Parathyroid hormone response to vitamin D insufficiency in elderly males with chronic heart failure

Biljana Bozic[1,2], Goran Loncar[3], Nenad Prodanovic[4], Toplica Lepic[5], Zoran Radojicic[6], Vojkan Cvorovic[7], Sinisa Dimkovic[3], Vera Popovic[8]

[1] Institute for Medical Research, Military Medical Academy, Belgrade, Serbia; [2] Institute for Physiology and Biochemistry, University of Belgrade, Serbia; [3] Cardiology Department, Clinical Medical Center Zvezdara, Belgrade, Serbia; [4] Clinic for Rheumatology and Clinical Immunology, Military Medical Academy, Belgrade, Serbia; [5] Clinic for Neurology, Military Medical Academy, Belgrade, Serbia; [6] Institute for Statistics, Faculty of Organizational Sciences, University of Belgrade, Serbia; [7] Clinical Hospital Center Zemun, Belgrade, Serbia; [8] Institute of Endocrinology, University Clinical Center of Serbia

PTH response in vitamin D insufficiency CHF patient

Corresponding author

Professor Vera Popovic, MD, PhD, FRCP

Neuroendocrine Unit, Institute of Endocrinology, University Clinical Center of Serbia

Dr Subotic 13, 11000 Belgrade

Fax: +381 11 2685 357

Phone: +381 11 3639702

e-mail: popver@eunet.rs

Summary

Secondary hyperparathyroidism (SHPT) may contribute to the systemic illness that accompanies chronic heart failure (CHF). Healthy elderly with vitamin D deficiency who did not develop hyperparathyroidism (functional hypoparathyroidism, FHPT) had lower mortality than those who did. This study was designed to examine determinants of the PTH response in the vitamin D insufficient CHF patients. Sixty five vitamin D insufficient males with NYHA class II and III and 20 control subjects age ≥ 55 years were recruited. Echocardiography, physical performance, NT-pro-BNP, PTH, 25-hydroxyvitamin D (25(OH)D), adiponectin and bone activity surrogate markers (OPG, RANKL, OC, β-CTx) were assessed. Increased NYHA class was associated with SHPT, while physical performance was inferior compared to FHPT. SHPT was associated with lower left ventricular ejection fraction (LVEF) and flow mediated dilatation, but with higher left heart dimensions, left ventricular mass index and right ventricular systolic pressure. CHF patients with SHPT had increased NT-pro-BNP, adiponectin and bone markers, but decreased 25(OH)D compared to those with FHPT. Independent determinants for SHPT in CHF patients with vitamin D insufficiency were LVEF, adiponectin and β-CTx, irrespective of renal function and serum vitamin D levels. In conclusion, increased PTH levels, but not low vitamin D, demonstrated close relation to CHF severity.

Key words: heart failure, PTH response, vitamin D insufficiency, adiponectin, bone markers

Introduction

Chronic heart failure (CHF) and osteoporosis are two common chronic conditions in elderly people that are gaining importance for healthcare. These conditions associated with poor quality of life and increased morbidity/ mortality (Levy et al. 2002, Bleumink et al. 2004). Worldwide, the prevalence of vitamin D deficiency is a high as almost 50% among the elderly, as well (Mosekilde 2005). Traditionally, vitamin D has been associated primarily with bone health. However, recently extended by reports with evidences that adequate vitamin D status is important for optimal function of many organs and tissues throughout the body, including the cardiovascular system. Vitamin D inadequate status linking with various disease including arterial hypertension and diabetes mellitus, as well (Forman et al. 2007, Pittas et al. 2007).

CHF results not only from cardiac overload or injury but also from a complex interplay among genetic, neurohormonal, inflammatory and biochemical changes (Braunwald 2008) Patients with CHF have been reported to have lower bone mineral density (BMD), in part related to lower vitamin D status and higher frailty rates (Kenny et al. 2006). High levels of serum parathyroid hormone (PTH) have been previously reported in CHF patients (Shane et al. 1997). It has also been reported that secondary hyperparathyroidism (SHPT) may contribute to the systemic illness that accompanies heart failure (Alsafwah et al. 2007). The age related rise in serum PTH can be accounted for by the age-related fall in serum 25-hydroxyvitamin D (25(OH)D) and/or decline in renal function with consequent loss of the calcemic action of vitamin D on bone (Lips 2001, Mosekilde 2005). The relation between PTH levels with different parameters of heart failure is modestly presented in the literature (Garakyaraghi et al. 2009). Recent study in healthy elderly demonstrated that in the presence of vitamin D deficiency, those who did not develop hyperparathyroidism had lower mortality than those who did (Chen et al.

2008). This blunted PTH response has been termed as functional hypoparathyroidism (FHPT) (Sahota et al. 2001, Sahota et al. 2006). Previous studies also in healthy subjects indicate functional hypoparathyroidism in vitamin D deficiency is not so uncommon (Souberbielle et al. 2001, Vieth et al. 2003, Isaia et al. 2003). In this study we aimed to examine determinants of the PTH response (SHPT vs FHPT) in the vitamin D insufficient group of CHF patients.

Methods

Study design

Having medical history archives of the Cardiology Department, Clinical Medical Center Zvezdara Belgrade reviewed, first contacts with eligible patients were made on the phone. For the baseline visit we screened 152 males aged 55 years and above with chronic heart failure (CHF) due to ischemic or idiopathic dilated cardiomyopathy. Following the baseline visit 73 patients were included all of whom met the study inclusion and exclusion criteria. *Inclusion criteria were*: 1. duration of CHF for longer than one year; 2. echocardiographically assessed left ventricular ejection fraction <40%; 3. etiology of CHF: ischemic or idiopathic dilated cardiomyopathy; 4. NYHA functional class II and III; 5. unchanged medication regimen within the previous 6 weeks; 6. clinically stable condition with no clinical evidence of decompensate heart failure, such as raised jugular venous pressure, ascites, hepatomegaly. *Exclusion criteria were*: 1. diabetes mellitus determined by either self-reported histories or evidence within the hospital case notes; 2. primary lung disease including chronic obstructive pulmonary disease; 3. musculoskeletal diseases; 4. uncontrolled hypertension of more than 170/110 mmHg; 5. myocardial infarction or unstable angina within previous 3 months; 6. acute or chronic infection, inflammatory diseases such as sepsis, arthritis or systemic connective tissue disease; 7.

symptomatic peripheral vascular disease; 8. alcohol abuse; 9. serum creatinine $\geq 200\mu$mol/l; 10. valvular cardiomyopathy or artificial heart valve; 11. malignant disease, significant liver, thyroid, suprarenal gland or pituitary disease; 12. cardiac cachexia defined as unintentional weight loss of $\geq 7.5\%$ body weight over 6 months (Anker et al. 1997). Sixty five patients of included 73 patients had vitamin D insufficiency (< 50 nmol/L) were studied. Twenty healthy male volunteers aged 55 years and above, who did not take medications, formed the control group. No previous medical illness was reported (including diabetes or any other cardiovascular disease). Written informed consent was obtained from all patients with CHF and healthy subjects prior to inclusion into the study. The study was conducted according to the principles outlined in the Declaration of Helsinki and was approved by Ethical Committee of Clinical Medical Center Zvezdara.

Clinical and cardiovascular assessment

After the patient gave his written consent, the medical history was reviewed, including the cause of heart failure, comorbidities and medical history. Each CHF patient was categorized according to the New York Heart Association (NYHA) criteria (The Criteria Committee of the New York Heart Association Criteria for diagnosis and treatment of heart failure 1994). A physical exam was performed to assess CHF stability. The six-minute walk test was performed according to the standard protocol (ATS statement: guidelines for the six-minute walk test 2002). All patients underwent a two-dimensional Doppler echocardiography examination (GE Vivid 7) which was performed in the left lateral position. Systolic function was quantified by measurement of left ventricular ejection fraction (LVEF) using the Simpson method. We also measured left ventricular end-diastolic diameter (LVEDD), right ventricular systolic pressure (RVSP) and left atrial volume (LAV) according to the ASE recommendation (Silvestry et al. 2009). LVMi was

calculated by dividing the value of LVM by body surface area. Grip strength was determined by Jamar dynamometer using standard protocol. Quality of life (QoL) was estimated from The "Minnesota-Living with Heart Failure Questionnaire" (MLHFQ) (Rector and Cohn, 1992). Endothelium-dependent, flow mediated dilation (FMD) as a measure of endothelial function of the brachial artery was determined as previously described in details (Corretti et al. 2002).

DEXA measurements

A dual energy x-ray absorptiometry machine (Lunar prodigy advance, USA) was used, according to standard protocol, to measure BMD (g/cm^2), total bone mineral content and body composition (lean and fat mass). BMD was measured at the lumbar spine, hip and hip total. The coefficient of variation of BMD measurement at the hip and lumbar spine was <1%. The difference between an individual's BMD and the mean BMD for a reference population was expressed in standard deviation term.

Laboratory analysis

Basal blood samples were taken at 8am from an antecubital vein. Participants were asked to refrain from smoking more than 8 h before blood sampling, to be fasted from 9pm the previous evening as well as to withhold vasoactive medication for 12h prior to appointment. Serum samples were immediately deep frozen and kept at -70°C until assay. Serum levels of parathyroid hormone (PTH), N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP), osteocalcin (OC) and β-CrossLaps (β-CTx) were measured with a fully automated "sandwich" electrochemiluminescence method using Elecsys analyzer (Roche Diagnostics, GmbH, Mannheim; measuring range from 1.2-5000 pg/ml, 5-35000 pg/ml, 0.5-300 ng/ml and 10-6000 pg/ml, respectively). Total adiponectin and leptin levels in serum were measured by RIA (Linco Diagnostics, Inc., St/ Charles, MO; lowest detectable concentration, 1 μg/ml and 0.5 ng/ml,

respectively). Commercial ELISA kits (Bender MedSystems GmbH, Austria) were used to measure serum levels of RANKL and OPG. The lower limits of detection were 2.2 pg/ml for RANKL and 2.5 pg/ml for OPG. Intra- and interassay coefficients of variation were <7.8 and <7.2% for RANKL and <7.0 and <8.0% for OPG, respectively. 25(OH)D was measured by chemiluminiscent immuno (CLIA) technology (DiaSorin Inc., USA; measuring range from 4-150 ng/ml). To convert results to SI ng/ml x 2.5 = nmol/L. Estimated creatinine clearance was calculated from serum creatinine values using the Cockroft-Gault formula (Cockroft and Gault 1976).

Definition of parathyroid status

Within CHF patients we selected those with vitamin D insufficiency defined as a 25(OH)D level below 50 nmol/L. Sixty-five patients with vitamin D insufficiency were divided into tertiles of PTH status. Group of patients who responded with PTH level in the highest tertile were defined as secondary hyperparathyroidism (SHPT). Functional hypoparathyroidism (FHPT) were defined as those patients with PTH level in the lowest tertile, whereas patients with PTH level in the mid-tertile were defined as having an intermediate parathyroid status.

Statistical analysis

Descriptive statistics were presented as mean values with standard deviation or median with interquartile range for numeric variables, or as absolute numbers with percentages for categorical variables. Evaluation of normality was performed with Kolmogorov-Smirnov test. The log10-transformations were performed for OPG, RANKL and NT-pro-BNP, which follow exponential distribution. Student t-test was used to calculate differences between mean values. Mann-Whitney U-test was used to determine differences between median values. χ^2 –test was used to test cross tabulation for categorical variables between studied groups. Comparisons

across three groups were done with ANOVA (group means). The Pearson coefficient was used for linear correlation between variables. Partial correlation analysis was performed to adjust for creatinine clearance. We used multivariable logistic regession to further examine the independent association between PTH status and variables that were significantly different between the high and low PTH groups. This was done by forward stepwise model with Nagelkerke's R^2 used to asses its explanatory ability. A p value $\leq$ 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the SPSS software for Windows, version 15 (SPSS, Inc., Chicago, IL).

Results

Demographic and clinical characteristics of elderly CHF patients with vitamin D insufficiency according to PTH response

The general characteristics of elderly CHF patients with vitamin D insufficiency according to PTH response are summarized in Table 1. Atrial fibrillation was noted in 28%, while pacemaker was implanted in 9% of patients. History of myocardial infarction was presented in 63% of patients. Angiotensin-converting enzyme inhibitors were presented in 79% of patients, 75% were on beta-blockers, and 83% of patients were on loop diuretics, 54% were on spironolactone, 65% were on aspirin and 26% on statins. Age, waist/hip ratio and body mass index did not differ between groups. SHPT was associated with increased NYHA functional class, while quality of life and physical performance was inferior compared to FHPT. In addition, SHPT was associated with lower LVEF and flow mediated dilatation, but with higher left heart dimensions, left ventricular mass index and right ventricular systolic pressure. In addition, FMD was decreased in SHPT patients compared to FHPT.

Bone mineral density and body composition of elderly CHF patients with vitamin D insufficiency according to PTH response

Total hip BMD was significantly lower in SHPT group of CHF patients compared to FHPT group (Table 2). On the other hand, hip and lumbar spine BMD, total bone mineral content, fat and lean mass were similar between studied groups.

Biohumoral parameters in groups of vitamin D insufficient CHF patients with different PTH response

The biohumoral variables are shown in Table 3. CHF patients in SHPT group had significantly higher serum NT-pro-BNP and adiponectin, while serum 25-hydroxy vitamin D levels were lower compared to those with FHPT. In addition, uric acid, serum alkaline phosphatase, osteocalcin and β-CrossLaps levels were increased in SHPT group of CHF patients. There was no significant difference in micronutrients, leptin levels and creatinin clearance between studied groups.

Multivariate logistic regression analysis

A stepwise forward logistic regression was performed. Odds ratio (OR), 95% confidence intervals (95% CI) and Nagelkerke's R squared (R^2) are presented for the last step (step 3) (Table 4). Independent association with PTH status, in CHF patients with vitamin D insufficiency, were noted for LVEF ($P = .030$), adiponectin ($P = .051$) and β-CTx ($P = .007$) which together had an R^2 of .729. As the odds ratio indicates, higher LVEF was associated with lower odds of being in the high PTH tertile (SHPT), whereas the opposite was true for adiponectin and β-CTx. Other variables had statistically insignificant contribution to the model including creatinine clearance and serum vitamin D levels.

Discussion

As far as we know, this is the first report of independent predictor of secondary hyperparathyroidism in elderly vitamin D insufficiency men with mild to moderate CHF. Our main finding is that diminished LVEF, increased adiponectin and β-CTx are independent determinants of secondary hyperparathyroidism (SHPT) in elderly CHF patients with vitamin D insufficiency irrespective of renal function and serum vitamin D levels.

The well-known reasons for bone loss in CHF patients could be low vitamin D levels, high PTH, diminished physical performance and specific drugs (vitamin K antagonists and loop diuretics) (Anker et al. 1999). In this study SHPT patients had lower hip total BMD and decreased 6-minute walk compared to FHPT. Eighty-one percent of our CHF patients had loop diuretics in their treatment, while around half patients have taken vitamin K antagonists.

Serum PTH levels increased as a function of NYHA classification. Recently, a relationship between the deteriorating NYHA functional classes in CHF patients with hyperparathyroidism has been reported (Garakyaraghi et al. 2009). Similarly, we demonstrated that increased serum PTH was associated with elevated left ventricular mass index and left ventricular wall thickness (Loncar et al. 2010). High prevalence of left ventricular hypertrophy, measured by left ventricular mass index in primary hyperparathyroidism has been already reported (Piovesan et al. 1999). After surgical removal of parathyroid gland, left ventricular mass index decreased. Men with left ventricular hypertrophy have higher PTH levels than men without left ventricular hypertrophy do (Saleh et al. 2003). In previous study we have shown that the relative risk of systolic CHF in elderly males was associated with elevated serum PTH levels above the calculated cut-off of 48 pg/ml (Loncar et al. 2010). Recently, it has been shown that serum PTH levels ≥ 47 pg/ml were optimal cut-off point for hospitalization for heart failure (Sugimato et al.

2009). Secondary hyperparathyroidsm, defined as serum PTH levels higher than 48 pg/ml, was associated with increased mortality and risk of hospitalization in elderly adults (Premaor et al 2009). Vitamin D insufficiency (< 50 nmol/L) was found in 89% of 73 CHF patients from our previous cohort. Vitamin D insufficiency usually results in increased PTH secretion in order to maintain calcium homeostasis (Sahota et al 1999). In our study, we showed that a subgroup of CHF group with vitamin D insufficiency had blunted PTH response namely had functional hypoparathyroidism (FHPT).This subgroup had less advanced heart failure compared to the group who had secondary hyperparathyroidism(SHPT). Therefore, serum PTH response in vitamin D insufficiency may be an important predictor of the severity of CHF. SHPT was also related to increased bone turnover, while there was no difference in renal function between these groups. Importantly in the multivariate analysis, the major determinants of SHPT in CHF patients with vitamin D insufficiency were left ventricular systolic function, adiponectin and marker of bone metabolism (β-CTx), irrespectively of serum vitamin D levels and creatinine clearance. These findings seem to be supported by in vitro studies which have shown that adiponectin has induced human osteoblast proliferation and differentiation (Luo et al 2005). The crosstalk between bone and fat mass was recently enriched by *in vivo* studies showing that bone markers (osteocalcin) can induce adiponectin expression in adipocytes (Gannagé-Yared et al. 2005, Lee et al. 2007). It is interesting that our finding of adiponectin and marker of bone metabolism as independent determinants of SHPT in CHF patients with vitamin D insufficiency is in accordance with discovered cross regulation between bone and energy metabolism.

Endothelial dysfunction has been previously demonstrated in heart failure syndrome as well as its association with an increased mortality risk (Katz et al. 2005, Fischer et al. 2005). Furthermore, endothelial dysfunction is detectable by measuring the flow-mediated dilation of

the brachial artery (Corretti et al. 2002). We found increased endothelial dysfunction in SHPT patients. Increased serum PTH, as a covariant of CHF, is known to provoke oxidative stress with consequent negative potential influence on vascular function (Chhokar et al. 2005).

The limitations of the study include the relatively small sample size and the cross-sectional design of the study. Nevertheless, because we enrolled a highly selected and clinically stable cohort of elderly male patients with CHF, we could confidently interpret our results. In addition, we did not measure serum ionized calcium or magnesium, which are important determinants of PTH secretion. Vitamin D receptor and calcium sensing receptor-polymorphism are known to have possible impact on PTH levels, but those factors were not studied.

In conclusion, this study provides evidence for an association between increased serum PTH levels and CHF severity. Vitamin D insufficient CHF patients with SHPT showed advanced heart disease compared with those with FHPT. Independent determinants for SHPT in CHF patients with vitamin D insufficiency were left ventricular ejection fraction, adiponectin and β-CTx, irrespective of renal function and serum vitamin D levels. Additionally, it could be challenging to investigate whether active vitamin D drug may exhibit suppressive effect on serum PTH without causing serious side-effects such as hypercalcemia in CHF patients. If so, may it have an impact on clinical outcomes?

Reference

ALSAFWAH S, LAGUARDIA S, ARROYO M, DOCKERY B, BHATTACHARYA S, AHOKAS R, NEWMAN K: Congestive heart failure is a systemic illness: a role for minerals and micronutrients. *Clin Med Res* **5**: 238-43, 2007.

ANKER SD, CHUA TP, PONIKOWSKI P, HARRINGTON D, SWAN JW, KOX WJ, POOLE-WILSON PA, COATS AJ: Hormonal changes and catabolic/anabolic imbalance in chronic heart failure and their importance for cardiac cachexia. *Circulation* **96**: 526-34, 1997.

ANKER SD, CLARK AL, TEIXEIRA MM, HELLEWELL PG, COATS AJ: Loss of bone mineral in patients with cachexia due to chronic heart failure. *Am J Cardiol* **83**: 612-615, 1999.

ATS statement: guidelines for the six-minute walk test. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories *Am J Respir Crit Care Med* **166**: 111-17, 2002.

BLEUMINK GS, KNETSCH AM, STURKENBOOM MC, STRAUS SM, HOFMAN A, DECKERS JW, WITTEMAN JC, STRICKER BH: Quantifying the heart failure epidemic: prevalence, incidence rate, life time risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J* **25**: 1614–19, 2004.

BRAUNWALD E: Biomarkers in heart failure. *N Engl J Med* **358**: 2148-59, 2008.

CHEN JS, SAMBROOK PN, MARCH L, CAMERON ID, CUMMING RG, SIMPSON JM, SEIBEL MJ: Hypovitaminosis D and parathyroid hormone response in the elderly: effects on bone turnover and mortality. *Clin Endocrinol (Oxf)* **68**: 290-98, 2008.

CHHOKAR VS, SUN Y, BHATTACHARYA SK, AHOKAS RA, MYERS LK, XING Z, SMITH RA, GERLING IC, WEBER KT: Hyperparathyroidism and the calcium paradox of aldosteronism. *Circulation* **111**: 871–78, 2005.

COCKROFT DW, GAULT MH: Prediction of creatinine clearance from serum creatinine. *Nephron* **16**: 31-41, 1976.

CORRETTI MC, ANDERSON TJ, BENJAMIN EJ, CELERMAJER D, CHARBONNEAU F, CREAGER MA, DEANFIELD J, DREXLER H, GERHARD-HERMAN M, HERRINGTON D, VALLANCE P, VITA J, VOGEL R: International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* **39**: 257-65, 2002.

DEVEREUX RB, ROMAN MJ, DE SIMONE G, O'GRADY MJ, PARANICAS M, YEH JL, FABSITZ RR, HOWARD BV: Relations of left ventricular mass to demographic and hemodynamic variables in American Indians: the Strong Heart Study. *Circulation* **96**: 1416-23, 1997.

FISCHER D, ROSSA S, LANDMESSER U, SPIEKERMANN S, ENGBERDING N, HORNIG B, DREXLER H: Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. *Eur Heart J* **26**: 65-9, 2005.

FORMAN JP, GIOVANNUCCI E, HOLMES MD, BISCHOFF-FERRARI HA, TWOROGER SS, WILLETT WC, CURHAN GC: Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. *Hypertension* **49**:1063–1069, 2007.

GANNAGÉ-YARED MH, FARES F, SEMAAN M, KHALIFE S, JAMBART S: Circulating osteoprotegerin is correlated with lipid profile, insulin sensitivity, adiponectin and sex steroids in an ageing male population. *Clin Endocrinol (Oxf)* **64**(6): 652-658, 2006.

GARAKYARAGHI M, KERDEGARI M, SIAVASH M: Calcium and vitamin D status in heart failure patients in Isfahan, Iran. *Biol Trace Elem Res* **135**(1-3): 67-73, 2010.

ISAIA G, GIORGINO R, RINI GB, BEVILACQUA M, MAUGERI D, ADAMI S: Prevalence of hypovitaminosis D in elderly women in Italy: clinical consequences and risk factors. *Osteoporos Int* **14**: 577–82, 2003.

KATZ SD, HRYNIEWICZ K, HRILJAC I, BALIDEMAJ K, DIMAYUGA C, HUDAIHED A, YASSKIY A: Vascular endothelial dysfunction and mortality risk in patients with chronic heart failure. *Circulation* **111**: 310-14, 2005.

KENNY AM, BOXER R, WALSH S, HAGER WD: Femoral bone mineral density in patients with heart failure. *Osteoporos Int* **17**: 1420–1427, 2006.

LEE NK, SOWA H, HINOI E, FERRON M, AHN JD, CONFAVREUX C, DACQUIN R, MEE PJ, MCKEE MD, JUNG DY, ZHANG Z, KIM JK,MAUVAIS-JARVIS F, DUCY P, KARSENTY G: Endocrine regulation of energy metabolism by the skeleton. *Cell* **130**(3): 456-469, 2007.

LEVY D, KENCHAIAH S, LARSON MG, BENJAMIN EJ, KUPKA MJ, HO KK, MURABITO JM, VASAN RS: Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* **347**: 1397–1402, 2002.

LIPS P: Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* **22**: 477–501, 2001.

LONCAR G, BOZIC B, DIMKOVIC S, PRODANOVIC N, RADOJICIC Z, CVOROVIC V, PUTNIKOVIC B, MARKOVIC N, POPOVIC V: Association of increased parathyroid hormone with neuroendocrine activation and endothelial dysfunction in elderly men with heart failure. *J Endocrinol Invest* DOI:10.3275/7256, 2010.

LUO XH, GUO LJ, YUAN LQ, XIE H, ZHOU HD, WU XP, LIAO EY: Adiponectin stimulates human osteoblasts proliferation and differentiation via the MAPK signaling pathway. *Exp Cell Res* **309**: 99-109, 2005.

MOSEKILDE L: Vitamin D and the elderly. *Clin Endocrinol (Oxf)* **62**: 265–81, 2005.

PIOVESAN A, MOLINERI N, CASASSO F, EMMOLO I, UGLIENGO G, CESARIO F, BORRETTA G: Left ventricular hypertrophy in primary hyperparathyroidism. Effects of successful parathyroidectomy. *Clin Endocrinol (Oxf)* **50**: 321-28, 1999.

PITTAS AG, LAU J, HU FB, DAWSON-HUGHES B: The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *J Clin Endocrinol Metab* **92**: 2017-2029, 2007.

PREMAOR MO, SCALCO R, DA SILVA MJ, FURLANETTO TW: Secondary hyperparathyroidism is associated with increased risk of hospitalization or death in elderly adults living in a geriatric institution. *Gerontology* **55**: 405-10, 2009.

RECTOR TS, COHN JN: Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: Reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. *Am Heart J* **124**:1017-25, 1992.

SAHOTA O, GAYNOR K, HARWOOD RH, HOSKING DJ: Hypovitaminosis D and ''functional hypoparathyroidism'' – the NoNoF (Nottingham Neck of Femur) study. *Age Ageing* **30**: 467–72, 2001.

SAHOTA O, MASUD T, SAN P, HOSKING DJ: Vitamin D insufficiency increases bone turnover markers and enhances bone loss at the hips in patients with established osteoporosis. *Clin Endocrinol (Oxf)* **51**: 217–21, 1999.

SAHOTA O, MUNDEY MK, SAN P, GODBER IM, HOSKING DJ: Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. *Osteoporos Int* **17**: 1013-21, 2006.

SALEH FN, SCHIRMER H, SUNDSFJORD J, JORDE R: Parathyroid hormone and left ventricular hypertrophy. *Eur Heart J* **24**: 2054-60, 2003.

SHANE E, MANCINI D, AARONSON K, SILVERBERG SJ, SEIBEL MJ, ADDESSO V, MCMAHON DJ: Bone mass, vitamin D deficiency, and hyperparathyroidism in congestive heart failure. *Am J Med* **103**: 197-207, 1997.

SILVESTRY FE, KERBER RE, BROOK MM, CARROLL JD, EBERMAN KM, GOLDSTEIN SA, HERRMANN HC, HOMMA S, MEHRAN R, PACKER DL, PARISI AF, PULERWITZ T, SEWARD JB, TSANG TS, WOOD MA: Echocardiography-guided interventions. *J Am Soc Echocardiogr* **22**: 213-31, 2009.

SOUBERBIELLE JC, CORMIER C, KINDERMANS C, GAO P, CANTOR T, FORETTE F, BAULIEU EE: Vitamin D status and redefining serum parathyroid hormone reference range in the elderly. *J Clin Endocrinol Metab* **86**: 3086–90, 2001.

SUGIMOTO T, TANIGAWA T, ONISHI K, FUJIMOTO N, MATSUDA A, NAKAMORI S, MATSUOKA K, NAKAMURA T, KOJI T, ITO M: Serum intact parathyroid hormone levels predict hospitalization for heart failure. *Heart* **95**: 395-98, 2009.

The Criteria Committee of the New York Heart Association Criteria for diagnosis and treatment of heart failure. Little, Brown and Company, 1994.

VIETH R, LADAK Y, WALFISH PG: 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, 2003.

Table 1. Demographic, clinical and echocardiography characteristics in groups with different

PTH response in CHF patients with vitamin D insufficiency

	Functional hypoparathyroidism (FHPT) PTH ≤ 57 (n = 22)	Intermadiate PTH status 57 < PTH < 88 (n = 22)	Secondary hyperparathyroidism (SHPT) PTH ≥ 88 (n = 21)	*P*-ANOVA	*P*-value (FHPT vs SHPT)
Age (years)	67 ± 7	69 ± 8	67 ± 9	.845	.991
Waist/hip ratio	1.02 ± .05	1.02 ± .04	1.04 ± .04	.427	.291
BMI (kg/m^2)	28 ± 5	27 ± 4	29 ± 7	.475	.564
Duration of disease (years)	6 ± 4	4 ± 3	6 ± 5	.148	.634
Ischemic / idiopathic dilated CMP, n (%)	18 (82)/4 (18)	18 (82)/4 (18)	18 (86)/3 (14)	.829	.736
NYHA class II/III, n (%)	20 (91)/2 (9)	17 (77)/5 (23)	11 (52)/10 (48)	.015	.005**
MLHFQ	25 ± 13	27 ± 12	39 ± 15	.003	.003**
Six-min walking distance	438 ± 80	390 ± 72	370 ± 87	.021	.007**
Grip strength (kg)	98 ± 21	93 ± 19	92 ± 20	.647	.397
Mean blood pressure (mmHg)	105 ± 10	101 ± 11	99 ± 11	.188	.081
FMD	.47 ± .19	.43 ± .15	.36 ± .15	.085	.029*
LVEF	32 ± 6	27 ± 9	27 ± 7	.066	.036*
LVMi	147 ± 41	156 ± 43	177 ± 41	.066	.023*
LVEDD	64 ± 9	67 ± 9	69 ± 6	.141	.050*
LAV	79 ± 28	94 ± 32	114 ± 55	.023	.006**
RVSP	37 ± 12	53 ± 17	48 ± 16	.006	.029*
Creatinine clearance	70 ± 22	59 ± 17	64 ± 26	.277	.362
Loop diretics, n (%)	17 (77)	17 (77)	20 (95)	.196	.089

Data are expressed as mean ± SD or absolute number (percentage)

BMI, body mass index; *CMP*, cardiomyopathy; *FMD,* flow mediated dilatation; *LAV*, left atrial volume;

LVMi, left ventricular mass index; *LVWT*, left ventricular wall thickness; *MLHFQ*, Minesota Living with

Heart Failure Questionnaire; *NYHA*, New York Heart Association; *RVSP*, right ventricular systolic

pressure.

Table 2. Bone mineral density and body composition in groups with different PTH response in

CHF patients with vitamin D insufficiency

	Functional hypoparathyroidism (FHPT) PTH ≤ 57 (n = 22)	Intermadiate PTH status 57 < PTH < 88 (n = 22)	Secondary hyperparathyroidism (SHPT) PTH ≥ 88 (n = 21)	P-ANOVA	P-value (FHPT vs SHPT)
BMD hip (g/cm^2)	.935 ± .152	.819 ± .151	.905 ± .164	0.043	.535
BMD hip (T score)	- .9 ± 1.3	-1.9 ± 1.2	- 1.2 ± 1.2	.021	.502
BMD hip total (g/cm^2)	1.031 ± .145	.892 ± .160	.937 ± .154	.013	.047 *
BMD hip total (T score)	- .4 ± 1.1	- 1.5 ± 1.2	- 1.1 ± 1.1	.007	.045 *
BMD L1-4 (g/cm^2)	1.167 ± .196	1.055 ± .163	1.092 ± .187	0.124	.203
BMD L1-4 (T score)	- .4 ± 1.6	- 1.4 ± 1.4	- 1.0 ± 1.6	.116	.204
BMC total (kg)	2.9 ± .6	2.8 ± .5	2.9 ± .4	.831	.684
Fat mass (kg)	20.7 ± 9.2	21.5 ± 9.3	25.9 ± 13.1	.244	.143
Lean mass (kg)	54.1 ± 8.0	51.9 ± 7.5	58.6 ± 11.5	.244	.145

Data are expressed as mean ± standard deviation (Mean±SD)

BMD-bone mineral density, *BMC*-bone mineral content

Table 3. Biohumoral parameters in groups with different PTH response in CHF patients with

vitamin D insufficiency

	Functional hypoparathyroidism (FHPT) PTH ≤ 57 (n = 22)	Intermadiate PTH status 57 < PTH < 88 (n = 22)	Secondary hyperparathyroidism (SHPT) PTH ≥ 88 (n = 21)	P-ANOVA	P-value (FHPT vs SHPT)
NT-pro-BNP	768 (1405)	1759 (2802)	2890 (3985)	.003	.001**
25(OH)D	31.1 ± 12.1	30.0 ± 10.4	23.8 ± 10.9	.080	.037*
Serum calcium (mmol/L)	2.47 ± .10	2.45 ± .11	2.44 ± .11	.648	.354
Serum phosphorus (mmol/L)	1.06 ± .24	1.05 ± .15	1.13 ± .17	.282	.253
Serum magnesium (mmol/L)	.89 ± .12	.89 ± .08	.96 ± .16	.138	.143
Serum potassium (mmol/L)	4.75 ± .37	4.68 ± .55	4.98 ± .42	.099	.066
Serum sodium (mmol/L)	144.39 ± 2.36	143.22 ± 3.67	144.35 ± 2.50	.328	.959
Urine calcium	2.66 ± 1.84	1.94 ± 1.16	2.15 ± 1.64	.300	.338
Uric acid	352 ± 69	432 ± 87	468 ± 118	< .0001	< .0001***
ALP	70.5 ± 27.7	82.0 ± 25.2	89.5 ± 32.0	.097	.033*
OC	30.0 ± 14.5	42.5 ± 21.7	46.4 ± 21.4	.020	.008**
β-CTx	348 ± 186	513 ± 279	682 ± 312	< .0001	< .0001***
OPG (pg/ml)	98.1 (839.9)	62.6 (266.4)	97.2 (497.2)	.681	.936
RANKL (pg/ml)	114.7 (1308.8)	126.0 (1013.9)	143.0 (442.8)	.489	.341
Adiponectin	12.4 ± 5.4	17.5 ± 9.2	20.5 ± 7.6	.003	.001**
Leptin (ng/ml)	6.8 ± 3.9	6.7 ± 5.7	9.1 ± 9.7	.435	.305
Creatinine clearance	70 ± 22	59 ± 17	64 ± 26	.277	.362
Loop diretics, n (%)	17 (77)	17 (77)	20 (95)	.196	.089

Data are expressed as mean ± standard deviation (Mean ± SD) or median ± interquartile range (Me ±

IQR)

ALP, alkaline phosphatase; *β-CTx,* β-CrossLaps; *NT-pro-BNP*, N-terminal pro-brain natriuretic peptide;

OC, osteocalcin; *OPG*, osteoprotegerin; *RANKL,* receptor activator of nuclear factor κB ligand; *25(OH)D*,

25-hydroxy vitamin D.

Table 4. Multivariable logistic regression for PTH status (SHPT versus FHPT) in vitamin D

insufficient CHF patients

	OR	95% CI	R^2
PTH status			
Constant (B= -1.802)	.165		
LVEF	.832	.705-0.982	.729
Adiponectin	1.216	.999-1.480	
β-CTx	1.009	1.002-1.015	

β-CTx, β-CrossLaps; *LVEF*, left ventricular ejection fraction.