Relationship between Parathyroid Hormone and Depression in Heart Failure

Hakan Altay[1], Ali Zorlu[2], Halil Tolga Kocum[1], Senol Demircan[1], Nuryil Yilmaz[3], Mehmet Birhan Yilmaz[4]

Department of Cardiology, Baskent University Faculty of Medicine[1], Adana; Department of Cardiology, Bulanık State Hospital[2], Mus; Department of Psychiatry, Sivas State Hospital[3]; Department of Cardiology, Cumhuriyet University Faculty of Medicine[4], Sivas - Turkey

Abstract

Background: Depression has been found to be a predictor of rehospitalization and mortality in heart failure (HF). Parathyroid hormone (PTH) is a novel promising biomarker that can predict hospitalization, functional status and mortality in HF.

Objective: We aimed to investigate the association of depression with serum PTH levels in patients with systolic HF.

Methods: A total of consecutive 100 outpatients with systolic HF having left ventricular ejection fraction (LVEF) < 40%, were prospectively studied. All patients underwent laboratory tests, including brain natriuretic peptide (BNP) and PTH analyses. The patients were asked to complete the Beck Depression Inventory- II (BDI).

Results: Fifty-one patients (51%) were shown to have poor BDI score (BDIS > 18). Patients with poor BDI score had significantly higher PTH levels compared to those with good BDIS (133 ± 46 pg/ml vs. 71 ± 26 pg/ml, p < 0.001). In multivariable logistic regression model, PTH level (Odds ratio (OR) = 1.035, p = 0.003), LVEF (OR = 0.854, p = 0.004), NYHA functional class III/IV (OR = 28.022, p = 0.005), C-reactive protein (CRP) (OR = 1.088, p = 0.020), and presence of pretibial edema (OR = 12.341, p = 0.033) were found to be independent predictors of moderate to severe depression after adjustment of other potential confounders.

Conclusion: Systolic HF patients with moderate to severe depression had higher serum levels of PTH and CRP, poor functional status and lower LVEF. The association of depression with such parameters might explain the contribution of depression to hospitalization and mortality in HF. (Arq Bras Cardiol 2012;99(4):915-923)

Keywords: Parathyroid hormone; depression; heart failure/mortality; C-reactive protein.

Introduction

Chronic heart failure (HF) is a highly prevalent and costly disease in the world. Depression and depressive symptoms occur in 24% to 42% of HF patients[1]. Clinically significant depression is more prevalent in advanced HF[1]. When present, depression and depressive symptoms are associated with poorer functional capacity and survival, decreased compliance and response to treatment and greater use of healthcare services, including hospitalization and outpatient services.

Several factors including hypovitaminosis D, aldosteronism, chronic use of furosemide and impaired renal function have been shown to contribute to the appearance of secondary hyperparathyroidism in HF patients[2]. The association of serum intact Parathyroid Hormone (PTH) levels with severity and prognosis of HF has been recently reported[3]. Heart failure and depression share common pathophysiological aspects, both increasing the levels of circulating inflammatory cytokines[4].

Mailing Address: Hakan Altay•
Baskent University. Postal Code 01250, Adana, Turkey.
E-mail: sakaltay@yahoo.com, sakaltay@gmail.com
Manuscript received April 22, 2012; manuscript revised April 30, 2012; accepted July 31, 2012.

In view of these findings, we sought to verify the role of PTH in the prediction of clinically significant depression in patients with systolic HF, admitted to a tertiary care hospital for outpatient control visit.

Methods

A total of 100 consecutive patients with systolic HF (left ventricular ejection fraction < 40%) were prospectively enrolled between November 2010 and September 2011 in participating centers. Patients with end stage renal disease undergoing dialysis treatment, primary lung disease including moderate to severe chronic obstructive pulmonary disease, musculoskeletal diseases, myocardial infarction or unstable angina within previous 3 months, acute or chronic infection, inflammatory diseases such as sepsis, arthritis or systemic connective tissue disease, symptomatic coronary or peripheral vascular disease, long term alcoholism, valvular cardiomyopathy or artificial heart valve, malignant disease, significant liver, thyroid, parathyroid, suprarenal gland or pituitary disease, patients with impending signs and symptoms of decompensation or those who were hospitalized for a recent decompensation and patients without stable symptoms at least for a month were excluded.

Following obtaining informed consent for the study, all patients underwent laboratory tests, including Brain

Natriuretic Peptide (BNP) and PTH. Serum intact PTH levels were measured by using an Immulite intact PTH assay (Diagnostics Product Corporation, 2000, Los Angeles, California). The established normal range for this assay was 10 to 65 pg/ml.

All patients underwent depression assessment using the Beck Depression Inventory- II (BDI) scale. In this scale, the patients were classified as follows:

- From 0 to 9 points, none or minimally depressed;
- From 10 to 18 points, patients with mild depression;
- From 19 to 29 points, moderate depression;
- From 30 to 63 points, severe depression.

According to the result of the assessment of BDI-II, the patients were classified into two groups: group 1 - comprising patients with less than or equal to 18 points in the BDI-II scale (none or minimal depression or mild depression, good BDIS), and group 2 - comprising patients with a score higher than 18 (moderate or severe depression, poor BDIS)[5]. Patients were classified into 4 groups based on New York Heart Association (NYHA) functional class. Consensus of 2 experienced clinicians blinded to each other was required for classification of functional classes. In case of disagreement, a third opinion was obtained from an expert physician.

Hypertension was defined as blood pressure >140/90 mm Hg on >2 occasions during office measurements or having antihypertensive treatment. Diabetes mellitus was defined as fasting blood glucose >126 mg/dl or use of antidiabetic treatment. Ischemia as etiology of HF was recorded if there was a history of myocardial infarction or coronary intervention or documented coronary stenosis >50%. Those who continued smoking during the index admission were considered current smokers. Body mass index was calculated via dividing weight in kilograms by squared height in meters. Estimated creatinine clearance was calculated from serum creatinine values using the Cockroft-Gault Formula[6]. Rhythm, medications, and hemodynamic findings such as heart rate and systolic and diastolic blood pressures were evaluated. Presence of HF related hospitalization within the previous six months was carefully considered.

All patients underwent two-dimensional transthoracic echocardiography during index visit. Echocardiographic examinations were performed with the Vivid 7 system (GE Healthcare, Wauwatosa, Wisconsin) with 2.5- to 5-MHz probes in all participating centers. Left ventricular ejection fraction (LVEF) was calculated by the modified Simpson method. Chamber sizes were defined according to recent guidelines[7]. Transmitral diastolic flow was obtained by pulsed-wave Doppler from an apical four-chamber view, with the pulsed Doppler sample volume placed perpendicular to the inflow jet previously identified with the use of color Doppler. Mitral early and late diastolic inflow velocities were designated as E and A, respectively. Two-dimensionally guided pulsed-tissue Doppler imaging sample volume was placed at the level of the lateral mitral valve annulus, measuring the mitral annular early diastolic velocity, designated as E'. Left ventricle filling pressure was estimated using the ratio of E to E', designated as E/ E' [8]. Tricuspid annular plane systolic excursion (TAPSE) was measured using 2-dimensional echocardiographically guided M-mode recordings from the apical 4-chamber view with the cursor placed at the free wall of the tricuspid annulus[9].

Continuous variables were expressed as mean ± SD or median (interquartile range) in the presence of abnormal distribution, and categorical variables as percentages. Receiver operator characteristic curve analysis was performed to identify the optimal cut-off point of PTH (at which sensitivity and specificity would be maximal) for the prediction of poor BDI score. Areas under the curve (AUC) were calculated as measures of the accuracy of the tests. We compared the AUC with use of the Z test. Patients were categorized into two as poor (Group I) or good (Group II) BDI score. Comparisons between groups of patients were made by use of a $\chi 2$ test for categorical variables, independent samples t test for normally distributed continuous variables, and Mann-Whitney U test when the distribution was skewed. Correlations were evaluated either via Pearson or Spearman correlation tests. We used univariate cox proportional-hazards analysis to quantify the association of variables with moderate to severe depression. Variables found to be statistically significant in univariate analysis and other potential confounders were used in a multivariable logistic regression model with forward stepwise method in order to determine the independent predictors of moderate to severe depression. All statistical procedures were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL). A p value of 0.05 was considered statistically significant.

The study was performed in accordance with the Declaration of Helsinki for human research and was approved by the institutional ethics committee as part of a large study.

Results

Considering the whole cohort, the mean age of the patients was 64 ± 12 years (54% men). The mean PTH level was 101 ± 48 pg/ml. The demographic, clinical and echocardiographic characteristics of the study patients according to BDI score are listed in Table 1. A total of 51 patients (51%) were shown to have moderate to severe depression (BDIS > 18). Patients with clinically significant depression (BDIS > 18) had significantly higher PTH levels compared to those with mild or minimal or no depression (BDIS ≤ 18) (133 ± 46 pg/ml vs. 71 ± 26 pg/ml, $p < 0.001$). Mean levels of PTH increased as BDIS increased (Figure 1). Patients with poor BDIS had significantly higher CRP and BNP levels and lower sodium and creatinine clearance. These patients also had lower LVEF and higher LA size and E/E' ratio compared to patients with mild or minimal or no depression (BDIS ≤ 18). Women were more frequent in those with poor BDIS (Table 1). Beck depression score index was correlated with NYHA functional class ($r = 0.862$, $p < 0.001$), BNP levels ($r = 0.625$, $p < 0.001$), PTH levels ($r = 0.753$, $p < 0.001$), E/E' ratio ($r = 0.374$, $p < 0.001$), LVEF ($r = -0.572$, $p < 0.001$), CC ($r = -0.404$, $p < 0.001$), and CRP levels ($r = 0.336$, $p = 0.001$).

Table 1 - Baseline characteristics of study patients

	All patients	Beck Depression Score		p value
		≤ 18	> 18	
	(n:100)	(n:49)	(n:51)	
Baseline characteristics				
Mean age (years)	65 ± 13	63 ± 11	67 ± 14	0.108
Female gender	46 (46%)	17 (35%)	29 (57%)	0.026
Body mass index (kg/m^2)	27 ± 4	27 ± 4	28 ± 4	0.711
Ischemic etiology	55 (55%)	30 (61%)	25 (49%)	0.219
Hypertension	52 (52%)	28 (57%)	24 (47%)	0.313
Diabetes mellitus	37 (37%)	15 (31%)	22 (43%)	0.194
Smoking	38 (38%)	22 (45%)	16 (31%)	0.163
Disease duration (years)	4 ± 4	3 ± 3	6 ± 5	0.001
Atrial fibrillation	26 (26%)	12 (25%)	14 (28%)	0.821
HF related rehospitalization	50 (50%)	10 (20%)	40 (78%)	< 0.001
Hemodynamic findings				
NYHA Functional Class (mean±SD)	2.3 ± 1.0	1.5 ± 0.6	3.0 ± 0.8	< 0.001
NYHA Functional Class III/IV	40 (40%)	2 (4%)	38 (75%)	< 0.001
Heart rate (beats/minute)	88 ± 19	85 ± 21	91 ± 17	0.110
Systolic blood pressure (mmHg)	124 ± 25	128 ± 25	121 ± 21	0.024
Diastolic blood pressure (mmHg)	76 ± 13	77 ± 11	75 ± 14	0.205
Pretibial edema	48 (48%)	12 (25%)	36 (71%)	<0.001
Echocardiography parameters				
LV ejection fraction (%)	31 ± 10	37 ± 8	25 ± 9	< 0.001
LV diastolic diameter (cm)	5.7 ± 0.8	5.6 ± 0.7	5.9 ± 0.8	0.047
LV systolic diameter (cm)	4.5 ± 0.9	4.2 ± 0.7	4.7 ± 0.9	0.003
Left atrium size (cm)	4.4 ± 0.5	4.3 ± 0.5	4.6 ± 0.5	0.002
E/A velocity (m/sn)	1.2 ± 1.1	1.1 ± 1.0	1.3 ± 1.3	0.309
E/E' ratio	12.2 ± 17	7.6 ± 5.1	16.7 ± 22.3	< 0.001
LV diastolic dysfunction	57 (57%)	27 (55%)	30 (59%)	0.707
Tricuspid Annular Plane Systolic Excursion	1.7 ± 0.4	1.9 ± 0.3	1.4 ± 0.4	< 0.001
Right ventricular dilation	13 (13%)	4 (8%)	9 (18%)	0.154
Laboratory findings				
Hemoglobin (g/dl)	12.8 ± 1.8	13.1 ± 1.5	12.5 ± 2.1	0.119
Brain natriuretic peptide (pg/ml)	1148 ± 1189	464 ± 525	1805 ± 1280	< 0.001
Parathyroid hormone (pg/ml)	103 ± 49	71 ± 26	133 ± 46	< 0.001
Thyroid-stimulating hormone	1.6 ± 1.9	1.5 ± 2.2	1.7 ± 1.5	0.172
Creatinine clearance (ml/min)	80 ± 41	93 ± 38	68 ± 39	< 0.001
C-reactive protein (mg/l)	13.5 ± 16.7	7.4 ± 5.8	19.4 ± 21	< 0.001
Alanine aminotransferase	66 ± 232	45 ± 137	87 ± 297	0.564
Aspartat aminotransferase	68 ± 199	64 ± 240	72 ± 151	0.148
Sodium (mmol/L)	137 ± 12	140 ± 3.0	134 ± 16	0.001
Potassium (mmol/L)	4.4 ± 0.7	4.3 ± 0.4	4.5 ± 0.9	0.071
Medication				

Beta-blockers	81 (81%)	38 (78%)	43 (84%)	0,388
ACE inhibitors/ARB	83 (83%)	41 (84%)	42 (82%)	0,860
Antiplatelet agents	84 (84%)	41(84%)	43 (84%)	0,930
Nitrate	29 (29%)	12 (25%)	17 (33%)	0,329
Statine	34 (34%)	18 (37%)	16 (31%)	0,571
Spironolactone	33 (33%)	8 (16%)	25 (49%)	< 0,001
Furosemide	65 (65%)	23 (47%)	42 (82%)	< 0,001

HF: Heart Failure, NYHA: New York Heart Association, LV: Left ventricle, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker

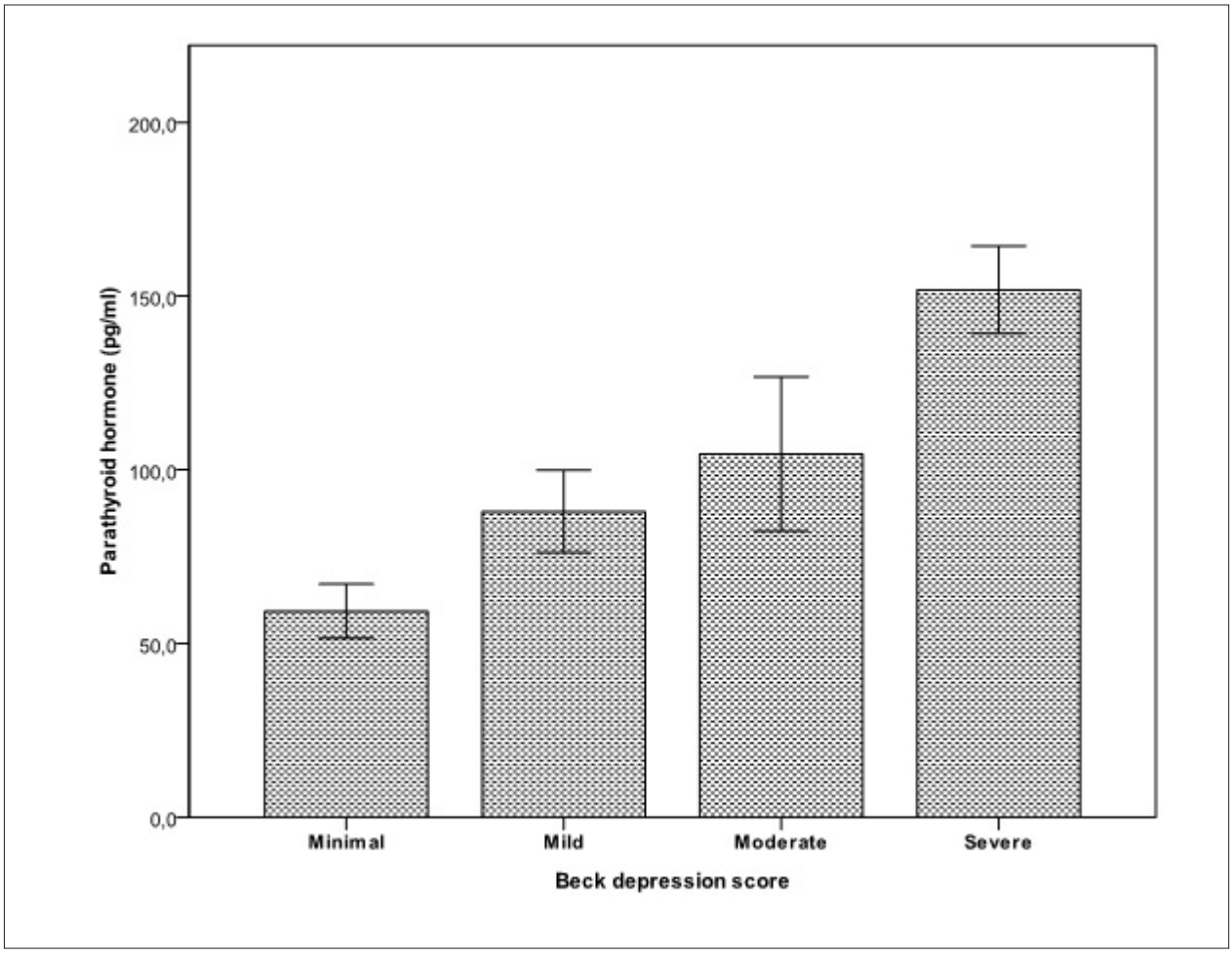

Figure 1 – *Comparison of parathyroid hormone levels between four groups.*

Furthermore, serum PTH levels were correlated with NYHA functional class ($p < 0.001$), BNP levels ($p < 0.001$), E/E' ratio ($p < 0.001$), TAPSE ($p < 0.001$), LVEF ($p < 0.001$), CC ($p < 0.001$), presence of pretibial edema ($p < 0.001$), HF related rehospitalization ($p < 0.001$), and CRP levels ($p = 0.002$) (Table 2).

Parathyroid hormone, LVEF, NYHA functional class III/IV, CRP, pretibial edema, HF related rehospitalization, E/E' ratio, TAPSE, BNP, disease duration, serum sodium, LA size, CC, left ventricular systolic diameter, and female gender were associated with poor BDIS in univariate analysis. In multivariable logistic regression model, PTH level (Odds ratio (OR) = 1.035, $p = 0.003$), LVEF (OR = 0.854, $p = 0.004$), NYHA Functional Class III/IV (OR = 28.022, $p = 0.005$), CRP (OR = 1.088, $p = 0.020$), and presence of pretibial edema (OR = 12.341, $p = 0.033$) were found to be independent predictors of poor BDIS after adjustment of other potential confounders (Table 3).

In face of the difference in PTH levels between the patients with clinically significant depression, i.e moderate or severe

depression (BDIS > 18) and no or minimal or mild depression (BDIS ≤ 18), a ROC curve was constructed which identified the PTH level of 99 pg/ml as the best cut off point with 76.5% sensitivity and 87.8% specificity (area under the curve 0.871, 95% confidence interval 0.789 to 0.929; Figure 2).

Discussion

Not only does the incidence of depression increase with the presence of HF, but it is also related to its severity, being more frequent in advanced HF[10]. This study demonstrated that depression was associated with clinical, echocardiographic and laboratory parameters all of which have been proven to be well established predictors of advanced HF. It also demonstrated that relationship between serum PTH and clinically significant depression was independent of clinical features and pertinent demographic characteristics, such as LVEF, NYHA functional class, CRP, HF related rehospitalization, disease duration and female gender.

A recent study demonstrated that high serum PTH levels were strongly associated with advanced HF[11]. This association has been explained by the fact that secondary hyperparathyroidism may contribute to the systemic illness that accompanies advanced HF[12]. This systemic illness and chronic nature of HF may contribute to depression. The association of depressive disorders and primary hyperparathyroidism has been shown before[13] where the resultant hypercalcemia was thought to be the mechanism responsible for the production of depressive symptoms. High serum PTH levels are thought to be related to the systemic induction of oxidative stress that leads to tissue injury and contributes to the pathophysiology of HF[14]. Increased oxidative stress may also play a critical role in the pathophysiology of depression in chronic HF[15]. Whether or not there is a cause-and-effect relationship, it is very obvious that high levels of circulating PTH and depression are highly associated especially in patients with advanced systolic HF.

The association of low Vitamin D and mortality in HF has recently been shown[16]. This association may occur directly or through activation of renin-angiotensin-aldosterone system (RAAS)[17]. The association of Vitamin D deficiency and depression has been shown both in general population[18] and HF population[19]. Vitamin D receptors are present in the brain, and the central nervous system contains enzymes necessary for vitamin D hydroxylation, making it biologically plausible for vitamin D to be associated with brain activity and thus depression[20]. Immobilization and antisocial behavior

Table 2 – Correlation coefficients for Parathyroid hormone

	r	p value
NYHA Functional Class	0.784	< 0.001
Brain natriuretic peptide (pg/ml)	0.748	< 0.001
Tricuspid Annular Plane Systolic Excursion	-0.731	< 0.001
E/E' ratio	0.709	< 0.001
HF related rehospitalization	0.690	< 0.001
Pretibial edema	0.653	< 0.001
Creatinine clearance (ml/min)	-0.552	< 0.001
Left ventricle ejection fraction (%)	-0.498	< 0.001
Sodium (mmol/L)	-0.494	< 0.001
Left atrium size (cm)	0.442	< 0.001
Disease duration (years)	0.437	< 0.001
Heart rate (beats/minute)	0.367	< 0.001
Left ventricle systolic diameter (cm)	0.317	0.001
Right ventricular dilation	0.314	0.001
C-reactive protein (mg/l)	0.302	0.002
Systolic blood pressure (mmHg)	-0.296	0.003
Female gender	-0.275	0.006
Diastolic blood pressure (mmHg)	-0.239	0.017
Atrial fibrillation	0.234	0.019
Potassium (mmol/L)	0.224	0.025
Spironolactone usage	0.499	< 0.001
Furosemide usage	0.710	< 0.001

HF: Heart Failure, NYHA: New York Heart Association, LV: Left ventricle, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker

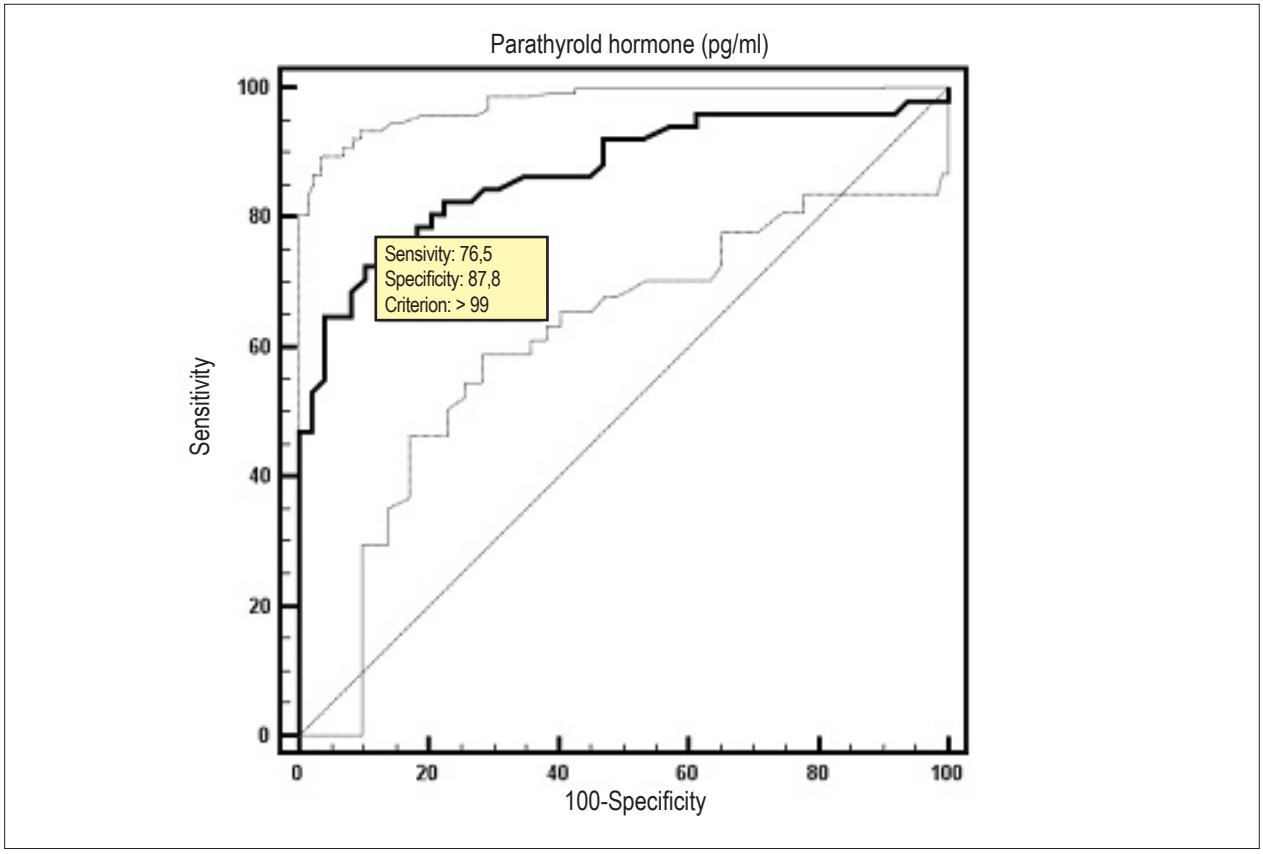

Figure 2 – *ROC Curve for PTH to predict poor BDI score.*

of HF patients, especially more prominent when they are depressive, may lead to inadequate exposure to sunlight and hence Vitamin D deficiency. Low serum Vitamin D levels or more accurately, inadequate biologic Vitamin D activity causes serum PTH excess. Because of this, one can hypothesize that the associations of lower Vitamin D activity concentrations with cardiovascular outcomes and depression could be indirectly demonstrated by the presence of serum PTH excess.

CRP was also found to be a strong independent predictor of clinically significant depression in our study. A vicious circle between HF and inflammation is present because inflammatory markers, such as IL-6 and CRP, have been found to be associated with worsening of cardiac function and advanced systolic HF[21]. Besides, higher levels of inflammatory markers are also found in patients with depression but without HF[22].

Further investigation is needed to understand the potential interaction of depression, increased PTH and CRP levels in the pathophysiology of systolic HF, all of which may simply be a marker or drive causality. It is well known that depression is under-recognized and undertreated in HF patients[23]. Our data shows that high PTH and CRP levels may aid early recognition of clinically significant depression in outpatients with HF who have concomitant low EF and high NYHA functional class.

BNP has been widely used as a biomarker to define the diagnosis and prognosis in patients with HF[24]. In our study, we demonstrated that patients with clinically significant depression had significantly higher BNP levels. However, when other potential confounders were included, high BNP levels did not predict poor BDI score. This result was different from the recently conducted study which reported that BNP predicted severe depression in HF patients[25]. The change in the loading (volume) status of the ventricles is known to affect its level in the blood. However, PTH seems to be secreted after a long chain of reactions in the body and not affected by the volume status[26].

Other independent predictors of clinically significant depression were low LVEF and high NYHA functional class both of which had been shown to have well established association with depression in patients with HF in the previous studies[1]. Consistent with previous studies, female gender was associated with clinically significant depression in this study[1]. Heart failure related rehospitalization were found to be significantly more common in patients with clinically significant depression (Table 1). This result is same as in the literature which reported that depressed patients were hospitalized approximately three times more frequently than non-depressed patients, and depression increased the costs of HF treatment by 25%-40%[9].

There are some limitations of the current study worthwhile mentioning. Sample size, though calculated before the study, is not enough to draw definitive conclusions. Furthermore, the behavior and serum level of PTH in patients with RAAS

Table 3 - Univariate and multivariate predictors of poor beck depression score

	Univariate			Multivariate		
Variable	**OR**	**p**	**95% CI**	**OR**	**p**	**95% CI**
Statistically significant variables						
Parathyroid hormone (pg/ml)	1.043	< 0.001	1.026-1.059	1.035	0.003	1.012-1.059
Left ventricle ejection fraction (%)	0.855	< 0.001	0.801-0.912	0.854	0.004	0.767-0.950
NYHA Functional Class III/IV	19.388	< 0.001	5.992-62.736	28.022	0.005	2.776-282.908
C-reactive protein (mg/l)	1.092	0.003	1.029-1.158	1.088	0.020	1.014-1.168
Pretibial edema	7.400	< 0.001	3.048-17.966	12.341	0.033	1.220-124.857
Female gender	2.481	0.028	1.106-5.567			
Disease duration (years)	1.243	0.001	1.089-1.418			
HF related rehospitalization	14.182	<0.001	5.412-37.160			
Left ventricle systolic diameter (cm)	2.153	0.005	1.255-3.694			
Left atrium size (cm)	3.415	0.004	1.479-7.886			
E/E' ratio	1.241	< 0.001	1.105-1.394			
Tricuspid Annular Plane Systolic Excursion	0.021	< 0.001	0.004-0.104			
Brain natriuretic peptide (pg/ml)	1.002	< 0.001	1.001-1.003			
Creatinine clearance (ml/min)	0.981	0.004	0.969-0.994			
Sodium (mmol/L)	0.812	0.001	0.719-0.917			
Spironolactone usage	4.928	0.001	1.934-12.559			
Furosemide usage	5.275	< 0.001	2.118-13.141			
Variables which correlated with Parathyroid hormone						
Potassium (mmol/L)	1.749	0.085	0.926-3.304			
Right ventricular dilation	2.411	0.168	0.690-8.419			
Atrial fibrillation	0.857	0.736	0.350-2.099			
Systolic blood pressure (mmHg)	0.987	0.127	0.970-1.004			
Diastolic blood pressure (mmHg)	0.986	0.374	0.956-1.017			
Heart rate (beats/minute)	1.018	0.115	0.996-1.041			

All the variables from Table 1 were examined and only those significant at P < 0.05 level and correlated with Parathyroid hormone are shown in univariate analysis. Multivariate logistic regression model including all the variables in univariate analysis. CI: Confidence interval; OR: Odds ratio

blockade is unpredictable, particularly among those having aldosterone-blocking agent. However, it is of note that this study was not designed to test the temporal behavior of PTH with the therapy, and all patients were clinically stable and under chronic stable HF therapy with stable doses. Hence, we think that the discussion of interaction between confounders and PTH cannot go beyond simple hypothetical link. However, the association of PTH to depression (poor BDIS) presented herein is strong, and independent and the univariate interaction between aldosterone blockade and poor BDIS was lost in the multivariate testing.

In conclusion, the prevalence of depression in advanced HF is high; patients with depression present higher PTH and CRP levels than non-depressed patients; and the higher the NYHA of the patient, the higher their chance of having clinically significant depression. High PTH and CRP levels in a stable systolic HF outpatient should suggest the possibility of clinically significant depression particularly in the presence of high NYHA functional class.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

References

1. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol. 2006;48(8):1527–37.
2. Khouzam RN, Dishmon DA, Farah V, Flax SD, Carbone LD, Weber KT. Secondary hyperparathyroidism in patients with untreated and treated congestive heart failure. Am J Med Sci. 2006;331(1):30–4.
3. Sugimoto T, Tanigawa T, Onishi K, Fujimoto N, Matsuda A, Nakamori S, et al. Serum intact parathyroid hormone levels predict hospitalisation for heart failure. Heart. 2009;95(5):395–8.
4. Ferketich AK, Fergusson JP, Binkley PF . Depressive symptoms and inflammation among heart failure patients. Am Heart J. 2005;150(1):132–6.
5. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561-71.
6. Cockroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.
7. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, *et al*. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685–713.
8. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol. 1997;30(6):1527–33.
9. Ghio S, Recusani F, Klersy C, Sebastiani R, Laudisa ML, Campana C, et al. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol.* 2000;85(7):837–42.
10. Norra C, Skobel EC, Arndt M, Schauerte P. High impact of depression in heart failure: early diagnosis and treatment options. Int J Cardiol. 2008;125(2):220–31.
11. Altay H, Zorlu A, Binici S, Bilgi M, Yilmaz MB, Colkesen Y, *et al*. Relation of serum parathyroid hormone level to severity of heart failure. Am J Cardiol. 2012;109(2):252–6.
12. Alsafwah S, Laguardia SP, Arroyo M, Dockery BK, Bhattacharya SK, Ahokas RA, *et al*. Congestive heart failure is a systemic illness: a role for minerals and micronutrients. Clin Med Res. 2007;5(4):238–43.
13. Watson LC, Marx CE. New onset of neuropsychiatric symptoms in the elderly: possible primary hyperparathyroidism. Psychosomatics. 2002;43(5):413–7.
14. Sun Y, Ahokas RA, Bhattacharya SK, Gerling IC, Carbone LD, Weber KT. Oxidative stress in aldosteronism. Cardiovasc Res. 2006;71(2):300–9.
15. Michalakeas CA, Parissis JT, Douzenis A, Nikolaou M, Varounis C, Andreadou I, *et al*. Effects of sertraline on circulating markers of oxidative stress in depressed patients with chronic heart failure: a pilot study. J Card Fail. 2011;17(9):748–54.
16. Schierbeck LL, Jensen TS, Bang U, Jensen G, Køber L, Jensen JE. Parathyroid hormone and vitamin D--markers for cardiovascular and all cause mortality in heart failure. Eur J Heart Fail. 2011;13(6):626–32.
17. Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 1,25-Dihydroxyvitamin D (3) is a negative endocrine regulator of the rennin-angiotensin system. J Clin Invest. 2002;110(2):229–38.
18. Schneider B, Weber B, Frensch A, Stein J, Fritz J. Vitamin D in schizophrenia,major depression and alcoholism. J Neural Transm. 2000;107(7):839–42.
19. May HT, Bair TL, Lappé DL, Anderson JL, Horne BD, Carlquist JF, *et al*. Association of vitamin D levels with incident depression among a general cardiovascular population. Am Heart J. 2010;159(6):1037–43.
20. Stumpf WE, Sar M, Clark SA, DeLuca HF. Brain target sites for 1,25-dihydroxyvitamin D3. Science. 1982;215(4538):1403–5.
21. Anand IS, Latini R, Florea VG, Kuskowski MA, Rector T, Masson S, *et al*; Val-HeFT Investigators. C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation. 2005;112(10):1428–34.
22. Bremmer MA, Beekman AT, Deeg DJ, Penninx BW, Dik MG, Hack CE, *et al*. Inflammatory markers in late-life depression: results from a population-based study. J Affect Disord. 2008;106(3):249–55.
23. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry. 1998;55(7):580–92.
24. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukai D, *et al*. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure:prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation. 1997;96(2):509 –16.
25. Aguiar VB, Ochiai ME, Cardoso JN, Del Carlo CH, Morgado PC, Munhoz RT, *et al*. Relationship between depression, BNP levels and ventricular impairment in heart failure. Arq Bras Cardiol. 2010;95(6):732-37.
26. Weber KT, Simpson RU, Carbone LD. Vitamin D and calcium dyshomoeostasis-associated heart failure. Heart. 2008;94(1):540 –1.

Original Article