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PTH in risk stratification in CHF

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***Abstract*---**Background: Although cardiac myocytes are the target cells for parathyroid hormone (PTH), there is limited data on the role of PTH in the setting of Congestive Heart Failure (CHF). The present study sought to evaluate the role of PTH in risk stratification among patientswith CHF. Methods: This cross-sectional study was carried outfor a period of 19 months among 50 patients admitted with CHF. The severity of CHF was graded based on New York Heart Association classification (NYHA) classificationbased on functional status and by the need for ICU care. Serum PTH levels were measured for all the study participants. Results: A total of 19 patients (38%) required ICU care and all belonged to the NYHA class 4.There was a significant difference in the PTH values among the different NYHA classes (NYHA 2 - 36pg/mL ±15; NYHA 3 - 51 pg/mL ± 30; NYHA 4 - 92 pg/mL ± 45; p<0.001). PTH levels among patients requiring ICU care was significantly higher when compared to those not requiring the same (109.3 pg/mL (95% CI: 87.4 to 131.3] vs 49.8 pg/mL [95% CI: 40.6 to 59]; p<0.001). Based on the subgroup analysis, a PTH value of 69.1pg/ml was the cut-off value to determine the need for ICU care among CHF patients. Conclusion: PTH levels play a significant role in the risk stratification among patients admitted with CHF.Inclusion of PTH in monitoring of cardiac parameters can help in preventing morbidity and mortality associated with congestive heart failure.

Keywords---parathyroid hormone, congestive heart failure, risk stratification.

Introduction

Parathyroid hormone (PTH) is essentially involved in systemic calcium homeostasis. It is a well established fact that the primary organs involved in synthesis and action of PTH are bone and kidneys, by promoting bone remodelling and calcium absorption in the intestine. However, increased expression of PTH in the cardiovascular cells was a recent finding and cardiomyocytes are the potential targets for PTH.[1] Further evidences prove that elevated levels of PTH have significant role to play in non-ischemic heart failure. [2] The action of PTH on cardiomyocytes have already been implicated in worsening of atherosclerosis, hypertension and left ventricular hypertrophy. [3,4] A meta-analysis demonstrated that higher serum level of parathyroid hormone was associated with an increased risk of cardiovascular mortality. [5] Certain studies have also demonstrated that serum levels of PTH increased as New York Heart Association (NYHA) functional class increased. PTH was further found to be directly correlated with several indicators of poor prognosis, including elevated brain natriuretic peptide (BNP), reduced ejection fraction of left ventricle, reduced creatinine clearance, loop diuretic usage, and atrial fibrillation. Therefore, the potential role of PTH in determining cardiovascular mortality has been explored.

Among the various cardiac morbidities, Heart failure is a growing public health problem, affecting 1–2% of the general population, with an estimated prevalence of 25 million patients worldwide and about 1.3 to 4.6 million Indians. [6] Despite recent scientific advances in the field of cardiology, there has been a substantial increase in worldwide prevalence of heart failure and years lost due to disability (YLDs).[6] Elevated levels of parathyroid hormone (PTH) have been found to be associated with heart failure, probably mediated by the presence of secondary hyperaldosteronism.[2] Prominent hyperaldosteronism, that occurs as a result of systolic heart failure, along with long-term and increased amounts of loop diuretics used in heart failure increase urinary loss of calcium and magnesium eventually leading to secondary hyperparathyroidism. [7] However, there is little evidence on the specific role of PTH levels in risk stratification and its role as a biomarker in predicting the prognosis of heart failure. In this background, the present study was carried out to evaluate the role of PTH levels in congestive heart failure.

Methodology

Study setting and participants

This cross-sectional study was conducted for a period of 19 months between March 2018 and September 2019 among 50 patients admitted with heart failure and reduced ejection fraction in our tertiary teaching institution. All adults who fulfilled the Framingham criteria for diagnosis of heart failure were included. Patients with a creatinine clearance > 60ml/min, sepsis, primary

hyperaldosteronism, cancer, liver disease, pancreatitis, acute ischemic heart failure and those on spironolactone therapy were excluded from the study.

Ethical approval and informed consent

Approval was obtained from the Institutional Ethics Committee prior to the commencement of the study. Each participant was explained in detail and informed consent was obtained from each participant prior to data collection.

Data collection

A structured proforma was used to document the demographic data and NYHA functional class of the participants. A 2D echocardiogram was carried out to document left ventricular ejection fraction (LVEF) and participants with LVEF <40% were diagnosed as heart failure. Chamber sizes were determined by recent guidelines. Effective volume of left ventricle was estimated and LVEF was determined by the modified Simpson method.

Blood samples were drawn to estimate brain natriuretic peptide (BNP) levels, PTH assay, 25-hydroxy vitamin D, serum calcium, phosphorus, and magnesium levels. Decision regarding Intensive Care Unit admission and care was based on the need of ventilation, infusion, inotropes and mechanical assist devices by the treating physician.

Data analysis

Data was entered and analysed using SPSS ver.17 software. Continuous variables were expressed as mean ± standard deviation while discrete variables were expressed in percentages. Analysis of variance (ANOVA) was used to estimate the significance of differences in variables amongst the different groups that were taken for analysis. PTH was individually correlated with the other variables using the Kendall Rank correlation coefficient. Mann-Whitney test was used to determine the difference in both BNP and PTH values between patients requiring ICU care and those not needing the same and also to determine outcome. A p value < 0.05 was considered as statistically significant.

Results

The mean age of the study participants was 60±11 years. Majority of the participants were males (60%) and about 58% of the study participants belonged to class 4 NYHA classification. Majority of the participants had type 2 diabetes mellitus (68%) while about 42% had systemic hypertension. (Table 1)

Tables

Table-1: Demographic characteristics of the study participants:

S. No	Characteristics	Frequency	Percentage
1	Gender		
	Male	30	60
	Female	20	40
Table : 2	Functional classification based on NYHA		
	Class 1	0	0
	Class 2	8	16
	Class 3	13	26
	Class 4	29	58
	Co-morbidities*		
	Diabetes	34	68
	Hypertension	21	42
	Atrial fibrillation	4	8

*percentage will not total to 100

Table-3: Correlation between PTH and various cardiac parameters

P
Correlation Coefficient * Value

BNP	0.51	<0.001
Creatinine Clearance	-0.317	0.001
BMI	-0.51	<0.001
Ejection Fraction	-0.288	0.003
LV Systolic		
Diameter	0.107	0.28

LV Diastolic Diameter	0.035	0.73
End Diagnostic Volume	0.131	0.188
End Systolic Volume	0.227	0.023
Stoke Volume	-0.147	0.14
Left Atrial Size	0.116	0.25
Vitamin D	-0.155	0.11
Magnesium	0.048	0.63
Phosphorus	-0.015	0.88
Calcium	-0.099	0.31
BUN	0.091	0.36

*Kendall rank correlation coefficient

The stratification of participants based on NYHA classification demonstrated that body mass index (BMI), BNP and PTH levels significantly varied with NYHA class. Participants in class 2 had higher mean BMI (26.1kg/m^2) compared to those in class 3 (23.4kg/m^2) and (21.8kg/m^2). The observed difference was statistically significant ($p<0.05$). The BNP levels were significantly elevated in NYHA class 4 group (2572 pg/mL) compared to class 3(1143pg/mL) and class 2 (629 pg/mL). The observed difference was statistically significant ($p <0.001$). Similarly, there was a statistically significant difference in the PTH levels in class 2 (36pg/mL), class 3 (51pg/mL) and class 4(92pg/mL) ($p<0.001$). (Table 2)

There was a statistically significant correlation between PTH levels and BNP, creatinine clearance, body mass index, ejection fraction and end systolic volume, with a correlation co-efficient of 0.51, -0.317, -0.51, -0.288 and 0.227 respectively ($p<0.05$). (Table 3) The present study demonstrated a high validity of PTH levels in detecting the need for ICU care, with a sensitivity of 84.2% and specificity of 80.6%, and area under curve as demonstrated in the ROC curve (figure 1) of 0.879, which was highly significant ($p<0.001$). The present study demonstrated a high validity of PTH levels in predicting the mortality among NYHA clas 4 patients, with a sensitivity of 100% and specificity of 68%, and area under curve as demonstrated in the ROC curve (figure 2) of 0.850, which was highly significant ($p<0.001$).

Discussion

Evaluating the role of parathyroid hormone levels in non-ischemic cardiac disorders provides scope in managing cardiovascular morbidities. More than half of the study participants in this study (58%) belonged to the NYHA IV class. A similar pattern was noted in the study published by Wu G et al showing a predominance in NYHA IV class admitted for heart failure compared to class III and class II. [76] The average PTH levels in the study participants with systolic heart failure was 72 ± 45 pg/mL. There was a significant difference in the PTH values in the different NYHA classes ($p<0.001$), and worsening of NYHA class was associated with increased PTH levels, similar to the findings of Altay H et al and Wu G et al. The present study also showed a positive correlation between PTH and BNP levels ($p<0.001$) similar to the study by Altay H et al. PTH levels in the present study did not have statistically significant correlation with other echocardiography parameters including left ventricular systolic diameter, left ventricular diastolic diameter, end-diastolic volume, stroke volume and left atrial size.

The outcome of hospitalization was evaluated based on the need for ICU care and recovery rates. About 38% of the participants were admitted to the ICU based on the requirement of non-invasive or invasive ventilation, diuretic infusion or ionotropic support. There was a statistically significant difference in the mean PTH levels in participants requiring ICU care (109.3 ± 21.9 pg/mL) compared to those who were managed in the ward (49.8 ± 9.2 pg/mL) ($p<0.001$). However, since all the patients treated in the ICU belonged to the NYHA IV class, there is little clinical relevance of this finding. Nevertheless, PTH levels were attributable to the prognosis of heart failure, showing statistically significant difference in the mean levels between those who recovered (66 ± 41 pg/mL) and those who succumbed to the disease was 138 ± 36 pg/mL ($p<0.01$).

According to receiver operator characteristics (ROC) curve analysis, the optimal cut-off value of parathyroid hormone to predict the need for ICU care and management was >69.1 pg/mL with a sensitivity of 84.2% and specificity of 80.6%. The area under the curve was 0.879 ($p<0.001$). The present study also observed that a value of PTH >84.2 pg/mL was predictive of mortality in NYHA IV patients according to the ROC curve with an area under the curve of 0.850 (p-value <0.001). In the study published by Altay H et al [8], a higher cut-off value of PTH levels was shown to predict advanced heart failure (>96.4 pg/mL) whereas in a study by Wu G et al, lower cut off value of >45.2 pg/mL at discharge was predictive of re-admission or death. It is of importance to note that lower or higher the cut-off values can alter the false positivity and false negativity rates, and this can significantly alter the course of management and prognosis. Although there are studies that conclude that elevated parathyroid hormone is a risk factor for mortality in heart failure, there are presently no studies published in literature that have demonstrated a specific cut-off of parathyroid hormone to predict mortality in heart failure.

Several studies have previously demonstrated the role of PTH levels in the context of cardiovascular diseases, specifically pertaining to hypertension, left ventricular hypertrophy and myocardial dysfunction. However, very few studies have

examined its potential role in non ischemic heart failure. The present study has not found any statistical correlation between these established risk factors. Therefore, the role of these potential confounders may be well eliminated in this study, evidently distinguishing between left and right heart failure. Similarly, it is of importance to note that the present study did not record any significant correlation between serum calcium levels and renal function, which further eliminates pre-existing abnormalities in the parathyroid metabolism, thereby establishing causal relationship. The underlying link between PTH levels and heart failure may be explained by the presence of positive correlation between PTH and BNP levels. The expression of BNP in conjunction with N-terminal pro BNP (NT-proBNP) in cardiomyocytes has been associated with increased stress in the myocardial wall, resulting in left ventricle remodelling, and cardiac injury. Presence of this chronic myocardial stress elevates PTH levels. [https://www.ahajournals.org/doi/full/10.1161/circheartfailure.114.001272]

Conclusion

The present study has elucidated the role of PTH levels in evaluating the cardiovascular morbidities, particularly non-ischemic heart failure. There has been a strong correlation between PTH levels and NYHA functional classification of heart failure. Based on the study findings, it may be concluded that monitoring of serum PTH levels in early functional class of NYHA can help in initiating aggressive management to prevent further deterioration. In addition, PTH levels negatively correlated with ejection fraction. Furthermore, PTH level greater than 69.1 pg/mL had a sensitivity of 84.2% and a specificity of 80.6% in determining if an individual required ICU care or not. The study has emphasized the importance of evaluating serum PTH levels on admission among patients with heart failure, so as to determine the prognosis and also predict mortality outcomes.

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