coefficient of variation was 11% on average levels of 27 nmol/l and 141 nmol/l.

Abdominal aortic calcification (AAC). To determine the extent of abdominal aortic calcification, a semi quantitative grading system developed by Kaupilla et al. was used, that is described in detail elsewhere (17). Calcium deposits in both the anterior and posterior wall of the aorta parallel to vertebra L1 up to L4 on lateral abdominal radiographs are visualized as scattered or linear areas of high density. These calcium lesions are scored on a 0–3 scale for each area parallel to the mentioned vertebra and separately for both the anterior and posterior wall. The calcium lesions are graded as follows: 0, no aortic calcium deposits; 1, small scattered calcium deposits filling less than 1/3 of the longitudinal wall of the aorta; 2, 1/3 - 2/3 of the longitudinal wall of the aorta calcified; 3, > 2/3 of the longitudinal wall of the aorta calcified. This gives eight wall and segment specific scores which are then summed to yield a Posterior-anterior score (PAS) between 0 and 24 for each subject. All radiographs were viewed by observers with no knowledge of the corresponding blood levels or clinical status. The reproducibility and validity of this method have been previously described and were not retested for this study (17).

Cardiovascular diseases (CVD). Cardiovascular diseases were assessed with a detailed questionnaire on self-reported chronic diseases. When a respondent reported a chronic disease to be present, branching questions concerning the specific disease

were asked. Pertinent medical history questions (questions that physicians use to get an impression of disease-severity) were selected in close cooperation with general practitioners with expert knowledge on the specific chronic diseases (www.lasa.nl). We used the information on heart diseases and peripheral arterial diseases. To be classified as CVD, suffering from either one was taken as sufficient condition in the analyses.

Potential Confounders

As potential confounders were considered sex, age, body mass index (BMI), diabetes mellitus (self-reported and/ or use of antidiabetic medicine), hypertension (diastolic > 90 mmHg, systolic > 140 mmHg and/ or use of antihypertensives), high-density lipoprotein cholesterol (HDL-C), total cholesterol, glomerular filtration rate (GFR), smoking (never, former, current smoker), alcohol use (no, light, moderate, excessive), diuretic use, season of blood collection, use of calcium tablets and osteocalcin. In multivariate models, the relation between serum PTH and CVD was adjusted for serum 25(OH)D levels and the relation between serum 25(OH)D and CVD for serum PTH levels.

The baseline information on age and sex was derived from the municipal registries. Body weight was measured without clothes and without shoes using a calibrated (18) bathroom scale. Height was measured using a stadiometer. BMI was calculated as weight (kg) divided by the square of height (m^2). Alcohol consumption, current smoking status and the presence of chronic diseases like diabetes were assessed in a face-to face medical interview. The alcohol consumption was classified by the Garretsen index (18). To obtain information on medication use, the respondent had to show all medication he/she used at the moment of the interview. Blood pressure (mmHg) was measured after 5 min of rest at the upper left arm with subjects in a lying position, using an oscillometric blood pressure (BP) monitor (model HEM-706; Omron Corporation, Tokyo, Japan). Glomerular filtration rate was calculated using the Cockcroft formula (19). Serum total cholesterol was determined by an enzymatic colorimetric test (Roche diagnostics, Mannheim, Germany). Serum creatinine levels were measured using the Jaffe alkaline picrate reaction with a Hitachi 747 analyzer. Serum levels of osteocalcin were measured using an IRMA (Biosource, Medgenix Diagnostics, Fleurus, Belgium) with an interassay variation of < 8% at all levels. The analyses were carried out at the Clinical Chemistry Laboratory and Endocrine Laboratory of the VU University Medical Center, Amsterdam.

Statistical analysis

Binary logistic regression models were performed to examine the associations between serum PTH and serum 25(OH)D levels with CVD. In additional analysis, ordinal regression models were performed to determine the relation between serum PTH and serum 25(OH)D levels with AAC. Serum PTH and serum 25(OH)D levels were divided into quintiles, using the lowest quintile of serum PTH and the highest quintile of serum 25(OH)D as reference value. AAC was divided into quartiles. The association between CVD and AAC was assessed by binary logistic regression models.

All models were fully adjusted for relevant confounders. Variables that, after inclusion in univariable models, showed an association with a P-value smaller than 0.20, were included as relevant confounder in the final model.

Because regression models showed a significant interaction effect between serum PTH and sex in the relationship between serum PTH and AAC ($P = .01$), men and women were analyzed separately in these models. Outcomes were considered statistically significant when two-tailed values for p were < 0.05. Analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics

Table 1 shows subjects' descriptive characteristics. In total, 5.4% (n = 32) of the men and 4.8% (n = 27) of the women had hyperparathyroidism (serum PTH > 7.0 pmol/L). These participants were excluded. The mean age of the participants in this study was 75.3 ± 6.6 y. There were no significant differences between levels of serum PTH in men and women (both 3.3 pmol/L). Cardiovascular diseases were found in 36.7% of the men and in 25.1% of the women. Severe vitamin D deficiency, using the proposed definition of a serum concentration less than 25 nmol/L, was observed for 6.5% of the men and 12.8% of the women. In the subgroup calcifications of the abdominal aorta were measured. Aorta calcifications (PAS ≥ 1) were found in 73.1% of the men and 68.8% of the women. There were no significant difference between the mean age, serum PTH levels and the number of cardiovascular diseases between the participants in the total study population and the subpopulation (data not shown).

Relation between PTH and 25(OH)D levels with cardiovascular diseases (CVD)

Subjects in the highest quintile of serum PTH (4.4–7 pmol/L) had a higher risk of CVD as compared to subjects in the lowest quintile, which remained significant after adjustment for confounding (OR = 2.22, CI = 1.39–3.56) (Table 2 and Figure 1).

Subjects in the lowest quintile of serum 25(OH)D (<34 nmol/L) had a significantly higher risk of CVD as compared to men and women in the highest quintile (OR = 1.7, CI = 1.14–2.55). After adjustment for serum PTH and other confounders, the association disappeared (fully adjusted without serum PTH: OR = 1.49, CI = 0.93–2.40, fully adjusted with serum PTH: OR = 1.21 CI = 0.73–1.99) (Table 2).

Relation between PTH and 25(OH)D levels with abdominal aortic calcifications (AAC)

Because regression models showed a significant interaction effect between serum PTH and sex in the relationship between serum PTH and AAC ($P = .01$), men and women were analyzed separately. Multivariate ordinal re-

Table 1. Descriptive characteristics of the total study population and the subpopulation with abdominal aorta calcification (AAC) assessment

	Study population		Subpopulation with AAC assessment		
	Men	Women	Men	Women	P
N	558	537	160	154	
Age (years)	75.4 ± 6.5	75.2 ± 6.6	74.6 ± 6.3	73.4 ± 6.4	.85
BMI (kg/m^2)	26.1 ± 3.3	27.3 ± 4.3	25.6 ± 3.2	27.1 ± 4.2	0.00*
Posterior-anterior score	-	-	3.0 (0–8)	5.1 ± 5.3	.44
25(OH)D (nmol/liter)	58.9 ± 23.7	49.7 ± 22.9	53.1 ± 20.9	47.9 ± 19.8	0.02*
PTH (pmol/liter)	3.3 ± 1.3	3.3 ± 1.1	3.6 ± 1.1	3.4 ± 1.1	.73
Osteocalcin (nmol/liter)	1.8 (1.3–2.3)	2.2 (1.7–2.8)	1.8 (1.4–2.4)	2.4 (1.9–3.0)	0.00*
Total cholesterol(mmol/liter)	5.4 (4.8–5.9)	5.9 (5.2–6.5)	5.5 ± 1.0	5.9 ± 1.0	.55
HDL-cholesterol (mmol/liter)	1.15 (.94–1.4)	1.36 (1.1–1.7)	1.2 (1.1–1.5)	1.65 ± .41	0.00*
GFR ml/min/1.73 m2	63 (51–74)	58 ± 15	63.1 ± 15.1	60 ± 14.1	.27
Testosterone (nmol/liter)	15.2 ± 5.4	-	15.4 ± 5.2	-	
Smoking	24.9%	12.5%	23.1%	16.2%	.13
Former	64.9%	29.2%	62.5%	40.3%	0.00*
Never	10.2%	58.3%	14.4%	43.5%	0.00*
Alcohol: none	13.3%	32.8%	13.1%	24.0%	0.00*
Light	49.6%	52.0%	51.9%	55.8%	.14
Moderate	27.4%	12.7%	25.0%	18.2%	0.01
Excessive	9.7%	2.6%	10.0%	1.9%	0.00*
Physical activity (min/day)	119 (64–184)	163 (114–227)	125 (73–194)	169 (124–223)	0.00*
BP; systolic (mmHg)	152 ± 23	153 ± 24	151 ± 24	153 ± 25	.75
BP; diastolic (mmHg)	81 ± 12	81 ± 12	83 ± 13	82 (75–88)	.36
Pulse pressure (mmHg)	71 ± 17	73 ± 19	68 ± 17	71 ± 19	.26
Cardiovascular diseases	36.7%	25.1%	38.8%	24.6%	0.03*
Diabetes Mellitus	5.9%	8.4%	4.4%	7.8%	.20
Hypertension	64.6%	70%	63.1%	68.2%	.35

In normal distributions, the mean ± SD are reported; in skewed distributions the median (IQ range) are reported. Calcification, smoking, alcohol use and different diseases are presented as percentages of the total (%). P = the difference beetween men and women in the subpopulation calculated using the independent *t* test in normal distributions and the Mann-Whitney test in skewed distributions. The difference between calcification, smoking, alcohol use and different diseases between men and women in the subpopulation was calculated using the χ- square test. BMI = Bone mineral density, PTH = Parathyroid hormone, HDL-cholesterol = High-density lipoprotein cholesterol, GFR = Glomerular filtration rate, BP = blood pressure.

gression models showed that men in the highest quintile of serum PTH had a significantly higher risk of AAC compared to men in the lowest quintile of serum PTH (OR = 4.03, CI = 1.50–10.83) (Table 3 and Figure 1). No relation has been found in women between serum PTH and AAC (OR = 0.44, CI = 0.16–1.18). Between serum 25(OH)D and AAC no statistically significant associations have been found in men and women (data not shown).

Relation between CVD and AAC

A strong relation was found between CVD and AAC (OR = 2.70, CI = 1.37–5.31). After adjustment for confounding the relation remained significant (OR = 2.41, CI = 1.17–4.95) (data not shown).

Table 2. Relationship between serum PTH and serum 25(OH)D with cardiovascular disease (CVD)

	Quintiles of PTH (pmol/liter)					
	1 (<2.3)	2 (2.3–2.8)	3 (2.8–3.4)	4 (3.4–4.3)	5 (4.4–7)	P
CVD	1.0	1.11	1.42	1.38	2.01	0.00
Unadjusted		(.73–1.71)	(.94–2.16)	(.91–2.10)	(1.34–3.03)	
Fully adjusted*	1.0	1.16	1.68	1.66	2.22	0.00
		(.73–1.84)	(1.06–2.65)	(1.04–2.66)	(1.39–3.56)	
	Quintiles of 25(OH)D (nmol/liter)					
	1 (>73)	2 (58–73)	3 (46–58)	4 (34–46)	5 (<34)	P
CVD	1.0	1.25	1.01	1.23	1.70	0.01
Unadjusted		(.83–1.89)	(.66–1.54)	(.81–1.86)	(1.14–2.55)	
Fully	1.0	1.37	1.02	1.12	1.49	.10
adjusted**-PTH		(.88–2.14)	(.64–1.61)	(.71–1.78)	(.93–2.40)	
Fully	1.0	1.29	.92 (.58–1.48)	.99 (.62–1.59)	1.21	.46
adjusted**+PTH		(.83–2.03)			(.73–1.99)	

ORs and 95% CIs of having cardiovascular diseases by quintiles of serum PTH and serum 25(OH)D.

* Fully adjusted for relevant confounders ($P < 0.20$) include sex, age, serum 25(OH)D, hypertension, high- density lipoprotein cholesterol, total cholesterol, smoking, physical activity, glomerular filtration rate, season of blood collection, calcium use, diuretic use and osteocalcin.

** Fully adjusted for relevant confounders ($P < 0.20$) include sex, age, hypertension, high-density lipoprotein cholesterol, total cholesterol, smoking, physical activity, glomerular filtration rate, season of blood collection, calcium use, diuretic use and osteocalcin.

Discussion

Although the side effects of evident hyperparathyroidism are well known, the role of serum PTH levels just within the upper normal range is not clear. Some studies indicate a relation with the prevalence of CVD, although the studies differ and are contradictory. In this population based study of older persons, the serum PTH levels within the upper normal range appeared to be associated with an increased risk of CVD. In men, this association may partly be explained by a direct relation of PTH to calcifications of the abdominal aorta, while the presence of calcifications of any arterial wall is found to be associated with a 3–4-fold higher risk of cardiovascular events (20). Indirectly related effects of serum PTH, including hypertension, serum 25(OH)D, renal function and several other important confounders did not play a role in these associations. In addition, no relation was found between serum 25(OH)D levels and either CVD or calcifications of the abdominal aorta in the presence of normal serum PTH levels.

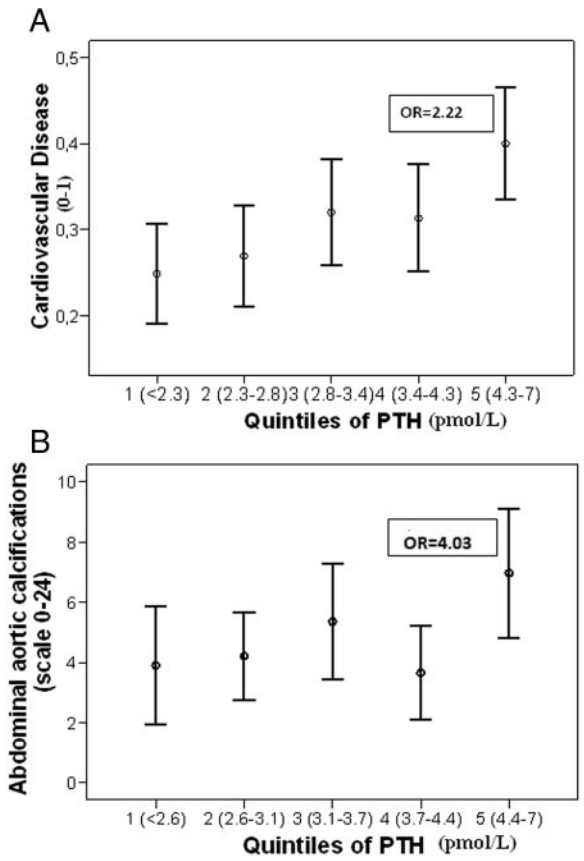

Figure 1. Association between PTH and CVD in the full sample (1A). Association between PTH and abdominal aortic calcifications (AAC) in men (1B).

This is the first study that investigated both the relation of serum PTH levels within the upper normal range with the risk of CVD and aorta calcifications in a large general older population. In the literature, a few studies support our results, of which the majority investigated the association between serum PTH levels within the normal range and cardiovascular mortality. Consistent with our results, a large community-based cohort study, among 868 older men with a mean age of 71 y, showed that serum PTH levels within the normal range (PTH: 5.27–6.8 pmol/L) predict cardiovascular mortality (11). After correcting for multiple confounders, including several risk factors for cardiovascular disease and factors associated with bone mineral metabolism, the relationship remained significant. A large study among 3232 Caucasian patients, who underwent coronary angiography, also showed that serum PTH levels are an independent risk factor for cardio-

Table 3. Relationship between serum PTH and abdominal aortic calcifications (AAC) in men and women

	Quintiles of PTH (pmol/liter)					
Men	1 (<2.6)	2 (2.6–3.1)	3 (3.1–3.7)	4 (3.7–4.4)	5 (4.4–7)	P
AAC	1.0	1.79	1.95	1.26	3.32	0.01
Unadjusted		(.74–4.32)	(.80–4.77)	(.52–3.06)	(1.35–8.17)	
Fully	1.0	2.97	2.50	1.49	4.03	0.01
adjusted*		(.78–4.94)	(.99–6.32)	(.58–3.81)	(1.5–10.83)	
	Quintiles of PTH (pmol/liter)					
Women	1 (<2.4)	2 (2.4–2.9)	3 (2.9–3.5)	4 (3.5–4.3)	5 (4.3–7)	P
AAC	1.0	.70 (.28–1.73)	.46 (.18–1.14)	.83 (.34–2.04)	.49 (.20–1.22)	.12
Unadjusted						
Fully	1.0	.65 (.25–1.71)	.51 (.19–1.36)	.77 (.30–2.00)	.44 (.16–1.18)	.10
adjusted**						

ORs and 95% CIs of having aortic calcifications by quintiles of serum PTH.

* Fully adjusted for relevant confounders ($P < 0.20$) in men include age, serum 25(OH)D, body mass index, total cholesterol, physical activity, alcohol consumption, glomerular filtration rate, diabetes mellitus and diuretic use.

** Fully adjusted for relevant confounders ($P < 0.20$) in women include age, serum 25(OH)D, hypertension, high-density lipoprotein cholesterol, total cholesterol, glomerular filtration rate and osteocalcin.

vascular mortality, even after adjustments for several common confounders (21). However, in this population coronary artery disease (CAD) was found in more than two-third (68.1%) of the subjects.

Several other studies, in which subjects with hyperparathyroidism were not excluded, support our results as well. The Tromsø Study, including 3212 subjects aged 25 to 79 y, showed that serum PTH levels within the highest quartile (> 3.5 pmol/L in men and 3.3 pmol/L in women) predicted coronary heart disease (CHD), versus serum PTH levels within the lowest quartile (12). Only subjects with serum calcium and creatinine levels within the reference ranges were included and several confounders were taken into account. Unfortunately serum 25(OH)D was not measured. Furthermore, in a 17 y follow up study it was shown that elevated serum PTH levels (≥ 63ng/L or ≥ 6.7 pmol/L) are associated with impaired long-term survival prognosis in several age cohorts (75, 80 and 85 y), although models were not corrected for vitamin D status (22). Another large study among 9369 subjects also found that hyperparathyroidism is associated with a greater prevalence and incidence of cardiovascular risk factors and with a greater likelihood of prevalent and incident disease, including mortality (23).

Other clinical studies have been focusing on the association between serum PTH levels and mortality in specific groups of patients only. In these studies subjects with hyperparathyroidism were not excluded. In a small prospective study among 148 outpatients with heart failure, both serum PTH and serum 25(OH)D levels were independently associated with all cause and cardiovascular mortality (24). In addition, two other studies reported that elevated serum PTH is a relatively independent predictor of mortality in frail bedridden elderly, living in care hospitals and nursing homes (25, 26).

Less is known about the relation between normal serum PTH levels and atherosclerosis. There is only one study among 107 postmenopausal women, recruited from an endocrinological outpatient clinic in Korea, showing that serum PTH levels within the reference range are an independent determinant of carotid intima-media thickness, which is known to reflect atherosclerosis (13). However, no association was found with carotid calcified plaque and it is not clear which confounders were taken into account. Thereby, conflicting results were found in two other studies in which subjects with hyperparathyroidism were not excluded (9, 14).

In our study, we found a significant relationship between serum PTH levels within the upper normal range and CVD in men and women. However, the relation between serum PTH levels and calcifications of the abdominal aorta was only found in men. The reason for the sex difference in this study is not clear. Maybe the number of women included in the subgroup where calcifications of the abdominal aorta were measured, was not large enough (n = 154). Secondly, the prevalence of CVD and aortic calcifications in our study was less in women compared to men. Recently, a direct and indirect effect of PTH induced aldosterone secretion was shown, which may be one of the factors underlying the relation between PTH with CVD (27). However, particularly in women circulating aldosterone levels are also independently related to echocardiographic parameters of LV structure, which could contribute to the different gender outcomes by masking the effect of PTH on aldosterone secretion (28). Furthermore, fibroblast growth factor-23 (FGF-23) has been correlated to ACC as well as to PTH in older men and could be another factor playing a role in the association between PTH and ACC. FGF-23 controls renal phosphate reabsorption and expression of renal 25-hydroxyvitmain D

1α-hydroxylase (29). Further studies are needed to elucidate the underlying mechanisms for our results.

There is increasing evidence that, in addition to the well-known effects on musculoskeletal health, vitamin D may also have various beneficial effects on the cardiovascular system, including antihypertensive, anti-inflammatory, antidiabetic and antiatherosclerotic actions (30). Several (31–34), but not all (35–38) epidemiological studies on this topic demonstrated that low levels of serum 25(OH)D are associated with cardiovascular events and cardiovascular mortality. In our study, no direct relationship between serum 25(OH)D and calcifications of the abdominal aorta was found. These findings may be influenced by the lack of very low serum 25(OH)D levels, or the inclusion of serum PTH levels within the normal range only. A large study among 1280 frail elderly demonstrated that subjects with vitamin D deficiency with low levels of serum PTH, so called functional hypoparathyroidism (FHPT), had a reduced mortality in follow-up, when compared with the subjects who manifested the physiological response of an elevated serum PTH in response to vitamin D deficiency (39). This indicates that the survival prognosis may at least partly be based on the harmful effects of elevated serum PTH than of the vitamin D deficiency only, which supports our results.

While the relationship between hyperparathyroidism and CVD has been known for decades, this is the first study demonstrating that serum PTH levels in the upper normal range (4.4–7 pmol/L) have a relationship with CVD and AAC as well, independent from serum 25(OH)D levels. The relation seems to be direct, as several confounders did not change the relationship. Thereby we excluded participants using vitamin D supplementation, statins, estrogens and bisphosphonates, while these drugs are found to influence serum PTH, 25(OH)D and calcium levels. Furthermore, we corrected our models for the use of diuretics (n = 158), because these drugs could induce calcium losses, which causes increased levels of serum PTH (40).

There are also limitations to our study. Lateral radiographs were used to determine the presence and severity of abdominal aortic calcification. This rough method did possibly not show all calcifications of the abdominal aorta on the radiographs. Secondly, in our study AAC was measured only in a relatively small subgroup of the LASA population, which may explain that we only found an association among men. Unfortunately we could not take along serum calcium, serum low density lipoprotein cholesterol (LDL-C) or serum triglyceride levels in our analyses, while these were only measured in a subgroup (n = 324) of our participants. When we repeated the analysis in this subgroup, neither was found to be a significant confounder (triglyceride: $P = .243$, LDL-C: $P = .520$ and calcium: $P = .841$) (data not shown). This finding is in line with the Helsinki Ageing Study showed that high serum PTH levels (serum PTH > 63 ng/l, IV quartile cut point) are associated with impaired long-term survival prognosis, independently of calcium levels (22). In addition, increased serum phosphorus levels may attribute to ACC, but no data were available. Due to its relation with chronic kidney disease, additional analyses were performed after excluding participants with a GFR < 30 mL/min/1.73 m^2 (n = 9), with no change in results (data not shown).

This study demonstrated that subjects with serum PTH levels within the upper normal range had an increased risk of CVD, independently of serum 25(OH)D, BP or other known confounders. In men, this association may partly be explained by a direct relation of PTH to calcifications of the abdominal aorta. No relation was found between serum 25(OH)D and CVD. Since CVD poses an important health risk, further elucidation of the role of serum PTH in CVD and arteriosclerosis is relevant.

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