Elevated Serum PTH Is Independently Associated with Poor Outcomes in Older Patients with Hip Fracture and Vitamin D Inadequacy

A. Fisher · S. Goh · W. Srikusalanukul · M. Davis

Received: 7 April 2009 / Accepted: 12 August 2009 / Published online: 11 September 2009
 © Springer Science+Business Media, LLC 2009

Abstract To determine whether serum 25(OH)D and/or PTH levels in older patients with hip fracture (HF) could predict short-term clinical outcomes, we conducted a prospective observational study of 287 consecutive HF patients (mean age 81.9 ± 7.5 [SD] years, 72% females). The prevalence of vitamin D inadequacy ($25[\text{OH}]\text{D} < 80$ nmol/l) was 97.1%, that of vitamin D deficiency ($25[\text{OH}]\text{D} < 50$ nmol/l) was 79.8%, and that of elevated PTH level (>6.8 pmol/l) was 35.5%. After adjustment for age and sex, PTH was significantly associated with in-hospital mortality (OR = 1.12, 95% CI 1.05–1.20, $P < 0.001$), myocardial injury (OR = 1.05, 95% CI 1.03–1.15, $P = 0.002$), prolonged length of stay (LOS ≥ 20 days; OR = 1.05, 95% CI 1.01–1.06, $P = 0.044$), and being discharged to institutional care (OR = 1.07, 95% CI 1.01–1.18, $P = 0.48$). Secondary hyperparathyroidism (SHPT), but not vitamin D deficiency, was associated with older age, a higher prevalence of trochanteric fracture, coronary artery disease, hypertension, previous stroke, renal impairment, increased levels of serum osteocalcin, bone-specific alkaline phosphatase, and adiponectin as well as a significantly higher in-hospital mortality (11.8 vs. 0.54%, $P = 0.001$), perioperative myocardial injury (32.7 vs. 22.5%, $P = 0.043$), LOS ≥ 20 days (40.2 vs. 26.9%, $P = 0.017$), and being discharged to institutional care (29.5 vs. 14.6%, $P = 0.019$). In multivariate regression analyses, SHPT was strongly associated with in-hospital mortality and LOS ≥ 20 days. We conclude that

elevated PTH (but not vitamin D deficiency per se) is a strong independent predictor of poor outcomes in older patients.

Keywords PTH · Hip fracture · Osteoporosis · Outcomes · Elderly

Osteoporotic hip fractures (HFs) are associated with substantial morbidity and mortality, prolonged hospital stay, increased need for institutionalization, and high social and economic costs. Understanding which clinical and laboratory characteristics are determinants of poor outcome might improve preventive and therapeutic strategies. The literature regarding this issue remains uncertain.

A variety of clinical factors have been reported as important causes predisposing to poor outcomes [1–8]. However, these findings were not consistent, and no general consensus has been reached.

Vitamin D ($25[\text{OH}]\text{D}$) deficiency and secondary hyperparathyroidism (SHPT) are very common among the elderly and have been associated with osteoporosis and fractures [9–12], including HF [9, 13–16]. Vitamin D insufficiency and SHPT are also linked with frailty and increased morbidity, including cardiovascular disorders, diabetes, infections, and cancer. All of these are important contributors to HF outcomes as well as increased mortality, especially in the elderly [17–22].

Surprisingly, the role of abnormal serum $25(\text{OH})\text{D}$ and PTH levels in the prediction of clinical outcomes in HF patients has not been evaluated. We hypothesized that both vitamin D deficiency and SHPT would be independent predictors for poor outcomes in older HF patients. Our aims were (1) to determine whether serum $25(\text{OH})\text{D}$ and PTH levels could predict short-term outcomes (all-cause in-hospital mortality, length of hospital stay [LOS], and

A. Fisher (✉) · W. Srikusalanukul · M. Davis
 Department of Geriatric Medicine, The Canberra Hospital,
 Canberra, ACT, Australia
 e-mail: alex.fisher@act.gov.au

A. Fisher · S. Goh · W. Srikusalanukul · M. Davis
 Australian National University Medical School, Canberra,
 ACT, Australia

discharge destination) in older patients with HF and (2) to investigate the associations of these variables with other factors shown to affect prognosis in the elderly. These include demographic characteristics, comorbidity, indices of anaemia, renal impairment, malnutrition, inflammation/infection, circulating adipocytokines and markers of bone turnover.

Patients and Methods

Patients

In this prospective observational study we evaluated 287 consecutive patients aged 60 years or older (mean age 81.9 ± 7.5 years; 72% females) with a primary diagnosis of low-trauma (osteoporotic) HF admitted to the orthopaedic ward of the Canberra Hospital during the years 2005-2006. Patients with pathological HF related to primary or metastatic bone cancer, multiple myeloma or Paget's disease and those with primary hyperparathyroidism were excluded. Data on demographic characteristics, residential status, type of HF, documented comorbidities, cognition, use of walking aids, smoking and alcohol consumption, medication use, physical examination, perioperative complications, ASA status, laboratory and imaging data and outcomes were prospectively recorded and maintained in an electronic database.

This study follows the Declaration of Helsinki and was approved by the local Human Research Ethics Committee and all participants or their carers gave informed consent.

Laboratory measurements

Venous blood samples were taken after an overnight fast and a second morning urine sample was collected usually within 48 hours of arrival at the Emergency Department. Laboratory tests included serum 25-hydroxyvitamin D [25(OH)D], intact parathyroid hormone (PTH), cardiac troponin (cTnI), leptin, adiponectin, resistin, thyroid-stimulating hormone (TSH), thyroxine (T₄), calcium, phosphorus, magnesium, markers of bone formation (serum osteocalcin (OC) and bone-specific alkaline phosphatase (BAP)) and bone resorption (urine deoxypyridinoline (DPD) and cross-linked N-teleopeptides of type I collagen (NTx)), complete blood count, C-reactive protein, (CRP), renal and liver function tests, serum iron, ferritin, transferrin, vitamin B₁₂ and folate. For assays of cTnI, leptin, adiponectin, resistin and markers of bone formation and resorption serum and urine samples were frozen and stored at – 70°C, subsequently thawed and analysed in a single batch. All other biochemical and haematological parameters were measured from the same sample on the day of collection.

The serum levels of 25(OH)D were determined by a radioimmunoassay kit (Dia Sorin, Stillwater, MN, USA), intact PTH by solid phase two-site chemiluminescent enzyme-linked immunometric assay on a DPC Immulite 2000 analyser (Diagnostic Products Corp, Los Angeles, CA, USA), cTnI by two step chemiluminescent micro particle immunoassay (Abbot Labs, Mississauga, Ontario, Canada), leptin by enzyme-linked immunosorbent assay (ELISA) method (Diagnostic System Lab Inc, Webster, TX, USA), total adiponectin and resistin by human ELISA kits (B-Bridge International, Inc), serum OC by electrochemiluminescence immunoassay (Elecsys 1010, Roche diagnostics Ltd Corp, Indianapolis, IN, USA), BAP by Metra

Biosystems BAP ELISA (Quidel Corp, San Diego, CA, USA), urinary DPD by solid phase two-site chemiluminescent enzyme-labelled immunoassay on a DPC Immunolite 2000 (Diagnostic Products Corp, Los Angeles, CA, USA), urinary NTx by ELISA (Wampole Labs Inc, Dist. Princeton, NJ, USA), TSH and T₄ by two step chemiluminescent microparticle immunoassay on Architect Ci 8200 (Abbott labs, IL, USA) and CRP by agglutination methodology on Architect Ci8200. All assays were performed with kits of the same lot number. In all of the above methods both inter- and intra-assay coefficient variations (CVs) ranged from 2.1% to 12.7% for a wide range of concentrations of the analysed variables. Routine haematological and biochemical parameters were measured by standardized methods on autoanalyzers. Serum calcium concentration was corrected for serum albumin, urine DPD and NTx levels were corrected for urinary creatinine (Cr) measured in the same sample. Glomerular filtration rate (GFR) was estimated by the formula developed by Levey et al [23].

For the analyses, deficiency of vitamin D was defined as 25(OH)D<50nmol/L and severe deficiency as 25(OH)D<25nmol/L based on current recommendations [18]. For levels of PTH, cTnI, adipocytokines (leptin, adiponectin, resistin) and bone turnover markers we used the standard laboratory reference ranges and data provided by the manufacturers. Secondary hyperparathyroidism (SHPT) was defined as elevated serum PTH (>6.8pmol/L, the upper limit of the laboratory reference range). Myocardial injury was defined as elevated cTnI (>0.06µg/L).

Outcome measurements

The following short-term outcome measurements were recorded:

(1) in-hospital death, (2) length of hospital stay (LOS) and (3) discharge destination, specifically need of a long-term residential care facility (RCF).

Statistical analyses

All analyses were performed with the use of Stata software (version 10. Stata Corp, College Station, TX, USA). Comparisons between groups were performed using analysis of variance and Student's *t*-tests for continuous variables and χ^2 tests for categorical variables. Continuous parameters are presented as means with SD values, and categorical data as percentages. The relationships between the continuous variables were examined by Pearson's linear correlation test. All continuous variables with a skewed distribution were logarithmically transformed before being used in the procedure. Univariate and multivariate logistic regression analyses were used to determine odds ratios (ORs) and 95% confidence intervals (CIs) for the associations of 25(OH)D and PTH with specific HF outcomes while adjusting for several potential confounding factors. To assess whether 25(OH)D and/or PTH are independently related to a specific outcome stepwise multiple regression analyses were performed. Backwards elimination process (P values for exclusion were ≥ 0.10) was used, and the results of the final steps are shown. A P value < 0.05 (two-sided) was considered statistically significant.

Results

Hip fracture outcomes

The all-cause mortality rate was 4.53% (13/287 patients). The causes of death were acute myocardial infarction (4 patients), congestive heart failure (3), infection/sepsis (4), stroke (1) and renal failure (1). Length of stay in the hospital was less than 10 days in 32.7% of patients, between 10 and 14 days in 24.6%, between 15 and 19 days in 11% and 20 days or more in 31.6%. The mean number of hospitalisation days per patient in the group with $LOS \geq 20$ days was more than 4 times higher than on the rest of the cohort (43.7 ± 29.4 vs 10.1 ± 4.3 days; $p=0.0001$). Of 196 patients admitted from their homes, 58 (29.6%) were discharged from the hospital to a long-term RCF.

Relationship between vitamin D and PTH status and potential clinical and laboratory indicators of hip fracture outcomes

The prevalence of vitamin D deficiency ($25(OH)D < 50 \text{ nmol/L}$) was 79.8%, with severe deficiency ($< 25 \text{ nmol/L}$) in 29.2% of patients. The serum PTH levels were elevated in 35.5% (in 45.7% with severe vitamin D deficiency). Only 2.9% of the study population had levels $\geq 80 \text{ nmol/L}$ which are considered desirable.

Demographic, clinical and laboratory characteristics as well as the main outcomes in HF patients according to $25(OH)D$ and PTH levels are presented in Tables 1 and 2.

The main findings were that the group with elevated serum PTH concentrations was significantly older, included more females and patients with trochanteric fracture, CAD, hypertension, history of stroke, and ASA score ≥ 3 than the group with PTH level within the reference range. (Table 1). Importantly, SHPT was associated with significantly higher rates of in-hospital mortality, peri-operative myocardial injury, $LOS \geq 20$ days and being discharge to a long-term RCF.

As expected, the group with SHPT had slightly lower mean concentrations of 25(OH)D and calcium (corrected for albumin) and a higher proportion of subjects with severe vitamin D deficiency than those with PTH levels in normal range (Table 2). SHPT was also associated with higher mean levels of osteocalcin, BAP, adiponectin, urea, creatinine and estimated GFR (Table 2). On multiple logistic regression analysis, only levels of 25(OH)D (OR=0.98; 95% CI 0.96-0.99; p=0.036), estimated GFR (OR=0.98; 95% CI 0.97-0.99; p=0.038), adiponectin (OR=1.06; 95% CI 1.00-1.11; p=0.026) and CAD (OR=2.55; 95% CI 1.00-6.44; p=0.048) independently predicted elevated PTH concentrations. Similarly by logistic regression analysis, vitamin D deficiency was predicted only by levels of PTH (OR=1.15; 95% CI 1.03-1.28; p=0.013), leptin (OR=1.04; 95% CI 1.00-1.07; p=0.020) and history of stroke (OR=4.18; 95% CI 1.62-10.82; p=0.003).

Further evaluation of the associations of 25(OH)D and PTH status with comorbid conditions and poorer HF outcomes confirmed that elevated PTH concentration (but not the vitamin D deficiency *per se*) is the main contributor of these associations. Serum PTH concentration in HF patients who died was approximately twice the value in the survivors (12.6 ± 9.30 vs 6.6 ± 5.21 pmol/L; p=0.001), and about 1.5 times higher in patients who developed myocardial injury (9.3 ± 8.45 vs 6.1 ± 3.91 pmol/L; p=0.001), have a LOS $\geq$ 20 days (7.9 ± 5.35 vs 6.4 ± 5.21 pmol/L; p=0.033) or were discharged to a long-term RCF (7.4 ± 6.28 vs 5.3 ± 3.27 pmol/L; p=0.004) than in persons without such characteristics. In contrast, mean 25(OH)D levels varied only by gender (females 35.3 ± 17.6 , males 42.4 ± 18.2 nmol/L; p=0.003) and need for a long-term RCF (35.9 ± 19.5 vs 40.9 ± 17.5 nmol/L; p=0.005).

The patients with vitamin D deficiency were categorized into two groups with and without SHPT. Both groups had similar concentrations of 25(OH)D but the mean PTH level was 3 times higher in the first (12.70 ± 6.91 vs 3.95 ± 1.53 pmol/L; $p < 0.001$). Those with SHPT demonstrated significantly higher rates of in-hospital mortality (12.0% vs 0.72%), perioperative myocardial injury (35.4% vs 22.7%), LOS ≥ 20 days (39.7% vs 23.7%) and new discharge to long-term RCF (29.3% vs 12.2%) (Figure 1). This group was also significantly older, had a higher proportion of females, subjects with CAD, hypertension, history of stroke, ASA ≥ 3 , and higher mean levels of BAP, NTx/Cr, creatinine and adiponectin and lower levels of calcium. When the analysis was repeated for severe vitamin D deficiency (25(OH)D < 25 nmol/L), the findings did not change significantly (data not shown).

PTH as a predictor of hip fracture outcomes

Logistic regression analyses were performed to test whether admission serum 25(OH)D and PTH levels could predict HF outcomes and to compare their predictive value with other clinical and laboratory risk factors. Initially data on laboratory parameters were evaluated as continuous variables and adjusted for age and sex. A large number of variables were identified as potential risk factors for poor HF outcomes. The most remarkable finding was that PTH as a continuous variable adjusted for age and sex was the only characteristic significantly associated with all outcome measures: in-hospital mortality (OR= 1.12 per 1pmol/L; 95% CI 1.05-1.2; $P < 0.001$), myocardial injury (OR=1.05; 95% CI 1.03-1.15; $P = 0.002$), LOS ≥ 20 days (OR= 1.05; 95% CI 1.01-1.06; $P = 0.044$) and being discharged to a long-term RCF

(OR= 1.07; 95% CI 1.01-1.18; P=0.048). In other words, a 1 pmol/L increase in serum PTH level was associated with a 12% increase in the risk of in-hospital death, a 5% increased risk of developing myocardial injury and LOS $\geq$ 20 days, and a 7% increased risk of the need of institutional care. This suggests that higher serum PTH levels, even in the reference range, may have some effects predisposing to poor outcomes. Moreover, after additional controlling for all clinical and laboratory parameters with $p \leq 0.10$ in the univariate analyses, PTH remained significantly related to in-hospital mortality (OR=1.17; 95% CI 1.07-1.27; $p \leq 0.001$), developing myocardial injury (OR=1.10; 95% CI 1.01-1.20; $p=0.021$) and LOS $\geq$ 20 days (OR=1.05; 95% CI 1.00-1.11; $p=0.050$). PTH, however, dropped out of the multivariate regression model for predicting the need of institutional care. On the contrary, 25(OH)D as a continuous variable adjusted for age and sex did not predict any of the outcomes.

The serum PTH and 25(OH)D levels were further analysed as categorical variables. Univariate linear regression showed that elevated PTH (>6.8 pmol/L) is significantly associated with in-hospital mortality, LOS $\geq$ 20 days and being discharged to a RCF (Table 3). To assess whether elevated serum PTH is independently related to HF outcomes stepwise multiple regression analyses were performed. A specific outcome was considered as the dependent variable, and the independent variables included in the analyses were age, sex, PTH >6.8 pmol/L, 25(OH)D <50 nmol/L, cTnI >0.06 mg/L, eGFR ≤ 60 ml/min/1.73m², ASA ≥ 3 , CAD, history of stroke and hypertension (Model 1). In Model 2 the following variables were added to the parameters listed above: haemoglobin, CRP, markers of bone formation (OC, BAP) and resorption (DPD/Cr, NTx/Cr), vitamin B₁₂, folate, leptin, adiponectin and resistin. Table 3 shows that in

these multivariate analyses the predictive power of elevated PTH was significant and independent of potential confounders for in-hospital mortality and LOS ≥ 20 days but not for need of a long-term RCF. Controlling for clinical and laboratory covariates values improved the fit of the models. The independent variables that best predicted discharge to institutional care were age and dementia. Neither 25(OH)D < 50 nmol/L, nor 25(OH)D < 25 nmol/L was associated with any of the outcome measures in models based on the same risk factors (data not shown). The analysis was repeated using a PTH cut-off of 4.8 pmol/L (46 pg/ml) as recently proposed by some researchers [24]. All patients who died in hospital had a PTH > 4.8 pmol/L. This characteristic (unadjusted) was predictive for LOS ≥ 20 days (OR=1.8; 95% CI 1.1-3.1; $p=0.024$) and need of institutionalisation (OR=2.1; 95% CI 1.2-3.7; $p = 0.012$), but these associations disappear in models 1 and 2.

The prognostic value of elevated serum PTH concentration for poor outcomes is summarized in Table 4. Data show that this parameter has a moderate accuracy for prognosis of each of the study outcomes, although its sensitivity for predicting in-hospital death is 92.3% and negative predictive value is 99.2%.

Discussion

Our study demonstrates for the first time in older patients with HF a strong positive association of serum PTH levels with in-hospital mortality, prolonged LOS and discharge to institutional care independent of numerous potential confounding factors. Although hypovitaminosis D is near universal in the HF population and vitamin D is the main determinant of PTH status, no significant relations between serum 25(OH)D

concentrations and outcomes were observed, indicating that increased PTH concentration rather than decreased 25 (OH) D levels is the independent contributor to poor outcomes. Elevated serum PTH levels but not vitamin D deficiency *per se*, was a strong independent predictor of fatal outcome and LOS $\geq$ 20 days. This abnormality as well as severe vitamin D deficiency (<25nmol/L) were also associated with the need of long-term RCF in univariate analysis but neither parameter reached significance in multivariate analysis.

Our data are consistent with numerous previous reports on the high prevalence of vitamin D deficiency and alteration in vitamin D – PTH homeostasis in older HF patients [9, 13-16]. The novel finding in this study is that the serum PTH level is a strong independent predictor of poor clinical outcomes. Our findings are in line with several previous observations. Raised serum PTH levels were related to severity of disease and mortality in a mixed emergency population [25], and in critically ill patients [26, 27]. Elevated serum PTH concentration has been found to be an independent predictor of mortality in frail elderly nursing home residents [17, 20], as well as in a general population [19]. Markedly increased PTH levels have been associated with increased mortality in patients with chronic renal disease [28, 29]. Primary hyperparathyroidism is also associated with excess mortality [30-32]. However, the mechanisms by which the elevated PTH concentration contribute to poor outcomes are not clear and remain to be elucidated.

Factors affecting outcomes in older HF patients are complex. Poor outcomes are likely to be multifactorial because of preexisting comorbidity, impaired cognitive status, malnutrition, anaemia and perioperative complications [1-8, 33]. In addition,

hypovitaminosis D [21], nutritional status, markers of bone turnover [34, 35], circulatory levels of adipocytokines such as leptin, adiponectin and resistin [36-38] have also been implicated as predictors of mortality and adverse outcomes in specific populations of the elderly.

The findings in our study, which included the majority of these prognostic variables, are consistent with the general observation of multiple risk factors for specific poor outcomes. The important novel observation is that negative clinical outcomes in HF patients and potential risk factors for poor outcomes were associated with higher serum PTH levels.

Our results are in line with previous observations that increases in serum PTH levels are associated with older age, female sex, renal impairment, cardiovascular diseases, and abnormal circulating adipocytokines [9, 33, 36, 38, 40, 41]. On the other hand, it is somewhat surprising that vitamin D status in our study was not associated with any of these potential risk factors for poor outcomes nor with in-hospital mortality and prolonged LOS. Many, but not all [34], previous studies reported a significant link between vitamin D deficiency and mortality [21, 28] and increased cardiovascular disease risk [18] in the elderly. In the majority of these studies PTH levels were not assessed simultaneously with 25 (OH)D. Most of our patients had vitamin D deficiency and less than 3% had a desirable level of 25(OH)D ($\geq 80\text{nmol/L}$). It is possible that the variability in 25(OH)D values in our cohort was not of sufficient magnitude to demonstrate such an association. Although our study supports the notion that in older HF patients, in whom vitamin D deficiency is prevalent, the relationship between PTH levels and outcomes is independent of vitamin D status, it does not rule out the potential negative effects of low 25 (OH) D concentrations in

development of poor outcomes. Given the fact that 25(OH)D level is an independent predictor of elevated PTH, it could be assumed that SHPT reflects a more severe state of altered calcium homeostasis, a tightly regulated process, responsible for poor outcomes. Because of the multiplicity of biological effects of calcium, signalling alterations in calcium homeostasis result in cell injury [42, 43] perpetuating a broad spectrum of diseases and excess mortality. Elevated PTH level may be a marker reflecting the pathophysiological pathways of these deteriorious effects. As PTH receptors are present throughout the body, excess serum PTH concentration affects the skeletal, cardiovascular, nervous, renal and other systems which may determine the prognosis in HF patients. Previous studies have shown that in the presence of hypovitaminosis D subjects with SHPT compared to those without elevated PTH have increased bone turnover [10, 20, 40], increased fracture risk [10] and higher mortality rate, especially cardiovascular deaths [17, 20]. Our results are in line with these findings.

One may argue that the link between PTH and outcomes may be the result of the combined impact of potentially harmful conditions such as older age, CAD, hypertension, history of stroke, renal impairment, and high ASA grade, each of which is associated with elevated PTH. However, in multivariate analyses after correction for these comorbidities and demographic and laboratory variables, elevated PTH level remains a strong independent predictor of in-hospital mortality and LOS>20 days. This indicates that elevated PTH causes unfavourable outcomes, and further studies to elucidate the mechanisms are warranted.

Like Chen et al [20] but in contrast to Sahota et al [10], we observed a small but significantly lower serum calcium concentration in the group with SHPT compared to

the group with normal PTH. This is consistent with the well known homeostatic mechanism: a drop in serum calcium due to vitamin D deficiency stimulates secretion of PTH, which in turn affects the intestine, kidneys and bones to increase circulating calcium concentration. The reason why vitamin D deficiency is often not associated with PTH elevation is not clear [13, 20, 44]. Postulated mechanisms include renal impairment [20, 39] with diminished 1-alpha hydroxylation of 25(OH)D, magnesium deficiency [45, 46], lower levels of testosterone and insulin-like growth factor in men, smoking and higher body mass index in women [38], abnormalities in calcium sensing receptor [45] and vitamin D receptor and shorter duration of exposure to low vitamin D levels. In our study SHPT was associated with renal impairment, but no difference in magnesium or leptin (index of body fat mass) levels nor in smoking history were observed in groups with and without SHPT in the presence of vitamin D deficiency. Other variables were not measured in our cohort. One alternative explanation of the relationship between 25(OH)D and PTH is that the upper limit of normal PTH level should be 30% lower than generally accepted: 4.8pmol/L (46pg/ml) not 6.8pmol/L (65pg/ml) [24]. However, in our cohort, among 126 patients with PTH <4.8pmol/L, 77.0% have vitamin D deficiency and 24.6% have severe deficiency indicating that factors other than calcium and vitamin D are also important in PTH response [39].

Our findings are of clinical relevance and may have implications for identification and risk stratification of vulnerable patients as well as for the development of targeted interventions to prevent HFs and reduce poor outcomes. As approximately 1.6 million HFs occur worldwide each year tests to identify patients at risk for poor outcomes are needed. Our study identified a novel marker to help recognize such patients. Our results indicate that HF patients with elevated PTH compared to those with serum

PTH in the normal range have a 15-time greater risk of fatal outcome and approximately 1.5-time greater risk of prolonged hospital stay (≥ 20 days) and being discharged to a long-term RCF. The predictive value of this test is modest with sensitivity of 92.3%, specificity of 58.7% and negative predictive value of 99.2% for in-hospital death.

Preexisting SHPT before HF should be recognized as significant risk factors for poor outcomes. The availability and relatively low cost of PTH measurement makes it an attractive clinical indicator. Both vitamin D deficiency and SHPT are common but often unrecognized and undertreated in the elderly, indicating the importance of early detection and management of these abnormalities. Further research is necessary to demonstrate that treatment of vitamin D deficiency and SHPT reduces poor outcomes.

There are strengths and limitations to our study. Prospective collection and registration of data, a large number of clinical and laboratory variables included in the study and use of multivariate analyses allowed examination of the relationships between serum PTH levels and outcomes in a cohort of older HF patients with a high prevalence of vitamin D deficiency, making adjustments for numerous possible confounders. The main limitation of the present study is its cross-sectional design and therefore is not amenable to establishing a cause-effect relationship. The findings with respect to in-hospital mortality, although statistically highly significant, should be treated with caution as the number of deaths was small. Finally, the cohort analysed here consisted mainly of Caucasian patients and therefore our results may not be applicable to the entire HF population as ethnicity has a role in vitamin D-PTH physiology.

In conclusion, we found that in older patients with HF, elevated serum PTH levels (but not vitamin D deficiency *per se*) are associated with older age, trochanteric fracture, hypertension, CAD, previous stroke, renal impairment, ASA $\geq$ 3, increased levels of osteocalcin, BAP and adiponectin, as well as with in-hospital death, perioperative myocardial injury, prolonged LOS $\geq$ 20 days) and being discharged to a long-term RCF. Independent of the effects of these demographic, clinical and laboratory factors, SHPT strongly predicts in-hospital mortality and prolonged LOS. Further studies are needed to validate our findings, to investigate the underlying pathophysiological mechanisms, and to determine whether intervention strategies could improve the outcomes in older HF patients.

References

1. Aharonoff, GB, KJ Koval, ML Skovron, and JD Zuckerman (1997) Hip fractures in the elderly: predictors of one year mortality. *J Orthop Trauma* 11:162-5
2. Cree, M, CL Soskolne, E Belseck, J Hornig, JE McElhaney, R Brant, and M Suarez-Almazor (2000) Mortality and institutionalization following hip fracture. *J Am Geriatr Soc* 48:283-8
3. Gruson, KI, GB Aharonoff, KA Egol, JD Zuckerman, and KJ Koval (2002) The relationship between admission hemoglobin level and outcome after hip fracture. *J Orthop Trauma* 16:39-44
4. Elliott, J, T Beringer, F Kee, D Marsh, C Willis, and M Stevenson (2003) Predicting survival after treatment for fracture of the proximal femur and the effect of delays to surgery. *J Clin Epidemiol* 56:788-95
5. Franzo, A, C Francescutti, and G Simon (2005) Risk factors correlated with post-operative mortality for hip fracture surgery in the elderly: a population-based approach. *Eur J Epidemiol* 20:985-91
6. Robbins, JA, ML Biggs, and J Cauley (2006) Adjusted mortality after hip fracture: From the cardiovascular health study. *J Am Geriatr Soc* 54:1885-91
7. Holt, G, R Smith, K Duncan, DF Finlayson, and A Gregori (2008) Early mortality after surgical fixation of hip fractures in the elderly: an analysis of data from the scottish hip fracture audit. *J Bone Joint Surg Br* 90:1357-63

8. Mizrahi, EH, Y Fleissig, M Arad, T Blumstein, and A Adunsky (2007)
Admission albumin levels and functional outcome of elderly hip fracture patients: is it that important? *Aging Clin Exp Res* 19:284-9
9. Lips, P (2001) Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 22:477-501
10. Sahota, O, MK Munday, P San, IM Godber, N Lawson, and DJ Hosking (2004) The relationship between vitamin D and parathyroid hormone: calcium homeostasis, bone turnover, and bone mineral density in postmenopausal women with established osteoporosis. *Bone* 35:312-9
11. Saquib, N, D von Muhlen, CF Garland, and E Barrett-Connor (2006) Serum 25-hydroxyvitamin D, parathyroid hormone, and bone mineral density in men: the Rancho Bernardo study. *Osteoporos Int* 17:1734-41
12. Kuchuk, NO, NM van Schoor, SM Pluijm, A Chines, and P Lips (2009)
Vitamin D Status, Parathyroid Function, Bone Turnover and Bone Mineral Density in Postmenopausal Women with Osteoporosis in Global Perspective. *J Bone Miner Res* 24:693-701
13. Sahota, O, K Gaynor, RH Harwood, and DJ Hosking (2001) Hypovitaminosis D and 'functional hypoparathyroidism'-the NoNoF (Nottingham Neck of Femur) study. *Age Ageing* 30:467-72
14. Giusti, A, A Barone, M Razzano, M Pizzonia, M Oliveri, E Palummeri, and G Pioli (2006) High prevalence of secondary hyperparathyroidism due to hypovitaminosis D in hospitalized elderly with and without hip fracture. *J Endocrinol Invest* 29:809-13

15. Fisher, AA, EK Southcott, W Srikusalanukul, MW Davis, PE Hickman, JM Potter, and PN Smith (2007) Relationships between myocardial injury, all-cause mortality, vitamin D, PTH, and biochemical bone turnover markers in older patients with hip fractures. *Ann Clin Lab Sci* 37:222-32
16. Bischoff-Ferrari, HA, U Can, HB Staehelin, A Platz, J Henschkowski, BA Michel, B Dawson-Hughes, and R Theiler (2008) Severe vitamin D deficiency in Swiss hip fracture patients. *Bone* 42:597-602
17. Sambrook, PN, JS Chen, LM March, ID Cameron, RG Cumming, SR Lord, J Schwarz, and MJ Seibel (2004) Serum parathyroid hormone is associated with increased mortality independent of 25-hydroxy vitamin d status, bone mass, and renal function in the frail and very old: a cohort study. *J Clin Endocrinol Metab* 89:5477-81
18. Holick, MF (2007) Vitamin D deficiency. *N Engl J Med* 357:266-81
19. Bjorkman, MP, AJ Sorva, and RS Tilvis (2008) Elevated serum parathyroid hormone predicts impaired survival prognosis in a general aged population. *Eur J Endocrinol* 158:749-53
20. Chen, JS, PN Sambrook, L March, ID Cameron, RG Cumming, JM Simpson, and MJ Seibel (2008) Hypovitaminosis D and parathyroid hormone response in the elderly: effects on bone turnover and mortality. *Clin Endocrinol (Oxf)* 68:290-8
21. Melamed, ML, ED Michos, W Post, and B Astor (2008) 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 168:1629-37
22. Shardell, M, GE Hicks, RR Miller, S Kritchevsky, D Andersen, S Bandinelli, A Cherubini, and L Ferrucci (2009) Association of low vitamin D levels with

the frailty syndrome in men and women. *J Gerontol A Biol Sci Med Sci* 64:69-75

23. Levey, AS, JP Bosch, JB Lewis, T Greene, N Rogers, and D Roth (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 130:461-70
24. Souberbielle, JC, E Lawson-Body, B Hammadi, E Sarfati, A Kahan, and C Cormier (2003) The use in clinical practice of parathyroid hormone normative values established in vitamin D-sufficient subjects. *J Clin Endocrinol Metab* 88:3501-4
25. Carlstedt, F, L Lind, L Wide, B Lindahl, A Hanni, J Rastad, and S Ljunghall (1997) Serum levels of parathyroid hormone are related to the mortality and severity of illness in patients in the emergency department. *Eur J Clin Invest* 27:977-81
26. Carlstedt, F, L Lind, J Rastad, H Stjernstrom, L Wide, and S Ljunghall (1998) Parathyroid hormone and ionized calcium levels are related to the severity of illness and survival in critically ill patients. *Eur J Clin Invest* 28:898-903
27. Lind, L, F Carlstedt, J Rastad, H Stjernstrom, M Stridsberg, O Ljunggren, L Wide, A Larsson, P Hellman, and S Ljunghall (2000) Hypocalcemia and parathyroid hormone secretion in critically ill patients. *Crit Care Med* 28:93-9
28. Melamed, ML, JA Eustace, LC Plantinga, BG Jaar, NE Fink, RS Parekh, J Coresh, Z Yang, T Cantor, and NR Powe (2008) Third-generation parathyroid hormone assays and all-cause mortality in incident dialysis patients: the CHOICE study. *Nephrol Dial Transplant* 23:1650-8

29. Tentori, F, MJ Blayney, JM Albert, BW Gillespie, PG Kerr, J Bommer, EW Young, T Akizawa, T Akiba, RL Pisoni, BM Robinson, and FK Port (2008) Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 52:519-30
30. Hedback, G and A Oden (1998) Increased risk of death from primary hyperparathyroidism--an update. *Eur J Clin Invest* 28:271-6
31. Wermers, RA, S Khosla, EJ Atkinson, CS Grant, SF Hodgson, WM O'Fallon, and LJ Melton, 3rd (1998) Survival after the diagnosis of hyperparathyroidism: a population-based study. *Am J Med* 104:115-22
32. Nilsson, IL, C Wadsten, L Brandt, J Rastad, and A Ekbom (2004) Mortality in sporadic primary hyperparathyroidism: nationwide cohort study of multiple parathyroid gland disease. *Surgery* 136:981-7
33. Fisher, AA, EN Southcott, SL Goh, W Srikusalanukul, PE Hickman, MW Davis, JM Potter, MM Budge, and PN Smith (2008) Elevated serum cardiac troponin I in older patients with hip fracture: incidence and prognostic significance. *Arch Orthop Trauma Surg* 128:1073-9
34. Sambrook, PN, CJ Chen, L March, ID Cameron, RG Cumming, SR Lord, JM Simpson, and MJ Seibel (2006) High bone turnover is an independent predictor of mortality in the frail elderly. *J Bone Miner Res* 21:549-55
35. Fahrleitner-Pammer, A, J Herberth, SR Browning, B Obermayer-Pietsch, G Wirnsberger, H Holzer, H Dobnig, and HH Malluche (2008) Bone markers predict cardiovascular events in chronic kidney disease. *J Bone Miner Res* 23:1850-8

36. Wannamethee, SG, PH Whincup, L Lennon, and N Sattar (2007) Circulating adiponectin levels and mortality in elderly men with and without cardiovascular disease and heart failure. *Arch Intern Med* 167:1510-7
37. Dekker, JM, T Funahashi, G Nijpels, S Pilz, CD Stehouwer, MB Snijder, LM Bouter, Y Matsuzawa, I Shimomura, and RJ Heine (2008) Prognostic value of adiponectin for cardiovascular disease and mortality. *J Clin Endocrinol Metab* 93:1489-96
38. Lee, SH, JW Ha, JS Kim, EY Choi, S Park, SM Kang, D Choi, Y Jang, and N Chung (2009) Plasma adiponectin and resistin levels as predictors of mortality in patients with acute myocardial infarction: data from infarction prognosis study registry. *Coron Artery Dis* 20:33-9
39. Gunnarsson, O, OS Indridason, L Franzson, and G Sigurdsson (2009) Factors associated with elevated or blunted PTH response in vitamin D insufficient adults. *J Intern Med* 265:488-95
40. Rejnmark, L, P Vestergaard, C Brot, and L Mosekilde (2008) Parathyroid response to vitamin D insufficiency: relations to bone, body composition and to lifestyle characteristics. *Clin Endocrinol (Oxf)* 69:29-35
41. Patel, S, S Hyer, and J Barron (2007) Glomerular filtration rate is a major determinant of the relationship between 25-hydroxyvitamin D and parathyroid hormone. *Calcif Tissue Int* 80:221-6
42. Dong, Z, P Saikumar, JM Weinberg, and MA Venkatachalam (2006) Calcium in cell injury and death. *Annu Rev Pathol* 1:405-34
43. Verkhatsky, A (2007) Calcium and cell death. *Subcell Biochem* 45:465-80
44. Vieth, R, Y Ladak, and PG Walfish (2003) Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different

reason why older adults require more vitamin D. J Clin Endocrinol Metab
88:185-91

45. Silver, J and R Levi (2005) Cellular and molecular mechanisms of secondary hyperparathyroidism. Clin Nephrol 63:119-26
46. Sahota, O, MK Munday, P San, IM Godber, and DJ Hosking (2006) Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. Osteoporos Int 17:1013-21

Table 1. Demographic and clinical characteristics and main outcomes in older patients with hip fracture by PTH level

Characteristic	PTH≤6.8pmol/L (n=185)	PTH>6.8pmol/L (n=102)	P value
Age, years (mean±SD)	81.3±8.2	83.7±6.8	0.009
Females (%)	68.1	80.4	0.017
Cervical/Trochanteric hip fracture (%)	56.2/43.8	44.1/55.9	0.033
Admitted from long-term RCF (%)	30.8	30.7	1.000
ASA score≥3 (%)	69.5	80.2	0.051
Coronary artery disease (%)	15.6	29.7	0.005
Previous myocardial infarction (%)	4.2	8.0	0.133
Hypertension (%)	48.0	64.4	0.006
Atrial fibrillation (%)	9.7	13.0	0.259
History of stroke (%)	10.9	19.0	0.046
TIA (%)	5.1	10.0	0.102
Dementia (%)	30.0	27.7	0.429
COPD (%)	10.9	12.0	0.459
Parkinson's disease (%)	4.5	5.0	0.531
Diabetes mellitus (%)	15.5	12.9	0.342
Current smoker (%)	8.0	3.0	0.476
Ex-smoker (%)	12.6	10.0	0.327
Alcohol overuser* (%)	6.3	10.0	0.181
User of walking device (%)	36.8	33.0	0.310
In-hospital death (%)	0.54	11.8	0.000
LOS<10 days (%)	34.3	29.9	0.274
LOS ≥15 days (%)	38.9	49.5	0.058
LOS≥20 days (%)	26.9	40.2	0.017
Peri-operative cTn I >0.06µg/L (%)	22.5	32.7	0.043
New discharges to long term RCF (%)	14.6	29.3	0.019

Abbreviations: ASA, American Society of Anaesthesiologists Physical Status; TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease; RCF, residential care facility; LOS, length of hospital stay; * ≥ 3 times per week.

Table 2. Biochemical and haematological characteristics of older patients with hip fracture by PTH level

Characteristic	PTH≤6.8pmol/L (n=185)	PTH>6.8pmol/L (n=102)	P value
25 (OH) vitamin D, nmol/L	39.2±18.8	33.8±16.1	0.016
PTH, pmol/L	4.0±1.51	12.1±6.39	0.000
Calcium,* mmol/L	2.29±0.12	2.24±0.13	0.001
Osteocalcin, ng/L	15.4±9.36	19.2±19.04	0.025
BAP, u/L	24.6±10.98	29.6±18.48	0.006
DPD/Cr, nmol/mmolCr	12.8±7.73	12.3±6.46	0.597
NTX/ Cr, nmol/mmolCr	144.8±161.5	183.9±180.6	0.087
Leptin, ng/ml	17.3±20.36	19.4±24.55	0.440
Adiponectin, ng/ml	16.6±7.28	19.1±7.33	0.010
Resistin, ng/ml	17.8±10.49	19.5±9.94	0.219
Urea, mmol/L	7.0±2.78	9.0±4.74	0.001
Creatinine, nmol/L	830±23.01	104.1±52.03	0.001
e GFR, ml/min	69.5±20.99	57.9±26.33	0.001
CRP, mg/L	132.2±82.7	127.3±78.4	0.628
Haemoglobin, g/L	125.0±16.7	125.0±17.7	0.977
Iron, mmol/L	4.9±4.08	5.8±4.75	0.147
25(OH) vitamin D: <25nmol/L, %	24.6	37.8	0.016
<50nmol/L, %	77.1	84.7	0.087
eGFR≤60ml/min /1.73m ² , %	33.5	58.8	0.000

Data are mean ± SD: PTH, parathyroid hormone; BAP, bone-specific alkaline phosphatase; DPD/Cr, urine deoxypyridinoline corrected by creatinine; NTX/Cr, urine cross-linked N-telopeptides of type I collagen corrected by creatinine. *corrected for albumin.

Liver and thyroid function parameters, serum phosphorus and magnesium as well as haematological characteristics, vitamin B₁₂, folic acid and iron study analytes did not differ between groups.

Table 3. Elevated serum PTH level (>6.8pmol/L) as an independent predictor of poor outcomes in older patients with hip fracture (stepwise regression analyses)

Outcome	Unadjusted		Model 1		Model 2	
	OR/95%CI	P Value	OR/95%CI	P Value	OR/95%CI	P Value
In-hospital death	24.5 (3.1-191.6)	0.002	25.4 (2.9-218.6)	0.003	17.3 (2.2-139.6)	0.007
LOS $\geq$ 20 days	1.8 (1.1-3.1)	0.024	2.5 (1.3-4.9)	0.007	3.4 (1.5 – 7.5)	0.003
Discharged to RCF	2.0 (1.1-3.8)	0.026				

CI, confidence interval; LOS, length of hospital stay.

Model 1 included age, sex, CAD, history of stroke, hypertension, ASA $\geq$ 3, eGFR $\leq$ 60ml/min/1.73m², cTn I>0.06µg/L, and 25(OH)D<50nmol/L.

Model 2 included variables listed above and haemoglobin, CRP, bone formation (OC, BAP) and bone resorption (NT_x/Cr, DPD/Cr) markers, vitamin B₁₂, folate, leptin, adiponectin and risitin.

Table 4. Prognostic value of elevated serum PTH level (>6.8pmol/L) for poor outcomes in older patients with hip fracture

	In-hospital death	Length of stay $\geq$ 20 days	Discharge to long-term RCF
Relative risk	15.2 (2.63-90.76)	1.45 (1.05-1.97)	1.39(1.05-1.79)
Sensitivity, %	92.3 (67.5-98.6)	40.2 (32.8-47.6)	37.1 (31.7-43.0)
Specificity, %	58.7 (57.2-59.1)	73.1 (69.0-77.3)	77.6 (71.2-83.4)
PPV, %	11.8 (8.6-12.6)	45.3 (36.9-53.7)	62.1 (51.3-72.0)
NPV, %	99.2 (96.7-99.9)	68.8 (64.9-72.7)	55.5 (50.9-59.7)

Data are values and 95% confidence intervals. PPV, positive predictive value; NPV, negative predictive value; RCF, residential care facility.

Figure 1. Comparison of outcomes in older patients with vitamin D deficiency (25(OH)D < 50nmol/L) with and without elevated PTH levels.