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RESEARCH ARTICLE

Study of Parathyroid Hormone as an Independent Risk Marker of Heart Failure

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ABSTRACT

Introduction: Heart failure (HF) is a clinical syndrome characterized by cardiac pump failure with signs and symptoms arising from salt and water retention. Heart failure is associated with considerable mortality and morbidity. Identification of modifiable risk factors may reduce incidence of HF and its complications. The aim of our study is to assess parathyroid hormone (PTH) as a risk marker for HF and its association with severity of HF.

Materials and methods: In this cross-sectional study, 120 subjects with HF were recruited and they were compared with 60 age- and sex-matched controls. Along with the routine parameters, N-terminal pro B-type natriuretic peptide (NT-proBNP), intact PTH, and vitamin D were estimated. The study group was divided into quartiles depending on PTH value.

Results: The median PTH (81.5 pg/mL) and NT-proBNP (3753 pg/mL) in HF patients are found to be significantly higher ($p < 0.0001$) when compared with control subjects. The median vitamin D concentration (18 ng/mL) though low in cases is not statistically significant when compared with controls. Demographic, clinical, and laboratory characteristics are compared across the quartiles of PTH. Highest number of New York Heart Association (NYHA) class IV HF cases are found in highest quartiles of PTH. Logistic regression analysis demonstrated that high concentration of PTH [odds ratio of 1.1113; 95% confidence interval (CI) 1.07–1.14; $p < 0.0001$] and low levels of vitamin D (odds ratio of 1.053; 95% CI 1.0079–1.1009) are significantly associated with HF.

Conclusion: This study has demonstrated that higher concentration of PTH is associated with severe form of HF. Vitamin D deficiency is also seen in the study group.

Keywords: Heart failure, Parathyroid hormone, Vitamin D

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INTRODUCTION

Heart failure is a clinical syndrome characterized by cardiac pump failure with signs and symptoms arising from salt and water retention. Heart failure is also associated with systemic illness, especially in advanced stages characterized by oxidative stress in various tissues causing damage to soft tissues and bone. Heart failure is a major epidemic and a significant public health burden associated with considerable morbidity and mortality.[1] It results not only from cardiac overload or injury but also from a complex relationship between genetic, neurohormonal, inflammatory, and biochemical changes.[2]

Hypertension and coronary artery disease are predominant causes of HF and account for 80% of all the cases. The well-recognized modifiable risk factors for HF are hypertension, impaired glucose tolerance, an elevated total and high-density lipoprotein cholesterol ratio, obesity, cigarette smoking,[3] and other potential modifiable risk factors that include altered mineral metabolism, deficiency of vitamin D, stimulation of inflammatory cytokines, and oxidative stress. Identification of modifiable risk factor of HF may reduce incidence of HF and its complications.

Parathyroid hormone, a peptide hormone secreted by parathyroid gland, helps in calcium homeostasis. A decrease in concentration of calcium releases PTH, which enhances calcium reabsorption from ascending limb of loop of Henle and causes excretion of phosphorus in proximal duct. Secondly, it stimulates 1-α-hydroxylation of 25-hydroxyvitamin D to 1, 25-dihyrdroxy vitamin D, which in turn causes reabsorption of calcium from the gut. Parathyroid hormone also acts on osteoclast causing bone resorption with release of phosphorus and calcium in the blood.[4] In order to maintain serum calcium within a narrow range, PTH and vitamin D act together in response to changes in serum calcium levels. Decreasing vitamin D levels leads to increasing PTH concentrations.[5]

Many studies have shown that PTH has chronotropic[6] and inotropic effects on cardiac muscle, along with a direct hypertrophic effect on cardiomyocytes.[7]

The aim of the present study is to assess PTH as a risk marker in HF and its association with severity of HF.

MATERIALS AND METHODS

In this cross-sectional study, 120 consecutive patients admitted in cardiac intensive care unit during the month

of June and July 2016 in Nizam's Institute of Medical Sciences, Hyderabad, India, with the diagnosis of HF based on clinical features and echocardiography were recruited. For every patient age, sex, NYHA class, left ventricular ejection fraction (LVEF), and medication, along with the history of diabetes, hypertension, heart rate and rhythm, and cause of HF were noted. Subjects with vitamin D supplementation were excluded. In control group, 60 age- and sex-matched healthy controls were included. Random blood sample was collected and analyzed for the following biochemical parameters: NT-proBNP and intact PTH were estimated by sandwich immunoassay, and total 25-hydroxyvitamin D was measured by competitive immunoassay on Cobas e411 (Roche Diagnostics Mannheim Germany).

Serum albumin and creatinine were measured by bromocresol green and Jaffe's rate blank colorimetric assay respectively; serum alkaline phosphatase was estimated by International Federation of Clinical Chemistry method; serum calcium, phosphorus, and magnesium were measured by colorimetric assays on Cobas C501 (Roche Diagnostics Mannheim Germany).

Echocardiography was performed by the same cardiologist for all these patients. All samples were analyzed on the same day of collection.

Statistical Analysis

As the data are not normally distributed, it is presented as medians and interquartile range for continuous variables. Mann–Whitney U test is used to compare cases with controls. Demographic, clinical, and laboratory characteristics were compared across quartiles of PTH by Kruskal–Wallis test for continuous variables. Logistic regression was used to correlate the association between serum PTH and congestive heart failure (CHF).

All reported p-values are two-tailed, with $p < 0.05$ indicating statistical significance. Analysis was performed using MedCalc version 16.8 software.

RESULTS

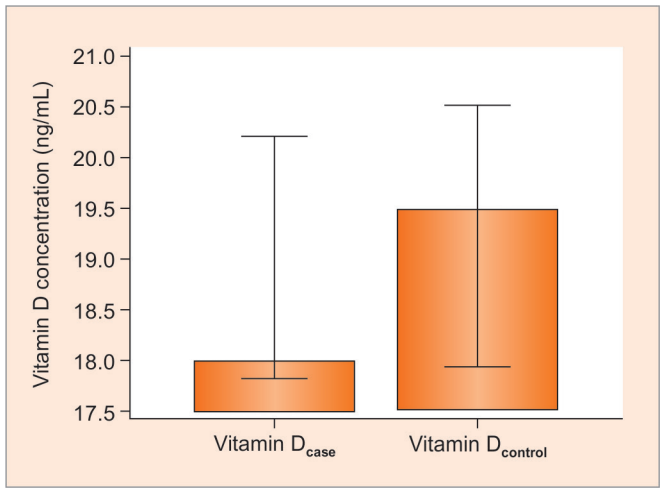
The study group consisted of 80 males and 40 females, with mean age group of 56 years. These cases were compared with 60 age- and sex-matched controls.

The mean NT-proBNP and PTH are 3752 pg/mL and 81.5 pg/mL respectively, which is higher in cases as compared with controls and is statistically significant.

The median LVEF is 30%, which is lower than controls and is statistically significant. The median vitamin D concentration in cases is 18 ng/mL and this is lower than the control group, but is not statistically significant (Graph 1).

The median alkaline phosphatase, creatinine, and phosphorus concentrations are 97 U/L, 1.2 mg/dL, and 4.2 mg/dL respectively, which are significantly higher in cases compared with controls.

The median serum albumin, calcium, and magnesium are 3.3 g/dL, 9 mg/dL, and 0.6 mmol/L respectively, and are significantly lower in cases compared with controls. A total of 104 (86.6%) cases had vitamin D insufficiency and 100 (83.3%) subjects have PTH concentration above the normal range (Table 1).



Graph 1: Concentration of Vitamin D in cases and controls

Table 1: Baseline characteristics of variables in study groups

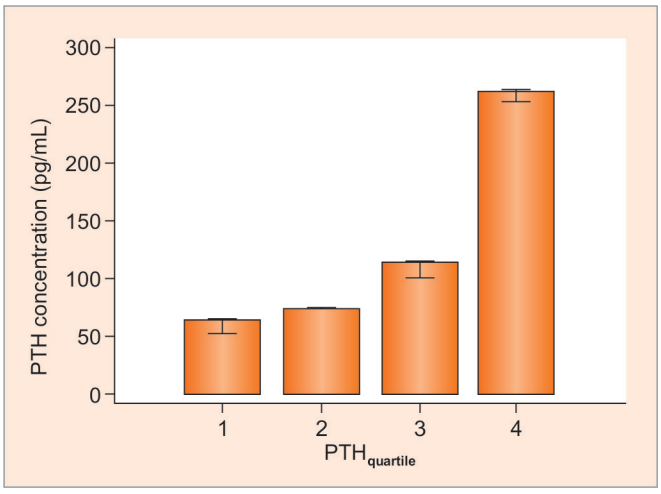
Variable	*Cases*	*Controls*	*p-value*
Number of subjects	n = 120	n = 60	
Age (years)	55 (50–62)	53 (50–58)	NS
Albumin (g/dL)	3.3 (3–3.5)	3.9 (3.5–4.4)	<0.0001
Alkaline phosphatase (U/L)	97 (81–111)	73 (66–84)	<0.0001
Calcium (mg/dL)	9 (8.7–9.2)	9.4 (9–9.6)	<0.0001
Creatinine (mg/dL)	1.2 (1.1–1.5)	0.9 (0.8–1.1)	<0.0001
LVEF (%)	30 (26–40)	60 (58–63)	<0.0001
Magnesium (mmol/L)	0.6 (0.6–0.8)	1.1 (1–1.2)	<0.0001
NT-proBNP (pg/mL)	3752 (1078–10857)	54 (34–55.6)	<0.0001
Phosphorus (mg/dL)	4.2 (3.6–4.8)	2.9 (2.5–3.3)	<0.0001
PTH (pg/mL)	81.5 (67–117)	34.5 (31.4–42)	<0.0001
Vitamin D (ng/mL)	18 (15–27)	19.5 (15–22)	NS

Values expressed are median (interquartile range); NS: Not significant

Table 2: Baseline demographics according to quartiles of PTH

Variable	*Lower quartile, median = 64.14 pg/mL, range 34.4–67*	*Second quartile, median = 75.31 pg/mL, range 68–78*	*Third quartile, m = 114 pg/mL, range 85–117*	*Highest quartile, median = 263 pg/mL, range 118–285*	*p-value*
Number of patients	30	30	30	30	
Age; years (interquartile range)	55 (54–58)	65 (49–70)	58 (50–60)	52 (48–62)	0.02
Male gender (%)	63.40	53	56.70	76.70	
NYHA class (%)					
II	11 (35.48)	16 (51.61)	4 (12.9)	0	
III	15 (37.5)	9 (22.5)	7 (17.5)	9 (22.5)	
IV	4 (8.16)	4 (8.16)	20 (40.8)	21 (42.85)	
LVEF (%)	35 (30–45)	45 (26–49)	25 (25–34)	30 (30–34)	<0.0001
Laboratory values (interquartile range)					
Albumin (g/dL)	3.4 (3.3–3.5)	3 (2.8–3.2)	3.7 (3.3–3.9)	3.2 (3–3.5)	<0.0001
Alkaline phosphatase (U/L)	90 (81–92)	113 (100–149)	97.5 (81–98)	95 (78–111)	<0.0001
Calcium (mg/dL)	9.5 (9.3–9.7)	9.1 (8.9–9.5)	9.4 (9.3–9.8)	9.2 (9–9.5)	<0.0001
Creatinine (mg/dL)	1.2 (1.1–1.4)	1.4 (1–1.7)	1.4 (1.1–1.6)	1.2 (1.1–1.3)	NS
Hemoglobin (g/dL)	12.8 (11–14)	11.3 (11–11.5)	13 (12.8–13)	11 (11–16)	<0.0006
Magnesium (mmol/L)	0.6 (0.6–0.7)	0.6 (0.5–0.6)	0.7 (0.6–0.8)	0.8 (0.5–0.9)	<0.0004
NT-proBNP (pg/mL)	1072 (940–2620)	6724 (4622–27270)	3652 (3553–5638)	17190 (2937–18777)	<0.0001
Phosphorus (mg/dL)	3.6 (3.1–4.3)	4 (3.9–6.4)	4.4 (3.6–5)	4.2 (3.7–4.6)	<0.002
Vitamin D (ng/mL)	16 (14–17.2)	22.2 (15–38.6)	22.4 (18–27)	18 (14–19)	<0.001

Values expressed are median (interquartile range)



Graph 2: Concentration of PTH in different quartiles

Demographic, clinical, and laboratory data were compared across quartiles of PTH. Significant difference is found in age, LVEF%, albumin, alkaline phosphatase, calcium, phosphorus, magnesium, NT-proBNP, and vitamin D across the quartiles of PTH (Table 2).

The mean concentration of PTH across different quartiles is depicted in Graph 2.

Highest quartile of PTH has more of NYHA class IV HF cases compared with other quartiles, indicating high PTH is associated with severe disease, which accounts for 42.85% (n = 21) of total class IV patients in the study.

The concentration of PTH showed significant positive correlation with NT-proBNP, r = 0.409 ($p<0.001$; 95% CI 0.248–0.548), and negative correlation with vitamin D, r = −0.26 ($p<0.001$, 95% CI −0.419 to −0.084) and LVEF, r = −0.343 ($p<0.0001$, 95% CI −0.492 to 0.17) (Table 3).

Table 3: Correlation for PTH

Dependent variable	*Variable*	*Correlation coefficient r*	*p-value*
PTH	Age	−0.06	NS
	NT-proBNP	0.41	<0.0001
	Vitamin D	−0.26	<0.0001
	EF%	−0.343	0.0001
	Alkaline phosphatase	−0.078	NS
	Calcium	−0.016	NS
	Hemoglobin	−0.035	NS

NS: Not significant

Logistic regression analysis demonstrated that high concentration of PTH (odds ratio of 1.1113; 95% CI 1.07–1.14; $p<0.0001$) and low levels of vitamin D (odds ratio of 1.053; 95% CI 1.0079–1.1009) are significantly associated with HF.

DISCUSSION

Heart failure is a syndrome with considerable morbidity and mortality. Hyperparathyroid disorders are associated with osteoporosis and altered mineral metabolism. Increased PTH concentration is responsible for overloading of calcium in cardiomyocytes through a receptor-mediated influx of calcium, which eventually results in necrosis of the cell and causes worsening of the cardiac function.[8]

Parathyroid hormone has been shown to be an independent predictor of all-cause and cardiovascular

mortality in patients with HF.[7] In this study, we found that high PTH is significantly associated with HF and can be considered as independent risk factor for CHF. These findings are consistent with a community-based study by Hagström et al,[9] who showed that PTH predicts HF hospitalization and is an independent risk factor for HF. Several factors are responsible for increase in PTH concentration in HF. Firstly, there is an increased calcium loss and impaired cation homeostasis, as a consequence of hormonal changes (hyperadrenergic state and secondary hyperaldosteronism).[10,11]

Calcium loss is also triggered by diuretics used to treat HF,[12] although conflicting results have also been reported.[11] In our study, we observed a normal serum calcium concentration.

Secondly, a low concentration of vitamin D can also lead to increased concentration of PTH.[13-15] In our study, 98 (81.67%) patients are vitamin D insufficient. This is consistent with Schierbeck et al,[7] who have reported a vitamin D insufficiency of 43% in their study subjects. Vitamin D deficiency is also associated with increased arterial wall stiffness in young population and this is independent of PTH concentration. The higher number of insufficiency in our study group is due to the deficiency of vitamin D seen in our population. High PTH has deleterious effect on heart by several mechanisms. High PTH causes endothelial dysfunction and atherosclerosis causing cardiac ischemia and consequently HF.

Parathyroid hormone has direct detrimental effect on myocardium as PTH receptors are also found on myocardium and high PTH may induce myocyte hypertrophy, fibrosis, left ventricular hypertrophy, and nonischemic HF.[9]

High concentration of PTH is associated with severity of CHF. There are several studies that have shown that high PTH concentration is associated with severity of disease indicated by NYHA functional classification and LVEF%.[13,16] In our study, we have also found that NYHA class IV patients (43%) are more in highest quartiles of PTH. Further, the EF% shows a significant negative correlation with PTH concentration, indicating that more severe form of disease is associated with high PTH. Circulating PTH levels also showed significant correlation with NT-proBNP levels. NT-proBNP is produced primarily within heart and is released into circulation in response to increased wall tension and is a sensitive marker of HF. Several studies have shown that high concentration of PTH is a predictor of hospitalization.[8,9]

The predictive value of PTH in cardiovascular and all-cause mortality in HF has been documented to be independent of known risk factors, such as estimated glomerular filtration rate, LVEF, NT-proBNP, and age.[17]

The cardiac impact of PTH is also related to calcium overloading in myocardial cells.

Hyperparathyroidism has also been documented to trigger oxidative stress.[4] When PTH levels are increased, a high H_2O_2 production is observed in peripheral mononuclear cells.[4,10] The increased intracellular calcium induced by PTH might impair the mitochondrial function and ATP production, inducing reactive oxygen species and leading to oxidative stress as well as inflammation and in the end to cardiomyocyte necrosis.[10,11]

Parathyroid hormone is found to stimulate the adrenal aldosterone synthesis.[17-19] A relative aldosterone excess can cause sodium retention and oxidative stress.[20,21]

The significance of demonstration of association of PTH and HF is that it can be an adjustable factor in the setting of low vitamin D concentration. In our study group, 83% of subjects have PTH above the normal range, while none of them have primary hyperparathyroidism. The secondary hyperparathyroidism found in these cases can be due to vitamin D insufficiency, which can be corrected with vitamin D supplementations.

Although large numbers of studies are available suggesting a causal role of high PTH in HF and our study also shows the same, there is no available evidence to suggest that decreasing PTH concentration will reduce the risk of HF. More interventional studies are needed to evaluate the potential role of PTH lowering to prevent HF.

CONCLUSION

Higher concentration of PTH is associated with severe form of HF. Parathyroid hormone estimation can help in risk stratification of CHF patients. Vitamin D insufficiency is seen in the study group; supplementation of vitamin D may be beneficial to the patients with HF.

LIMITATION

Due to relatively small sample size of the study group, the results cannot be generalized, and milder cases that do not need hospitalization are not included in the study.

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