

Cardiovascular diseases in older patients with osteoporotic hip fracture: prevalence, disturbances in mineral and bone metabolism, and bidirectional links

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Background: Considerable controversy exists regarding the contribution of mineral/bone metabolism abnormalities to the association between cardiovascular diseases (CVDs) and osteoporotic fractures.

Aims and methods: To determine the relationships between mineral/bone metabolism biomarkers and CVD in 746 older patients with hip fracture, clinical data were recorded and serum concentrations of parathyroid hormone (PTH), 25-hydroxyvitamin D, calcium, phosphate, magnesium, troponin I, parameters of bone turnover, and renal, liver, and thyroid functions were measured.

Results: CVDs were diagnosed in 472 (63.3%) patients. Vitamin D deficiency was similarly prevalent in patients with (78.0%) and without (82.1%) CVD. The CVD group had significantly higher mean PTH concentrations (7.6 vs 6.0 pmol/L, $P < 0.001$), a higher prevalence of secondary hyperparathyroidism (SPTH) (PTH > 6.8 pmol/L, 43.0% vs 23.3%, $P < 0.001$), and excess bone resorption (urinary deoxypyridinoline corrected by creatinine [DPD/Cr] > 7.5 nmol/ μ mol, 87.9% vs 74.8%, $P < 0.001$). In multivariate regression analysis, SHPT (odds ratio [OR] 2.6, $P = 0.007$) and high DPD/Cr (OR 2.8, $P = 0.016$) were independent indicators of CVD. Compared to those with both PTH and DPD/Cr in the normal range, multivariate-adjusted ORs for the presence of CVD were 17.3 ($P = 0.004$) in subjects with SHPT and 9.7 ($P < 0.001$) in patients with high DPD/Cr. CVD was an independent predictor of SHPT (OR 2.8, $P = 0.007$) and excess DPD/Cr (OR 2.5, $P = 0.031$). CVD was predictive of postoperative myocardial injury, while SHPT was also an independent predictor of prolonged hospital stay and in-hospital death.

Conclusion: SHPT and excess bone resorption are independent pathophysiological mediators underlying the bidirectional associations between CVD and hip fracture, and therefore are important diagnostic and therapeutic targets.

Keywords: cardiovascular disease, hip fracture, PTH, 25(OH)D, secondary hyperparathyroidism, bone turnover, mineral metabolism

Introduction

There is little doubt that cardiovascular diseases (CVDs) and osteoporotic fractures are two important public health-care problems worldwide with a high impact on morbidity and mortality and increasing prevalence as the population ages. Although there are similarities in bone formation and vascular calcification and both disorders share several common risk factors (aging, female sex, low physical activity, smoking, alcohol overuse, renal and metabolic diseases),¹ traditionally they are regarded as

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separate but coexisting diseases.² In the last decade, emerging data suggest a positive association between CVD and osteoporosis beyond these factors and indicate that this link may have common underlying biological mechanisms.³⁻⁵ However, there is still a considerable amount of controversial literature on this important topic. Many studies report that low bone mineral density (BMD) or bone mass, independently of age and classical cardiovascular risk factors, is related to increased cardiovascular morbidity,^{4,6-8} especially vascular calcification,^{5,9,10} as well as increased cardiovascular and all-cause mortality.^{11,12} Conversely, bone loss and fracture risk is significantly increased in subjects with CVD.¹³⁻¹⁶ In other studies, however, no significant associations between BMD and CVD or mortality were observed.^{17,18} Peripheral arterial disease was not associated with risk of hip fracture (HF) during a 21-year follow-up.¹⁹

Among several potential pathophysiological mechanisms linking CVD and osteoporotic fractures, dysregulation in mineral and bone metabolism appears as the most important, but published data are conflicting. Disturbances in mineral and bone metabolism well established in osteoporosis have been implicated in the pathogenesis of CVD. These include vitamin D deficiency,²⁰⁻²⁶ abnormalities in serum levels of parathyroid hormone (PTH),²⁷⁻³⁴ calcium and phosphorus homeostasis,³⁵⁻⁴⁰ and in bone-turnover markers.⁴¹⁻⁴⁶ Other researchers, however, did not support these findings and concluded that the evidence for association of these parameters and CVD is currently insufficient.^{35,40,41,47-50} In one study, for example, the development of incident coronary artery disease (CAD) in men without chronic kidney disease (CKD) was not associated with PTH, phosphorus, or fibroblast growth factor 23 (FGF23).⁴⁹ The contribution and relative importance of specific abnormalities in mineral/bone metabolism in the genesis of CVD remain unclear.

The relationship between CVD and HF, the most devastating consequence of osteoporosis, remains uncertain. Although CVDs are the main causes of morbidity and death after HF surgery,⁵¹⁻⁵³ their prevalence in patients with HF has not been reported. Previous studies have focused mostly on individual biomarkers of mineral or bone metabolism, and were often limited to women or patients with HF, or subjects with CVD. To our knowledge, no previous investigation has simultaneously evaluated parameters of mineral and bone metabolism in older HF patients with respect to CVDs.

The aims of this study of a cohort of consecutive older patients with osteoporotic HF were (1) to examine the prevalence of CVDs, (2) to compare the markers of mineral and bone metabolism in those with and without CVD,

(3) to determine whether these factors explain similarities and differences between the two groups, and (4) to estimate the contribution of CVD and mineral/bone biomarkers to short-term outcomes.

Materials and methods

Study patients

A total of 847 consecutive patients aged 60 years and older who were admitted to the Canberra Hospital with low-trauma HF and underwent surgery were investigated. After the exclusion of 86 patients with pathological HF (metastatic bone cancer, multiple myeloma, Paget's disease) or primary hyperparathyroidism and 15 patients in whom data were incomplete, a total of 746 patients (536 women and 210 men) were included in the analysis.

All patients or their guardians gave informed consent to undergo examination and surgical treatment. The study was conducted according to the Helsinki Declaration and approved by the regional Human Research Ethics Committee.

Clinical data collection

In all patients, a detailed medical history and full physical examination was performed. The presence of comorbidities with a focus on CVD (hypertension, CAD, previous myocardial infarction, stroke or transient ischemic attack, atrial fibrillation, peripheral vascular disease, and congestive heart failure) was identified based on clinical manifestations, review of hospital medical records, physicians' progress notes/letters, and medications prescribed. The data collected prospectively included medical, demographic, lifestyle, and residential characteristics, as well as in-hospital management, perioperative complications, and short-term outcomes recorded.

Outcome measures included (1) postoperative myocardial injury as defined by cardiac troponin I (cTnI) rise, (2) prolonged length of stay (LOS) (≥ 20 days), (3) discharge to a permanent residential care facility for patients who were admitted from home, and (4) all-cause in-hospital death.

Sample collection and laboratory analyses

In each patient, venous blood and second morning urine samples were collected under standardized conditions after a 12-hour overnight fast, usually within 24 hours after arrival at the emergency department. After centrifugation of blood, one serum sample as well as the urine sample were frozen and stored at -70°C until further analysis. The following biochemical parameters of mineral and bone metabolism were determined: serum concentrations of

25-hydroxyvitamin D (25[OH]D), intact PTH, total calcium, phosphate, magnesium, osteocalcin (OC), and bone-specific alkaline phosphatase (BAP) as markers of bone formation and urinary concentrations of deoxypyridinoline (DPD/Cr), and cross-linked N-telopeptide of type 1 collagen (NTx) as markers of bone resorption (both corrected for urinary creatinine concentrations in the same sample).

Serum 25(OH)D was measured by radioimmunoassay kit (Dia Sorin, Stillwater, MN, USA) and intact PTH by two-site chemiluminescent enzyme-linked immunoassay on DPC Immulite 2000 (Diagnostic Products, Los Angeles, CA, USA). Serum OC was determined by electrochemiluminescent immunoassay (Elecsys 1010; Roche Diagnostics, IN, USA), serum BAP by Metra BAP enzyme-linked immunosorbent assay (Quidel, San Diego, CA, USA), urinary cross-linked N-telopeptide of type I collagen (NTx) by enzyme-linked immunosorbent assay (Wampole Labs, Princeton, NJ, USA), and urinary DPD by two-site chemiluminescent enzyme-labeled immunoassay (DPC Immulite 2000; Diagnostic Products). All samples were analyzed with commercially available kits of the same lot number according to the manufacturer's protocol, and blind to any clinical information. In these methods, both the intra- and interassay coefficient of variations (CVs) ranged from 2.1% to 12.7%.

On the day of arrival and blood sampling, the following routine laboratory tests also were performed: full blood count, creatinine, urea nitrogen, albumin, liver and thyroid function tests (by standard automated methods), and serum cTn, by two-step chemiluminescent microparticle immunoassay (Chemiflex; Abbott Labs, Mississauga, ON, Canada). Full blood count and serum cTnI were also assessed within 24 hours postoperatively and subsequently if clinically indicated. Serum calcium concentrations were corrected for serum albumin. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study equation.⁵⁴

For the analyses, deficiency of vitamin D was defined as 25(OH)D < 50 nmol/L and moderate–severe deficiency as 25(OH)D < 25 nmol/L, based on current guidelines. Secondary hyperparathyroidism (SHPT) was defined as elevated serum PTH (>6.8 pmol/L, the upper limit of the laboratory reference range). For levels of bone-turnover markers, we used the standard laboratory reference ranges and data provided by the manufacturer.

Statistics

Stata software version 10 (StataCorp, College Station, TX, USA) was used for all statistical analyses. Descriptive statistics

included means (\pm standard deviation of mean) for continuous variables or percentages for categorical variables. Comparisons between groups were performed using analysis of variance and Student's *t*-test (for continuous variables) and χ^2 test (for categorical variables). Pearson's correlation coefficient with log-transformed data (to achieve normal distribution) was used to study the correlation between variables; Bonferroni and Sidak adjustments for multiplicity were performed. Univariate and multivariate linear regression analyses were performed to determine the associations between different parameters of mineral and bone metabolism and presence of CVD as well as short-term outcomes; all potential confounding variables (demographic, clinical, biochemical) with statistical significance ≤ 0.15 on univariate analyses were included in multivariate analysis. To quantify the significance of multicollinearity phenomena in regression analysis, the variance inflation factor was calculated. Two-sided $P < 0.05$ values were considered statistically significant.

Results

General characteristics of study patients

Demographic and clinical characteristics of the study patients are shown in Table 1. A history of CVD was present in 472 (63.3%) of 746 patients included in the study. This group was older (on average 2.2 years) and had a higher proportion of patients with American Society of Anesthesiologists (ASA) score ≥ 3 (+22%) and renal impairment (CKD ≥ 3 , +10.9%). No significant differences between patients with and without CVD were observed in regard to sex, residential status, use of walking device, current and former smoking status, alcohol consumption, dementia, type 2 diabetes mellitus, chronic obstructive pulmonary disease, Parkinson's disease, thyroid dysfunction, anemia, or hypoalbuminemia.

The group with CVD comprised 337 (45.2% of the total cohort) patients with hypertension, 171 (22.9%) with CAD, including 39 (5.2%) with a previous myocardial infarction, 100 (13.4%) with history of stroke, 55 (7.4%) with a history of transient ischemic attack, and 99 (13.2%) with atrial fibrillation (AF). Among the patients with CVDs, one condition was present in 290 (61.4%), two in 121 (25.6%) and three or more in 66 (14.0%) subjects. Chronic heart failure was diagnosed in 384 (59.5% of the total cohort, 81.4% of patients with CVD). Hypertension was associated with CAD (Pearson correlation $r = 0.146$, $P = 0.014$) and history of stroke ($r = 0.186$, $P = 0.002$). CAD was also associated with history of stroke ($r = 0.221$, $P = 0.033$) and AF ($r = 0.221$, $P < 0.001$).

Table 1 Socio-demographic and clinical characteristics of older patients with hip fracture included in the study (n = 746)

Characteristic	CVD		P-value
	Yes (n = 472)	No (n = 274)	
Age, years (mean \pm SD)	83.0 \pm 7.1	80.8 \pm 9.2	0.032
Females, %	73.7	68.7	0.448
Admitted from long term RCF, %	28.7	33.7	0.386
Dementia, %	22.4	30.3	0.151
Diabetes mellitus, %	15.2	15.3	0.967
COPD, %	11.2	11.1	0.987
Parkinson's disease, %	3.4	4.0	0.768
Current smoker, %	3.9	5.0	0.654
Ex-smoker, %	10.1	14.1	0.307
Alcohol overuser,* %	5.6	4.0	0.572
User of walking device, %	37.4	30.9	0.233
ASA score \geq 3	79.3	57.3	0.001
Cervical HF, %	53.1	48.5	0.543
Hemoglobin < 120 g/L, %	65.4	62.6	0.745
Albumin < 33 g/L, %	25.1	34.3	0.103
eGFR < 60 mL/minute/1.73 m ² , %	48.3	37.4	0.036
eGFR < 30 mL/minute/1.73 m ² , %	5.1	5.2	1.000

Notes: *Three or more times per week. Values in bold indicate statistically significant *P* values.

Abbreviations: CVD, cardiovascular disease; RCF, residential care facility; COPD, chronic obstructive pulmonary disease; HF, hip fracture; eGFR, estimated glomerular filtration rate; ASA, American Society of Anesthesiologists; SD, standard deviation.

Among patients with CVD, angiotensin-converting enzyme (ACE) inhibitors were used by 26.5%, angiotensin 2-receptor blockers (ARBs) by 23.3%, beta blockers by 27.4%, calcium-channel blockers by 12.7%, and statins by 21.5%. Antiosteoporotic medications were used as follows: vitamin D supplement by 19.1% of patients with CVD and 17.7% without CVD, calcium supplement by 22.5% and 19.9%, bisphosphonate by 13.5% and 12.3%, and raloxifene by 1.12% and 0.72%, respectively.

Parameters of mineral and bone metabolism in patients with and without cardiovascular disease

The mean values of serum 25(OH)D concentrations in the group of patients with CVD in total and with each analyzed cardiovascular condition separately were low and did not differ from patients without CVD (Table 2). In contrast, serum PTH levels were significantly higher in all groups with CVD compared to non-CVD patients. Patients with hypertension and CAD also had higher serum phosphate levels, and subjects with CAD, history of stroke, and AF demonstrated higher magnesium levels.

The prevalence of vitamin D deficiency (25[OH]D < 50 nmol/L) was high in both patients without CVD and in the total group with CVD (82.1% and 78.0%, respectively), but slightly lower in patients with CAD (73.1%, *P* = 0.032) and history of stroke (68.0%, *P* = 0.006). The percentage of

patients with moderate–severe vitamin D deficiency (25[OH]D < 25 nmol/L) did not differ between groups either: 28.9% in the non-CVD group and 31.2% among subjects with CVD, including those with hypertension (34.0%), CAD (33.3%), history of stroke (27.0%), and AF (34.5%).

Conversely, compared to patients without CVD, the proportion of subjects with elevated PTH levels (>6.8 pmol/L) indicating SHPT was about two times higher among the patients with CVD (43% vs 23.3%, *P* < 0.001), and the highest percentages were observed in patients with CAD (53.8%) and history of stroke (51.0%), despite the lower prevalence of vitamin D deficiency in these two groups. Among patients with both vitamin D deficiency and elevated PTH, there was a higher prevalence of subjects with CVD (35.5% vs 21.1%, *P* = 0.024), including those with hypertension (37.7%, *P* = 0.012), CAD (46.4%, *P* = 0.003), history of stroke (37.8%, *P* = 0.013), and AF (35.5%, *P* = 0.041). Of 267 patients (35.8% of the total cohort) with SHPT, 203 (76.03%) had CVD. Subjects with CVD and SHPT compared to those with normal PTH status (12.3 \pm 1.8 vs 4.0 \pm 1.6 pmol/L) had a lower level of serum calcium (2.24 \pm 0.12 vs 2.30 \pm 0.12; *P* = 0.002) and eGFR (54.4 \pm 24.6 vs 68.1 \pm 20.0 mL/minute/1.73 m²; *P* < 0.001), but there were no differences in age or other biochemical and clinical parameters, except a higher proportion of patients with ASA \geq 3 among the first group (88.3% vs 73.9%; *P* = 0.038).

Table 2 Parameters of mineral and bone metabolism in older hip-fracture patients with and without cardiovascular disease

	No CVD (n = 274)	Hypertension (n = 337)	CAD (n = 171)	Stroke (n = 100)	AF (n = 99)	Any CVD (n = 472)
Age, years	80.8 (9.2)	82.4 (7.3)*	83.9 (7.1)***	83.9 (6.4)***	83.8 (6.3)***	83.0 (7.1)***
25(OH)D, nmol/L	36.5 (18.9)	36.1 (17.5)	39.1 (18.1)	40.1 (20.0)	36.8 (13.3)	37.8 (18.1)
PTH, pmol/L	6.0 (4.3)	7.2 (5.1)**	9.9 (8.5)***	10.0 (7.5)***	10.3 (7.1)***	7.6 (6.2)***
Calcium, mmol/L	2.27 (0.13)	2.29 (0.13)	2.27 (0.12)	2.26 (0.10)	2.26 (0.12)	2.28 (0.13)
Phosphate, mmol/L	0.91 (0.27)	0.99 (0.26)**	1.02 (0.56)**	0.86 (0.29)	0.87 (0.34)	0.99 (0.56)*
Magnesium, mmol/L	0.77 (0.11)	0.76 (0.14)	0.81 (0.12)***	0.80 (0.19)*	0.81 (0.13)**	0.78 (0.14)
Osteocalcin, ng/mL	17.4 (16.0)	16.6 (10.6)	20.6 (22.9)	16.2 (14.5)	17.5 (13.4)	17.6 (15.2)
BAP, IU	26.3 (17.8)	26.6 (12.6)	27.6 (11.8)	26.2 (11.3)	25.5 (8.8)	26.8 (12.2)
Osteocalcin/BAP ratio	0.79 (0.88)	0.76 (0.70)	0.77 (0.86)	0.59 (0.37)	0.76 (0.58)	0.74 (0.67)
DPD/Cr, nmol/μmol	11.6 (5.6)	12.1 (4.8)	15.3 (13.4)***	14.8 (7.2)***	13.6 (7.1)**	13.3 (8.2)***
NTx/Cr, nmol/μmol	162 (174.9)	135.4 (104.3)	214.3 (258.1)	154.7 (154.5)	127.8 (97.3)	157.2 (163.7)
25(OH)D < 50 nmol/L, n (%)	225 (82.1)	277 (87.2)	125 (73.1)*	68 (68.0)**	85 (85.9)	368 (78.0)
PTH > 6.8 pmol/L, n (%)	64 (23.3)	146 (43.3)***	92 (53.8)***	51 (51.0)***	42 (42.4)***	203 (43.0)***
DPD/Cr > 7.5 nmol/μmol, n (%)	205 (74.8)	296 (87.8)***	157 (91.8)***	94 (94.0)***	90 (90.9)**	415 (87.9)***

Notes: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. Data are presented as means (standard deviation) for continuous variables and as n (%) for categorical. Calcium was albumin-corrected. Statistically significant differences in variables in patients with CVD compared to those without CVD are shown in bold.

Abbreviations: CVD, cardiovascular disease; AF, atrial fibrillation; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; BAP, bone-specific alkaline phosphatase; DPD/Cr, urinary deoxypyridinoline adjusted for creatinine; NTx/Cr, urinary cross-linked N-telopeptides of type I collagen adjusted for creatinine; CHD, coronary heart disease.

The mean serum levels of both bone-formation markers (OC and BAP) and the OC/BAP ratios (indicator of osteoblastic differentiation) did not differ among the groups with and without CVD. Low OC levels (<14 ng/mL, below reference range) were observed in approximately half of the patients (53.1% without CVD and 51.7% with CVD), while low BAP levels (<14 IU) occurred in 9.7% (13.3% and 7.7%, respectively). The different behaviors of OC and BAP, each of which reflects different aspects of bone metabolism and different stages of osteoblastic differentiation, have previously been observed in other clinical settings.⁵⁵

The urinary excretion of DPD adjusted for creatinine (DPD/Cr), a bone-resorption marker, was significantly higher in patients with CAD (31.9%), history of stroke (27.6%), atrial fibrillation (17.2%), and in the total group with CVD (14.7%). However, the association between CVD and urinary NTx/Cr, the collagen product which resembles DPD, was not significant. In other studies, these two bone-resorption markers have also shown clinically distinct properties.^{56–58} The prevalence of elevated DPD/Cr (>7.5 nmol/μmol) was significantly higher in the group with CVD (87.9% vs 74.8%; $P < 0.001$), including those with hypertension (87.8%, $P < 0.001$), CAD (91.8%, $P < 0.001$), history of stroke (94%, $P < 0.001$), and AF (90%, $P = 0.002$). Among patients with CVD and high DPD/Cr excretion compared to those with DPD/Cr in the normal range, the proportion of subjects with SHPT (40.9% vs 66.7%; $P = 0.038$) and low serum OC (49.6% vs 83.3%; $P = 0.007$) was lower.

With an increasing number of CVDs, there was a gradient increase in mean levels of serum PTH (in subjects with one CVD 7.4 pmol/L, with two CVDs 9.1 pmol/L, and with three or more CVDs 10.2 pmol/L; P for trend = 0.001), as well as in the prevalence of secondary hyperparathyroidism (35.5%, 45.5%, and 60.0%, respectively; P for trend = 0.001). Similarly, increasing the number of CVDs increased the mean levels of urinary DPD/Cr (12.1, 14.3, and 15.8 nmol/μmol, respectively; P for trend = 0.030) and the proportion of patients with abnormally high bone-resorption status (83.8%, 88.0%, and 95.2%, respectively; P for trend = 0.016).

Correlations between biomarkers of mineral and bone metabolism by cardiovascular disease

To evaluate further the associations between CVD and altered parameters of mineral and bone metabolism in HF patients, Pearson correlation coefficients were estimated separately in subjects with and without CVD. Values for PTH, 25(OH)D, mineral- and bone-metabolism parameters, and eGFR were logarithmically transformed before analysis. This analysis revealed similarities and differences in patients with and without CVD. In both groups, serum PTH levels were positively correlated with age and inversely with serum calcium, eGFR, and cervical type of HF (Table 3).

However, only in patients with CVD, PTH correlated positively with BAP, troponin I, and in-hospital death, while only in the non-CVD group higher PTH levels were significantly associated with female sex and dementia. BAP correlated

Table 3 Pearson correlation coefficients between serum PTH levels and selected clinical, mineral, and bone metabolism factors in older hip-fracture patients with and without cardiovascular disease

	With CVD		Without CVD	
	r	P	r	P
Age	0.178	0.017	0.329	0.001
Sex (m)	-0.127	0.092	-0.242	0.018
HF type (cervical)	-0.148	0.05	-0.225	0.028
Dementia	-0.076	0.31	0.229	0.026
Calcium	-0.312	<0.001	-0.221	0.034
BAP	0.165	0.032	0.072	0.491
eGFR	-0.373	<0.001	-0.249	0.015
Troponin I	0.161	0.036	0.1937	0.056
In-hospital death	0.227	0.002	0.178	0.084

Note: Values for PTH, 25-hydroxyvitamin D, mineral and bone turnover parameters, and eGFR were log-transformed. Values in bold indicate statistically significant *P* values.

Abbreviations: PTH, parathyroid hormone; CVD, cardiovascular disease; BAP, bone-specific alkaline phosphatase; eGFR, estimated glomerular filtration rate; HF, hip fracture.

positively with serum magnesium ($r = 0.176$, $P < 0.022$) in the CVD group and with calcium ($r = 0.349$, $P < 0.001$) and phosphate ($r = 0.286$, $P = 0.049$) in patients without CVD. Only in the later group, OC correlated positively with BAP ($r = 0.264$, $P = 0.009$), calcium ($r = 0.240$, $P = 0.020$), and magnesium ($r = 0.279$, $P = 0.007$). In both groups, OC correlated inversely with eGFR ($r = -0.456$, $P < 0.001$ for the CVD group and $r = -0.202$, $P = 0.046$ for the non-CVD group) and in-hospital death ($r = -0.210$, $P = 0.006$ and $r = -0.254$, $P = 0.012$, respectively). In both groups, DPD/Cr positively correlated with serum phosphate ($r = 0.165$, $P = 0.048$ and $r = 0.268$, $P = 0.014$, respectively), and the two urinary bone-resorption markers (DPD/Cr and NTx/Cr) were significantly intercorrelated ($r = 0.446$, $P < 0.001$ and $r = 0.349$, $P < 0.001$, respectively). 25(OH)D correlated negatively only with NTx/Cr only in the non-CVD patients ($r = -0.260$, $P = 0.021$). There was no correlation between PTH and resorption markers (DPD/Cr and NTx/Cr), which is consistent with previous reports.^{59,60}

Factors associated with cardiovascular disease

In univariate analyses of twelve biochemical (25[OH]D, PTH, calcium, phosphate, magnesium, OC, BAP, DPD/Cr, NTx/Cr, hemoglobin, albumin, eGFR) and seven clinical (age, sex, HF type, dementia, smoking, alcohol overuse, use of walking device) parameters, presence of CVD was significantly associated only with age (OR 1.03, 95% confidence interval [CI] 1.00–1.07; $P = 0.034$), high bone resorption (urinary DPD/Cr > 7.5 nmol/ μ mol, OR 2.44, 95%

CI 1.23–4.87; $P = 0.011$), and elevated serum PTH levels (> 6.8 pmol/L, OR 2.36, 95% CI 1.35–4.11; $P = 0.003$). PTH as a continuous variable was also associated with CVD (OR 1.06, 95% CI 1.00–1.13; $P = 0.033$), indicating that the risk of CVD increases by 6% per 1 pmol/L increment in PTH.

To evaluate further whether higher serum PTH levels were associated with CVD, and given the wide range of PTH in our cohort, age-, sex- and 25(OH)D-adjusted ORs were estimated by quartiles of PTH concentration. For the total CVD group as well as for each of the four studied diseases separately, the adjusted ORs increased with quartiles of serum PTH (P for trends < 0.01 in all groups). Compared to the first quartile (PTH < 3.5 pmol/L), in the fourth quartile (PTH > 8.7 pmol/L) the OR for the total CVD group was 2.5 times higher (95% CI 1.12–5.61; $P = 0.006$), and the highest values were for CAD (OR 3.34, 95% CI 1.35–8.33; $P = 0.009$) and history of stroke (OR 2.93, 95% CI 1.04–8.21; $P = 0.011$).

Using serum PTH at a cutoff of 6.8 pmol/L, it was possible to discriminate between presence and absence of CVD with a sensitivity of 42.9%, specificity of 75.8%, positive predictive value of 76.8% and negative predictive value of 41.6%, and using PTH > 8.7 pmol/L with 30.5%, 84.2%, 78.3%, and 39.4%, respectively. A sensitivity of 88.0%, specificity of 25.0%, positive predictive value of 66.7%, and negative predictive value of 55.0% were yielded using DPD/Cr > 7.5 nmol/ μ mol. These data suggest that SPTH (more specific) and high bone resorption (more sensitive) may be useful indicators of CVD (if previously not diagnosed).

We then examined which factors are independently associated with CVD. Multiple logistic regression analysis with PTH, 25(OH)D, DPD/Cr, albuminemia, eGFR, smoking status, alcohol consumption, HF type, dementia, and sex entered as independent categorical variables and corrected for age showed that elevated serum PTH (> 6.8 pmol/L), high urinary DPD/Cr (> 7.5 nmol/ μ mol), and advanced age were the only significant indicators of presence of CVD (Table 4), and together explained 32.1% of the variability in presence of CVD. Elevated PTH levels were independently and significantly associated with each of the analyzed CVDs (Table 5), and the OR ranged between 1.91 (for AF) and 3.43 (for CAD). Of note, in our models we did not include medication use (see below) as independent variables, as their use was a consequence of presence of CVD.

Further, we examined the unique and combined effects of abnormally high PTH and DPD/Cr levels as indicators of presence of CVD (Table 6). Compared to subjects with normal serum PTH and urinary DPD/Cr levels (reference group),

Table 4 Independent factors associated with the presence of cardiovascular disease in older hip-fracture patients

	OR	95% CI	P-value
PTH > 6.8 pmol/L	2.60	1.30–5.20	0.007
DPD/Cr > 7.5 nmol/μmol	2.77	1.21–6.55	0.016
Age	1.04	1.01–1.09	0.046

Notes: Adjustments for age, sex, eGFR < 60 mL/minute/1.73 m², 25(OH)D < 50 nmol/L, urinary DPD/Cr > 7.5 nmol/μmol, osteocalcin < 14 ng/mL, albumin < 33 g/L, smoking status (current and previous), alcohol consumption (≥3 times per week), dementia, type 2 diabetes mellitus and hip-fracture type. These associations remained robust after adjustment for aforementioned confounding factors and 25(OH)D < 25 nmol/L (eg, for elevated PTH: OR 2.48, 95% CI 1.25–4.92; *P* = 0.009).

Abbreviations: PTH, parathyroid hormone; OR, odds ratio; CI, confidence interval; DPD/Cr, urinary deoxypridinoline adjusted for creatinine; 25(OH)D, 25-hydroxyvitamin D; eGFR, estimated glomerular filtration rate.

the age- and sex-adjusted OR for CVD (model 1) was significantly greater in patients with high DPD/Cr and normal PTH levels (OR 4.26, *P* = 0.005), but the highest risk of CVD was in patients with elevated PTH and both normal (OR 10.27, *P* = 0.004) and high DPD/Cr (OR 7.61, *P* < 0.001). After adjustment for seven additional factors was made, the OR for the presence of CVD further increased (model 2, Table 6): 17.32 in patients only with SHPT, 9.68 in patients with SHPT and high DPD/Cr, and 5.33 in subjects only with excess bone resorption. These associations are displayed in Figure 1. In total, the OR for presence of CVD among HF patients with SHPT or excess bone resorption compared to those with both parameters in the normal range was 7.54 (Table 6).

Independent factors associated with serum PTH elevation and high bone resorption

Multivariate logistic regression analyses were performed to determine independent factors associated with elevated PTH

Table 5 Multivariate-adjusted odds ratio for the presence of cardiovascular disease in older hip-fracture patients with elevated serum parathyroid hormone levels (>6.8 pmol/L)

	OR	95% CI	P-value
Hypertension	1.97	1.08–3.60	0.028
CAD	3.43	1.60–7.32	0.001
Stroke	2.57	1.07–6.15	0.034
AF	1.91	1.03–3.45	0.048
CVD (total)	2.68	1.36–2.88	0.005

Notes: Adjustments for age, sex, eGFR < 60 mL/minute/1.73 m², 25(OH)D < 50 nmol/L, urinary DPD/Cr > 7.5 nmol/μmol, osteocalcin < 14 ng/mL, albumin < 33 g/L, smoking status (current and previous), alcohol consumption (≥3 times per week), dementia, type 2 diabetes mellitus and hip-fracture type.

Abbreviations: OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease; CAD, coronary artery disease; AF, atrial fibrillation; DPD/Cr, urinary deoxypridinoline adjusted for creatinine; 25(OH)D, 25-hydroxyvitamin D; eGFR, estimated glomerular filtration rate.

(SHPT) and high bone resorption (DPD/Cr > 7.5 nmol/μmol) in older HF patients. These models included age, sex, CVD (yes/no), dementia (yes/no), type 2 diabetes mellitus (yes/no), HF type, smoking status, alcohol consumption, eGFR < 60 mL/minute/1.73 m² (yes/no), albumin < 33 g/L (yes/no), OC < 14 ng/mL (yes/no), 25(OH)D, calcium, phosphate, magnesium, and DPD/Cr > 7.5 nmol/μmol (in the first model) or PTH > 6.8 pmol/L (in the second model) as independent variables. Independent predictors of SHPT were CVD (any) (OR 2.76, 95% CI 1.30–5.86; *P* = 0.008), renal impairment (OR 4.70, 95% CI 2.10–10.56; *P* < 0.001), female sex (OR 2.42, 95% CI 1.03–5.71; *P* = 0.043), 25(OH)D (OR 0.97, 95% CI 0.95–0.99; *P* = 0.014), serum calcium corrected for albumin (OR 0.003, 95% CI 0.0002–0.054; *P* < 0.001), and serum phosphate (OR 4.07, 95% CI 1.26–13.18; *P* = 0.019). The combined effect of these factors explained 48.7% of the variability in SHPT. These associations remained significant when the analyses were repeated with each CVD separately: OR ranged between 1.7 for AF and 2.9 for CAD.

Independent indicators of high bone resorption were the presence of CVD (OR 2.57, 95% CI 1.11–6.00; *P* = 0.028), low eGFR (OR 0.19, 95% CI 0.07–0.52; *P* = 0.001), and low OC (OR 6.20, 95% CI 2.23–17.25; *P* < 0.001), which explained 38.3% of the variability in high DPD/Cr. The “preventive” effect of renal impairment reflects the fact that DPD is mainly released by degradation of peptide-bound cross-links through renal metabolism⁶¹ and is not directly generated from osteoclastic bone resorption.⁶² Of note, CVD emerged as the second-most significant independent predictor (after eGFR < 60 mL/minute/1.73 m²) of both SHPT and excess bone resorption in this cohort.

Taken together, these data indicate that in older HF patients both SHPT and high bone resorption are significant independent indicators of the presence of CVD and vice versa. The OR for the presence of CVD is 2.68 times higher among subjects with SHPT and 2.58 times higher among patients with high bone resorption compared to patients without such a condition. Furthermore, compared to subjects with both PTH and DPD/Cr in the normal range, the OR for presence of CVD is 17.3 times higher in patients with SHPT and 5.3 times higher in subjects with excess bone resorption. On the other hand, CVD predicts SHPT (OR 2.82) and excess bone resorption (OR 2.53). These findings suggest bidirectional links between CVD and mineral/bone parameters related to osteoporosis. As the 25(OH)D levels in patients with and without CVD were low and did not differ significantly, our results highlight the significance of the independent

Table 6 Odds ratios for presence of cardiovascular disease according to serum PTH concentrations as urinary deoxyypyridinoline excretion in older patients with hip fracture

Parameters	Model	OR	95% CI	P-value
PTH > 6.8 pmol/L and DPD/Cr ≤ 7.5 nmol/μmol	1	10.27	2.11–44.93	0.004
	2	17.32	2.79–107.37	0.002
PTH > 6.8 pmol/L and DPD/Cr > 7.5 nmol/μmol	1	7.61	2.54–22.76	<0.001
	2	9.68	3.02–31.02	<0.001
PTH ≤ 6.8 pmol/L and DPD/Cr > 7.5 nmol/μmol	1	4.26	1.55 – 11.70	0.005
	2	5.33	1.83 – 15.50	0.002
PTH > 6.8 pmol/L or DPD/Cr >7.5 nmol/μmol	1	5.37	2.00–14.43	0.001
	2	7.54	2.65–21.42	<0.001

Notes: The OR compared to the reference group (both PTH and DPD/Cr in the normal range) is shown. Model 1: adjustment for age and sex. Model 2: adjustment for age, sex, smoking status, alcohol consumption, dementia, hip-fracture type, eGFR < 60 mL/minute/1.73 m², 25(OH)D < 50 nmol/L, and albumin < 33 g/L.

Abbreviations: PTH, parathyroid hormone; DPD/Cr, deoxyypyridinoline corrected by urinary creatinine; OR, odds ratio; CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; eGFR, estimated glomerular filtration rate.

associations between SHPT, high bone resorption, and CVD, supporting the hypothesis that osteoporosis and CVD share common biological mechanisms.

PTH and use of cardiovascular medications

In order to determine potential effects of different cardiovascular medications on vitamin D and PTH status, the serum mean values of 25(OH)D and PTH in patients receiving and not receiving such drugs were compared. Table 7 shows that if compared with nonusers, serum PTH levels were significantly higher in users of ACE inhibitors (65.7%) and beta blockers (49.3%), but significantly lower in patients receiving calcium channel blockers (34.6%). PTH levels did not differ in respect to use of ARBs. No significant associations between serum 25(OH)D concentrations and

use of any of the five classes of cardiovascular medications have been found.

Multiple logistic regression analyses with use of the aforementioned medications as independent variables and controlling for age, sex, CVD, renal impairment, HF type, 25(OH)D, calcium, phosphate, magnesium, and DPD/Cr showed that among these five medication classes only the use of ACE inhibitors was significantly and independently associated with elevated PTH (SHPT) (OR 3.76, 95% CI 1.01–14.16; $P = 0.049$).

Cardiovascular disease and PTH as predictors of short-term outcomes

In multivariate regression models that considered age, sex, preexisting comorbidities including CAD, hypertension, history of stroke, AF, dementia, CKD ≥ 3 stage,

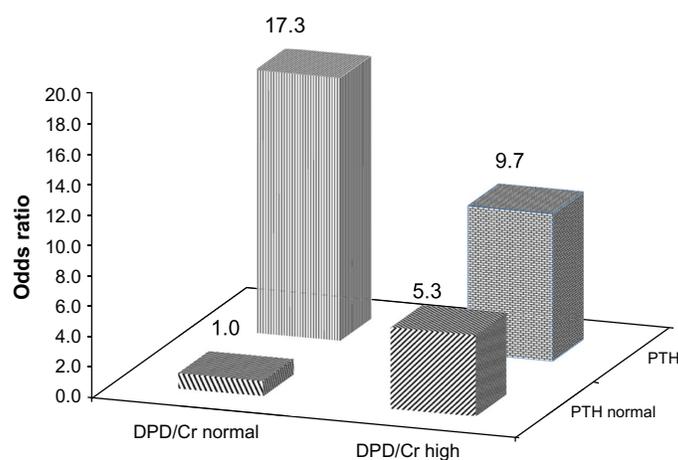


Figure 1 Odds ratios for presence of cardiovascular disease in older patients with hip fracture according to serum parathyroid hormone and urinary deoxyypyridinoline levels.

Notes: High levels were defined as exceeding the upper limits of normal range: >6.8 pmol/L for serum PTH and >7.5 nmol/μmol for urinary DPD/Cr. Adjustment was made for age, sex, smoking status, alcohol consumption, dementia, hip-fracture type, eGFR < 60 mL/minute/1.73 m², 25(OH)D < 50 nmol/L and albumin < 33 g/L. The odds ratios compared to the reference group (both PTH and DPD/Cr in the normal range) are shown.

Abbreviations: PTH, parathyroid hormone; DPD/Cr, deoxyypyridinoline corrected by urinary creatinine; 25(OH)D, 25-hydroxyvitamin D; eGFR, estimated glomerular filtration rate.

Table 7 Use of cardiovascular medications and serum parathyroid hormone and vitamin D status

Drugs	PTH, pmol/L	P-value	25(OH)D, nmol/L	P-value
ACE inhibitors				
Yes	11.1 ± 9.9	0.001	38.5 ± 17.0	0.849
No	6.7 ± 4.7		39.2 ± 18.6	
ARBs				
Yes	6.8 ± 3.8	0.477	35.6 ± 19.0	0.298
No	7.8 ± 6.7		39.8 ± 18.0	
Beta blockers				
Yes	10.1 ± 7.8	0.015	36.4 ± 17.9	0.882
No	6.5 ± 5.0		39.6 ± 15.9	
Ca-channel blockers				
Yes	5.1 ± 2.4	0.016	41.6 ± 17.1	0.621
No	7.8 ± 6.5		38.8 ± 18.4	
Statins				
Yes	7.3 ± 4.7	0.766	41.2 ± 21.8	0.540
No	7.7 ± 6.6		38.6 ± 17.5	

Note: Values in bold indicate statistically significant *P* values.

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II-receptor blockers; Ca, calcium; 25(OH)D, 25-hydroxyvitamin D.

ASA score ≥ 3 , and smoking status, having CVD was a strong independent predictor of postoperative myocardial injury (cTnI rise) (OR 6.13, 95% CI 1.57–24.00; $P = 0.009$) and prolonged hospital stay (LOS > 20 days) (OR 4.27, 95% CI 1.53–11.88; $P = 0.005$). After further adjusting for SHPT, vitamin D deficiency, and high urinary DPD/Cr excretion, patients with CVD were 2.3 times more likely to develop postoperative myocardial injury (OR 2.25, 95% CI 1.10–4.58; $P = 0.006$); however, the association between CVD and prolonged length of stay was no longer significant. In fully adjusted models (all clinical and laboratory parameters), CVD did not predict long-term residential care facility need or in-hospital death either. In contrast, SHPT was a strong independent predictor of in-hospital mortality (OR 17.39, 95% CI 3.32–78.63; $P < 0.001$), LOS > 20 days (OR 2.82, 95% CI 1.47–5.41; $P = 0.002$), and myocardial injury (OR 1.42, 95% CI 1.25–1.88; $P < 0.001$). This does not mean that CVD is unrelated to outcomes. It does imply that SHPT is an important pathway contributing to and mediating poorer outcomes. Elevated PTH (>6.8 pmol/L) occurred in 76.9% of in-hospital deaths, 59.2% of postoperative cTnI rises, and in 45.3% of prolonged hospital stays.

Discussion

Main findings

In this study of 746 consecutive older patients with osteoporotic (low-trauma) HF, preoperatively CVD was diagnosed in 63.3% of subjects, among whom 24.9% had two or more

cardiovascular diseases. There are three main findings. Firstly, elevated serum PTH levels (SHPT) independently of 25(OH)D and other parameters of mineral and bone metabolism as well as age, sex, smoking status, alcohol consumption, renal impairment, hypoalbuminemia, dementia, and HF type were associated with 2.68-fold greater prevalence of CVD (for hypertension, CAD, history of stroke, and AF 1.97-, 3.43-, 2.57-, and 1.91-fold, respectively) and predictive of poorer short-term outcomes. Secondly, high bone resorption (urinary DPD/Cr > 7.5 nmol/ μ mol) was also a significant independent indicator of presence of CVD (OR 2.58). With an increasing number of CVDs, mean serum levels of PTH and urinary DPD/Cr levels as well as the proportion of patients with SHPT and excess bone resorption increased significantly. SHPT or excess bone resorption predicted the presence of CVD by factors of 17.32 and 9.68, respectively, compared to subjects with both these parameters in the normal range. Because renal impairment (eGFR < 60 mL/minute/1.73 m²) was prevalent (in 48.3% with CVD and in 37.4% without CVD) and related to SHPT and DPD/Cr in opposite directions, these parameters in combination did not provide additive prognostic information. Thirdly, the presence of CVD was an independent predictor of both SHPT and high DPD/Cr, indicating that links between CVD and osteoporotic HF are bidirectional. Our main findings are shown in Figure 2.

PTH elevation

In agreement with numerous previous reports,^{63–65} vitamin D insufficiency was highly prevalent in our HF cohort (about 80%).

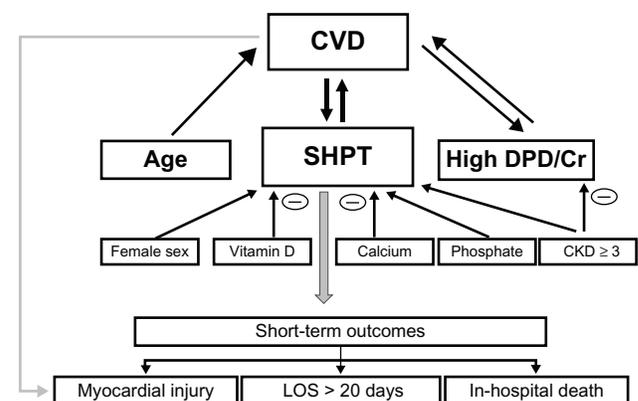


Figure 2 Diagram showing significant independent relationships (as documented by multiple regression analyses) between cardiovascular disease and parameters of mineral-bone metabolism, age and sex and short-term outcomes.

Notes: Minus signs imply a negative (inverse) relationship; myocardial injury defined as cardiac troponin I rise (>0.06 μ mol/L).

Abbreviations: CVD, cardiovascular disease; SHPT, secondary hyperparathyroidism (PTH > 6.8 pmol/l); high DPD/Cr, deoxyypyridinoline corrected by urinary creatinine excretion > 7.5 nmol/ μ mol; CKD ≥ 3 , chronic kidney disease stage 3 or higher (eGFR < 60 mL/minute/1.73 m²); LOS, length of hospital stay; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate.

The mean values of 25(OH)D and the prevalence of vitamin D deficiency were similar in patients with and without CVD. However, despite similarity in vitamin D status, in patients with CVD compared to those without CVD, mean serum PTH levels and the prevalence of SHPT were significantly higher, and these increased with increasing number of CVDs. Among patients with SHPT, 76% had CVD.

According to the traditional view, the consequence of vitamin D deficiency is SHPT, leading to bone resorption, osteoporosis, and fractures. However, in a substantial percentage of subjects with hypovitaminosis D, the serum PTH levels were found to be in the reference range. A concept of “functional hypoparathyroidism” with a protective role in bone health has been proposed.^{64,66} The prevalence of this condition ranges between 16% and 88%.^{64,67–71} On the other hand, in one study of community-dwelling older women, vitamin D deficiency (25[OH]D < 50 nmol/L) was found in 2%, but elevated PTH (>65 ng/L > 6.9 pmol/L) in 17.4%.⁷² A recent analysis of a large general health-care database revealed that increased PTH levels are common, even in the absence of 25(OH)D deficiency and renal dysfunction.⁷³

It has been reported that in the presence of hypovitaminosis D, subjects with SHPT compared to those without SHPT demonstrated lower BMD, higher bone loss and bone turnover,^{64,66,74,75} increased risk of fracture,⁷⁶ increased severity of heart failure⁷⁷ and higher mortality rates.^{29,43,69,77–79}

Contrary to these reports, other researchers in postmenopausal women with altered vitamin D status did not observe any difference in hip or spine BMD,⁶⁸ nor in the incidence of HF or vertebral fractures⁵⁸ associated with PTH levels. Increased incidence of vertebral fractures and altered bone turnover (including high urinary DPD) has been reported in postmenopausal women with vitamin D insufficiency without SHPT.⁵⁶ A recent prospective cohort study of older persons found no evidence of an association between PTH and hip or any nonspine fractures, as well as between 25(OH)D and any nonspine fractures.⁸⁰ In postmenopausal women with type 2 diabetes and vitamin D insufficiency, functional hypoparathyroidism (not SHPT) was a risk factor for bone fragility.⁸¹ In nursing home residents with type 2 diabetes, decreased PTH levels were associated with lower bone turnover and hip-fracture risk.²⁴ A U-shaped association between PTH and mortality has been reported in a hemodialysis population,⁸² while a recent meta-analysis failed to demonstrate consistent associations between PTH and cardiovascular events and mortality in CKD.⁴⁰ Thus, it appears that the existing

theoretical framework does not fully account for clinical observations, and the pathophysiological role and significance of SHPT remain unclear.

Phylogenetic data demonstrated that although PTH plays a key role in the development of bony skeleton,⁸³ PTH-like peptides and their receptors occurred before the transition from an aquatic to a terrestrial environment and not as adaptation to calcium-depleted milieu.⁸⁴ The PTH gene family was identified in cartilaginous fish,^{85,86} indicating that these genes played important metabolic roles other than bone formation and before their recruitment to bone formation. The PTH receptors are present not only in bones but also in a variety of other tissues and organs, including the cardiovascular system (cardiomyocytes, vascular smooth muscle, and endothelial cells), kidneys, adrenal cortex, pancreas, breast, and skin.^{87–89} Not surprisingly, PTH is involved in numerous physiological functions independent of vitamin D status and beyond calcium regulation, and hyperparathyroidism therefore may have profound effects on morbidity and mortality.

Our findings of the association of elevated PTH levels with CVD are in line with several (many but not all) aforementioned reports and supported by the following lines of evidence. First, *in vitro*, PTH has direct hypertrophic, inotropic,⁹⁰ and chronotropic^{91–93} effects on cardiac muscle. Second, primary hyperparathyroidism is associated with left ventricular hypertrophy,⁹⁴ aortic valve calcification,⁹⁵ significant dysfunction in coronary microcirculation,⁹⁶ increased arterial stiffness,⁹⁷ CAD, hypertension, and increased cardiovascular and all-cause mortality.^{98,99} Parathyroidectomy leads to reversal of these effects.^{27,28,100} Third, SHPT caused by chronic kidney disease is linked to CVD, hypertension, vascular and valvular calcification, left ventricular hypertrophy, fibrosis, and dyslipidemia.¹⁰¹ Fourth, PTH is associated with cardiovascular risk factors in the general population.^{29,73,102,103} Increased PTH levels are associated with hypertension,^{31,104–109} CAD,^{34,73,102} left ventricular hypertrophy,^{110,111} cardiac arrhythmias,¹¹² heart failure,^{30,33,110,113–116} and insulin sensitivity,¹¹⁷ as well as cardiovascular and all-cause mortality in patients with^{87,118,119} and without chronic kidney disease.^{29,32,43,70,78,79,120–122}

Some studies, however, did not find a link between PTH and CAD,^{8,49,123} left ventricular hypertrophy,^{124,125} and cardiovascular death.¹²⁶ PTH levels were not predictive of cardiovascular events in CKD patients¹²⁷ and did not emerge as a cardiovascular risk factor in adolescents.¹²⁸ In primary hyperparathyroidism, parathyroidectomy does not improve renal impairment and may have little effect

on hypertension prevalence.^{28,129} In laboratory animals, PTH infusion was shown to cause vasodilatation, myocardial cell contraction and regeneration attenuating ischemic cardiomyopathy.^{111,130–132} Although the discrepancy between the studies may reflect, at least in part, differences in patient characteristics (age, comorbidities, etc), experimental conditions, modes of PTH administration, PTH assay methodology, and in the covariates included in the multivariate analyses (in some studies, even 25[OH]D has not been simultaneously measured), they also indicate the complexity of multiple and sometimes contradictory/paradoxical effects of PTH (and PTHrP) on different signaling and metabolic pathways in the cardiovascular system as in the bones.^{49,111,125,133,134}

Our analysis of PTH as a continuous variable demonstrated that increase in serum PTH is associated with CVD, confirming the results of the categorical analysis, in which an arbitrary cutoff point for SHPT was used. Of note in our study, associations of SHPT with CVDs persisted when controlling for multiple covariates, including 25(OH)D, adjusted calcium, and other parameters of mineral and bone metabolism, indicating that pathways linking PTH and CVD are independent from and not mediated by the latter. These data suggest the possibility that PTH acts on the cardiovascular system through other biological mechanisms besides 25(OH)D and bone metabolism.

Experimental and clinical studies revealed that multiple and complex pathways may be involved in the development and progression of CVD in the presence of PTH excess. These include direct effects on cardiomyocytes, endothelial and smooth-muscle cells,^{111,135} stimulation of endothelial expression of atherosclerotic, inflammatory, and growth¹³⁶ factors, reduction of endothelial osteoprotegerin (OPG) secretion (a vascular-protective factor that controls vascular calcification),¹³⁷ increase in sympathetic nerve activity (by facilitating norepinephrine release),¹³⁸ increase in circulating ionized calcium (because of release from bone and decreased renal excretion), decreased expression of the calcium-sensing receptor,¹³⁹ stimulation of renin, angiotensin II, and aldosterone synthesis,^{140–147} indirect effects of PTH-induced hyperphosphatemia¹⁴⁸ and hyperlipidemia,¹⁴⁹ and decreased insulin sensitivity.¹¹⁷ Furthermore, the effects of hyperparathyroidism may be amplified by vitamin D insufficiency, as vitamin D is known to contribute directly or indirectly to the (patho)physiological functions mentioned above, such as renin–angiotensin–aldosterone system (RAAS) activation, insulin resistance, and systemic and vascular inflammations.¹⁵⁰

Taken together, it may be postulated that SHPT is a significant biomarker of CVD, and in older HF patients predicts postoperative myocardial injury, prolonged hospital stay, and in-hospital death.

Excessive bone resorption

Our finding that in older HF patients excess bone resorption (as defined by high urinary DPD/Cr excretion, the degradation product of the collagen telopeptide cross-linking molecule, which is one of the most specific and sensitive markers of osteoclastic bone resorption)^{151–156} independently of traditional risk factors is associated with CVD is in accordance with the results reported previously. Prospective studies,^{58,157,158} although not all,¹⁵⁹ showed that high bone-resorption markers were predictive of increased risk for fractures (including hip) in postmenopausal women. Elevated DPD levels predicted a twofold increased risk of cardiovascular events in men⁸ and mitral annular calcification in patients with renal stone formation.¹⁶⁰ Serum bone-resorption markers (which showed good correlation with DPD¹⁶¹) predicted an increased carotid intima-media thickness in the elderly,¹⁶² arterial stiffness in predialysis CKD,¹⁶³ cardiovascular and all-cause mortality in subjects living in residential care,⁴³ and in CKD patients.¹²⁷

The exact mechanism linking CVD and excess bone resorption is not known, and appears multifactorial. Accumulating evidence supports the hypothesis that CVD and bone resorption share several common cellular, metabolic, and signaling pathways. Both form cells in atheromatous plaques and bone osteoclasts derived from monocyte/macrophage lineage,^{164,165} and cells resembling osteoclasts have been identified in calcified atherosclerotic plaques.^{166–168} The receptor activator of nuclear factor-kappaB (RANK), RANK ligand (RANKL), and OPG play an essential role in osteoclastogenesis,¹⁶⁹ bone remodeling and resorption, and an imbalance in the RANK/RANKL/OPG system caused by hormones (PTH, 1,25[OH]₂D, estrogens, glucocorticoids), inflammatory cytokines, T-helper cells, oxylipids, oxidative stress, and other interrelated factors mediates both bone loss and vascular/atherosclerotic calcification.^{170–180} OPG has recently been proposed as a predictor of cardiovascular mortality and morbidity, although its role in CVD is still controversial.^{180–182} Interestingly, in patients with rheumatoid arthritis, etanercept caused a parallel reduction in serum RANKL and urinary DPD levels, while urinary NTx and serum OPG levels did not change significantly.¹⁸³

Bidirectional links between CVD and elevated PTH and excess bone resorption

Finally, our data indicate a bidirectional link between CVD and abnormalities in mineral/bone metabolism characteristic for osteoporosis. In older HF patients, both SHPT and excess bone resorption are significant independent indicators of presence of CVD, and CVD is highly predictive of SHPT and/or high bone resorption. The nature of these associations is complex and involves age- and disease-dependent changes, declining renal function, and different altered metabolic and signaling pathways. New information reveals remarkably close interactions between impaired PTH signaling, dysregulation of RAAS, RANK/RANKL/OPG system (axis), FGF23- α -Klotho complex, and *Wnt* signaling pathway,^{184–188} all of which have important physiological roles in both cardiovascular and bone health. Recent findings also indicate that oxidative stress, hyperlipidemia, oxidized lipids, and inflammation reciprocally regulate vascular and bone mineralization involving feedback mechanisms interacting with PTH and RANKL.^{5,171,189}

Our findings, when considered together with previous literature data, suggest that the bidirectional PTH–CVD relationships may form a vicious circle in which the interaction between PTH and RAAS plays an important role.^{146,147,190} It has been hypothesized that in patients with CVD (especially with hypertension and chronic heart failure) inappropriate activation of the RAAS and salt retention causes marked losses of cations (calcium, magnesium) with a consequent increase of PTH production, which in turn stimulates RAAS. PTH elevation leads to paradoxical intracellular calcium overloading, oxidative stress, degeneration of mitochondria followed by cardiomyocyte necrosis and myocardial fibrosis.^{146,190,191} As PTH increases secretion of aldosterone from the adrenals directly and indirectly (by activating the RAAS),¹⁴⁷ this might further contribute to arterial hypertension and cardiovascular injury. In other words, through RAAS-mediated mechanism(s) CVD could contribute to and be the result of SHPT. Furthermore, animal studies (angiotensin II-receptor knockout mice) revealed that the RAAS has a physiologic function in bone metabolism, and that signaling through angiotensin II receptor negatively regulates bone turnover and bone mass.¹⁹² Given the lack of data on the status of RAAS in our cohort, we may only speculate regarding its role in CVD and bone pathology. In our study, the group with CVD had a higher proportion of patients with renal impairment (stage CKD > 3), which is known to be associated with

higher plasma renin activity.^{193,194} Moreover, multiple logistic regression analysis showed that the use of ACE inhibitors was significantly and independently associated with elevated PTH. This observation may be explained by the fact that use of ACE inhibitors is associated with increase in plasma renin activity.^{195,196} Activation of RAAS, both disease-related and drug-related, should be considered in future studies among factors causing and aggravating SHPT. In the setting of CVD and especially with renal impairment, many other factors may also contribute to and be a consequence of SHPT; these include 1,25(OH)₂D deficiency, hypocalcemia, hyperphosphatemia, downregulated receptors for vitamin D, calcium (calcium-sensing receptor), and FGF23 (FGFR1c-Klotho complex).¹⁹⁷ We observed impaired serum phosphate homeostasis in our cohort: patients with hypertension and CAD as the CVD group in total demonstrated significantly elevated serum phosphate levels compared to the non-CVD group. Furthermore, there was not only a negative correlation between serum calcium and PTH, but serum calcium (inversely) and phosphate (positively) levels were independently associated with SHPT.

Clinical implications

Taken together, ours and previous data on bidirectional bone–cardiovascular regulatory axis suggest the need to revisit conventional patterns of care for older patients: all subjects with osteoporosis and fractures should be screened for CVD, and in patients with CVD the mineral and bone status should be determined, as in both conditions clinical signs may be absent, making their recognition difficult. Moreover, there is increasing evidence that bisphosphonates are effective not only in prevention of osteoporotic fractures but also reduce cardiovascular and total mortality,^{198–202} while lipid-lowering statins^{1,203,204} and beta blockers²⁰⁵ may have a positive effect on osteoporosis.

On the other hand, it should be emphasized that SHPT and excess bone resorption, important pathophysiological characteristics linking CVD and osteoporotic fractures, are present only in a proportion of HF patients with or without CVD, reflecting the disease diversity and significant variations in the related variables exhibited by individual patients. Therefore, identification of the PTH and bone-resorption status may improve the diagnostic and prognostic evaluation of the patient and might offer opportunities for individualized treatment. However, much further work is needed to clarify the hierarchy of genetic, environmental, and modulating factors causing the heterogeneity of both CVD and osteoporotic

fractures in regard to PTH and bone-resorption status, and to find if a syndrome-specific approach (eg, interventions targeting SHPT and/or high DPD/Cr excretion) will improve the preventive and therapeutic strategies for these common diseases.

Limitations and strengths

Our study has several limitations as well as strengths. First, because of the cross-sectional design, the described associations do not prove causality. Second, the presence of subclinical CVD was not assessed; therefore, the prevalence of CVD was probably underestimated and the duration and severity of CVD was not analyzed. Third, our results are based on a single measurement of mineral/bone metabolism parameters on hospital admission, and these may change and fluctuate. Fourth, our cohort was of predominantly white Caucasians, so the results may not be applicable to other races or ethnic groups. The relatively large number of consecutive older HF patients that reflects a real-life situation, prospective follow-up for short-term outcomes, simultaneous estimation of 25(OH)D, PTH, calcium, phosphate, magnesium, and four bone-turnover markers levels, and adjustments for multiple confounding factors (sociodemographic, eGFR, albumin, comorbidities) strengthen our results. On the other hand, in multivariate regression analysis, multiple comparisons may potentiate the significance of multicollinearity phenomena. However, the variance inflation factor in all our models (Tables 4–6) was between 1.14 and 1.02, indicating that the amount of multicollinearity was not significant.

Conclusion

In older HF patients, CVD and vitamin D deficiency are highly prevalent (in about 63% and 80%, respectively). Although serum 25(OH)D levels in subjects with and without CVD were similar, serum PTH levels and urinary DPD/Cr excretion as well as the prevalence of SHPT and excess bone resorption were significantly higher in patients with CVD. Both SHPT and high DPD/Cr were strong independent indicators of presence of CVD and vice versa. Presence of CVD was predictive of postoperative myocardial injury, while SHPT was also an independent predictor of prolonged hospital stay and in-hospital death. These findings suggest that: (1) CVD and osteoporotic fractures share common pathogenetic mechanisms, (2) elevated levels of PTH and hypovitaminosis D affect the cardiovascular system and bones through multiple biochemical mechanisms and pathways, (3) SPTH and high urinary DPD/Cr excretion may be

used as biomarkers of both osteoporosis and CVD and be helpful for individualized preventive and therapeutic interventions, and (4) patients with one of these diseases should be evaluated and treated for the other.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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