

## Parathyroid Hormone Response to Vitamin D Insufficiency in Elderly Males With Chronic Heart Failure

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Received January 4, 2011

Accepted March 30, 2011

On-line July 19, 2011

### 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  $\geq 55$  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,  $\beta$ -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  $\beta$ -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

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### 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 as 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, 2006). Previous studies also in healthy subjects indicate functional hypoparathyroidism in vitamin D deficiency is not so uncommon (Souberbielle *et al.* 2001, Isaia *et al.* 2003, Vieth *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 mm Hg; 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  $\geq 200$   $\mu\text{mol/l}$ ; 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 ( $\text{g}/\text{cm}^2$ ), 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 8 am from an antecubital vein. Participants were asked to refrain from smoking more than 8 h before blood sampling, to be fasted from 9 pm the previous evening as well as to withhold vasoactive medication for 12 h prior to appointment. Serum samples were immediately deep frozen and kept at  $-70\text{ }^\circ\text{C}$  until assay. Serum levels of parathyroid hormone (PTH), N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP), osteocalcin (OC) and  $\beta$ -CrossLaps ( $\beta$ -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  $\mu\text{g}/\text{ml}$  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  $\times 2.5 = \text{nmol}/\text{l}$ . Estimated creatinine clearance was calculated from serum creatinine values using the

Cockcroft-Gault formula (Cockcroft 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.  $\chi^2$ -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 regression 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 assess 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

**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)	Intermediate 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	0.845	0.991
Waist/hip ratio	1.02 ± 0.05	1.02 ± 0.04	1.04 ± 0.04	0.427	0.291
BMI (kg/m <sup>2</sup> )	28 ± 5	27 ± 4	29 ± 7	0.475	0.564
Duration of disease (years)	6 ± 4	4 ± 3	6 ± 5	0.148	0.634
Ischemic / idiopathic dilated CMP, n (%)	18 (82)/4 (18)	18 (82)/4 (18)	18 (86)/3 (14)	0.829	0.736
NYHA class II/III, n (%)	20 (91)/2 (9)	17 (77)/5 (23)	11 (52)/10 (48)	0.015	0.005**
MLHFQ	25 ± 13	27 ± 12	39 ± 15	0.003	0.003**
Six-min walking distance	438 ± 80	390 ± 72	370 ± 87	0.021	0.007**
Grip strength (kg)	98 ± 21	93 ± 19	92 ± 20	0.647	0.397
Mean blood pressure (mm Hg)	105 ± 10	101 ± 11	99 ± 11	0.188	0.081
FMD	0.47 ± 0.19	0.43 ± 0.15	0.36 ± 0.15	0.085	0.029*
LVEF	32 ± 6	27 ± 9	27 ± 7	0.066	0.036*
LVMi	147 ± 41	156 ± 43	177 ± 41	0.066	0.023*
LVEDD	64 ± 9	67 ± 9	69 ± 6	0.141	0.050*
LAV	79 ± 28	94 ± 32	114 ± 55	0.023	0.006**
RVSP	37 ± 12	53 ± 17	48 ± 16	0.006	0.029*
Creatinine clearance	70 ± 22	59 ± 17	64 ± 26	0.277	0.362
Loop diuretics, n (%)	17 (77)	17 (77)	20 (95)	0.196	0.089

Data are expressed as mean ± S.D. 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, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure.

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

**Table 2.** Bone mineral density and body composition in groups with different PTH response in CHF patients with vitamin D insufficiency.

	<b>Functional hypoparathyroidism (FHPT) PTH ≤ 57 (n = 22)</b>	<b>Intermediate PTH status 57 &lt; PTH &lt; 88 (n = 22)</b>	<b>Secondary hyperparathyroidis m (SHPT) PTH ≥ 88 (n = 21)</b>	<b>P- ANOVA</b>	<b>P-value (FHPT vs SHPT)</b>
<i>BMD hip (g/cm<sup>2</sup>)</i>	0.935 ± 0.152	0.819 ± 0.151	0.905 ± 0.164	0.043	0.535
<i>BMD hip (T score)</i>	-0.9 ± 1.3	-1.9 ± 1.2	-1.2 ± 1.2	0.021	0.502
<i>BMD hip total (g/cm<sup>2</sup>)</i>	1.031 ± 0.145	0.892 ± 0.160	0.937 ± 0.154	0.013	0.047 *
<i>BMD hip total (T score)</i>	-0.4 ± 1.1	-1.5 ± 1.2	-1.1 ± 1.1	0.007	0.045 *
<i>BMD L1-4 (g/cm<sup>2</sup>)</i>	1.167 ± 0.196	1.055 ± 0.163	1.092 ± 0.187	0.124	0.203
<i>BMD L1-4 (T score)</i>	-0.4 ± 1.6	-1.4 ± 1.4	-1.0 ± 1.6	0.116	0.204
<i>BMC total (kg)</i>	2.9 ± 0.6	2.8 ± 0.5	2.9 ± 0.4	0.831	0.684
<i>Fat mass (kg)</i>	20.7 ± 9.2	21.5 ± 9.3	25.9 ± 13.1	0.244	0.143
<i>Lean mass (kg)</i>	54.1 ± 8.0	51.9 ± 7.5	58.6 ± 11.5	0.244	0.145

Data are expressed as mean ± standard deviation (mean ± S.D.). *BMD* - bone mineral density, *BMC* - bone mineral content.

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<sup>2</sup>) 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=0.030), adiponectin (P=0.051) and β-CTx (P=0.007) which together had an R<sup>2</sup> of 0.729. 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

**Table 3.** Biohumoral parameters in groups with different PTH response in CHF patients with vitamin D insufficiency.

	<b>Functional hypoparathyroidism (FHPT) PTH ≤ 57 (n = 22)</b>	<b>Intermediate PTH status 57 &lt; PTH &lt; 88 (n = 22)</b>	<b>Secondary hyperparathyroidis m (SHPT) PTH ≥ 88 (n = 21)</b>	<b>P- ANOVA</b>	<b>P-value (FHPT vs SHPT)</b>
<i>NT-pro-BNP</i>	768 (1405)	1759 (2802)	2890 (3985)	0.003	0.001**
<i>25(OH)D</i>	31.1 ± 12.1	30.0 ± 10.4	23.8 ± 10.9	0.080	0.037*
<i>Serum calcium (mmol/l)</i>	2.47 ± 0.10	2.45 ± 0.11	2.44 ± 0.11	0.648	0.354
<i>Serum phosphorus (mmol/l)</i>	1.06 ± 0.24	1.05 ± 0.15	1.13 ± 0.17	0.282	0.253
<i>Serum magnesium (mmol/l)</i>	0.89 ± 0.12	0.89 ± 0.08	0.96 ± 0.16	0.138	0.143
<i>Serum potassium (mmol/l)</i>	4.75 ± 0.37	4.68 ± 0.55	4.98 ± 0.42	0.099	0.066
<i>Serum sodium (mmol/l)</i>	144.39 ± 2.36	143.22 ± 3.67	144.35 ± 2.50	0.328	0.959
<i>Urine calcium</i>	2.66 ± 1.84	1.94 ± 1.16	2.15 ± 1.64	0.300	0.338
<i>Uric acid</i>	352 ± 69	432 ± 87	468 ± 118	< 0.0001	< 0.0001***
<i>ALP</i>	70.5 ± 27.7	82.0 ± 25.2	89.5 ± 32.0	0.097	0.033*
<i>OC</i>	30.0 ± 14.5	42.5 ± 21.7	46.4 ± 21.4	0.020	0.008**
<i>β-CTx</i>	348 ± 186	513 ± 279	682 ± 312	< 0.0001	< 0.0001***
<i>OPG (pg/ml)</i>	98.1 (839.9)	62.6 (266.4)	97.2 (497.2)	0.681	0.936
<i>RANKL (pg/ml)</i>	114.7 (1308.8)	126.0 (1013.9)	143.0 (442.8)	0.489	0.341
<i>Adiponectin</i>	12.4 ± 5.4	17.5 ± 9.2	20.5 ± 7.6	0.003	0.001**
<i>Leptin (ng/ml)</i>	6.8 ± 3.9	6.7 ± 5.7	9.1 ± 9.7	0.435	0.305
<i>Creatinine clearance</i>	70 ± 22	59 ± 17	64 ± 26	0.277	0.362
<i>Loop diuretics, n (%)</i>	17 (77)	17 (77)	20 (95)	0.196	0.089

Data are expressed as mean ± standard deviation (mean ± S.D.) 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.

(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 (Sugimoto *et al.* 2009). Secondary hyperparathyroidism, 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

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

	OR	95 % CI	R <sup>2</sup>
<i>PTH status</i>			
Constant (B= -1.802)	0.165		
LVEF	0.832	0.705-0.982	0.729
Adiponectin	1.216	0.999-1.480	
β-CTx	1.009	1.002-1.015	

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

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 (Fischer *et al.* 2005, Katz *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, irrespectively 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?

### Conflict of Interest

There is no conflict of interest.

### Acknowledgements

This work was supported by Serbian Ministry of Science (grant 175033). We thank Merck Sharp & Dohme for their unrestricted educational grant. This work was also supported by biochemical laboratory "Zavod za laboratorijsku dijagnostiku Konzilijum" Belgrade, Serbia.

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