Original Research Article

A cross-sectional observational study of serum parathyroid hormone levels and its relation with severity and duration of heart failure

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Abstract

Background: Congestive Heart Failure is a systemic illnesscharacterized by neuro-endocrine immune system dysregulation, oxidative stress, release of proinflammatory cytokines leading to a catabolic state and secondary hyperparathyroidism. Abnormal elevation of serum PTH leads to excessive intracellularcalcium accumulation in cardiomyocytes leading to myocyte necrosis, replacementfibrosis and contributes to progressive heart failure. Objectives: To study the levels of serum PTH in patients of congestivecardiac failure and to establish the relation of serum PTH with duration and severity of heart failure.Methods: The study was conducted on 50 patients diagnosed to have CCF on the basis of symptoms, clinicalexamination, NYHA grading and 2-D Echocardiography. SerumPTH was measured by chemiluminescence and its correlation with severity and duration of heart failure was analysed statistically. Results: Among the patients studied, 56% of the patients with EF ≤ 35% hadelevated serum PTH levels(Mean: 70.1±14.6 pg/ml, p<0.001). 56% in the NYHA functionalclassification Grade III had elevated serum PTH levels (Mean: 69.8±14.73pg/ml, p<0.001). 60.9% ofpatients with duration of heart failure >2 years had elevated serum PTH levels>72pg/ml (p< 0.001). Conclusion: There was a significant positive correlation ofserum parathyroid hormone levels with the duration and negative correlation withseverity of heart failure as measured by ejection fraction. Therefore, serum PTH levels can be used as an individualprognostic marker to assess the severity of heart failure.

Keywords: Serum PTH, Serum calcium, NYHA grade, Ejection Fraction, Duration of Heart failure.

Introduction

Heart failure (HF) is a clinical syndrome that occurs in patients who, becauseof an inherited or acquired abnormality of cardiac structure and/or function, develop aconstellation of clinical symptoms (dyspnea and fatigue) and signs (edema and rales)that lead to frequent hospitalizations, a poor quality of life, and a shortened life expectancy.[1] Globally, 38% of heart failure cases were caused by Ischaemic Heart Disease and 34% by the next three largest causes: hypertensive heart disease,rheumatic heart disease and cardiopulmonary disease. IHD was responsible for 61%of heart failure in North America, 50% in Western Europe and only 9% in SubSaharan Africa. Hypertensive heart disease, cardiomyopathy and myocarditis cause40-45% of heart failure in Sub-Saharan Africa regions.[2]A broader perspective of CHF recognizes its systemic nature which has been described as a neuroendocrine-immune system dysregulation.

This illness includes

1. The presence of oxidative stress with reactive oxygen and nitrogen intermediates that overwhelm endogenous antioxidant defenses in such diverse tissues as skin,skeletal muscle, heart, peripheral blood mononuclear cells (lymphocytes andmonocytes) and blood

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2. A proinflammatory phenotype with activated peripheral blood mononuclear cells and elevations in circulating chemokines and cytokines, such as interleukin-6 and tumor necrosis factor(TNF)-α
3. A catabolic state with loss of soft tissues and bone due, in part, to negative caloric and nitrogen balance that eventuates in a wasting syndrome termed cardiac cachexia.[3]

Factors contributing to the appearance of this systemic illness include

1.Secondary hyperparathyroidism, based on urinary and fecal wasting of Ca^{2+} and$Mg^{2+,}$ and reduced plasma ionized $[Ca^{2+]}$ and $[Mg^{2+]}$ which raise plasma PTH levels.

2. PTH-mediated Ca^{2+} overloading of diverse cells, in turn, leads to the induction of oxidative stress.

3. Micronutrient deficiencies also contribute to the induction of oxidative stress byreducing the activity of antioxidant defenses provided by Cu/Zn- superoxide dismutase and Se-glutathione peroxidase.[4]

Abnormal elevation of serum PTH leads to excessive intracellular calcium accumulation in cardiomyocytes contributing to myocyte necrosis and replacement fibrosis.[5] In mitochondria, Ca^{2+} overloading and oxidative stress lead to a nonphysiological opening of the mPTP, with the ensuing osmotic-based structural andfunctional degeneration of these organelles that triggers the downhill final common cell death pathway leading to cardiomyocyte necrosis and subsequent replacement fibrosis.The cumulative loss of contractile elements, together with the deposition of fibrous tissue, stiff in-series and in-parallel elastic elements composed primarily

oftype I fibrillar collagen having the tensile strength of steel, each contributes to the progressive failure of this previously efficient muscular pump during systolic and/ordiastolic phases of the cardiac cycle.[6]Serum-derived bio-markers of cardiomyocyte necrosis are associated withincreased in-hospital and overall cardiac morbidity and mortality. Insights intocellular and molecular pathways involved in ongoing cardiomyocyte necrosis areessential in developing novel cardioprotective strategies that would salvage them andprevent myocardial fibrosis.Elevated PTH levels are found in patients hospitalized with decompensated HF and serve as an independent predictor of CHF, the need for hospitalization and cardiovascular mortality.

Methodology

This was a cross-sectional study conducted on 50 patients diagnosed to have CCF based on history, clinical examination and 2-D echocardiography. They were categorized based on duration of symptoms, NYHA functional classification and the severity measured in terms of ejection fraction. Relevant data about diabetes mellitus, hypertension and renal disease was taken in the history after taking written and informed consent. CBC, Urine microscopy, RFT, LFT, RBS, Serum electrolytes, Lipid profile were done for all patients and Thyroid function tests wherever applicable. Serum parathyroid hormone levels were measured by chemiluminescence immunoassay technique. The patients included were older than 18 years of age, had HF symptoms for longer than one year, belonged to NYHA functional class II and III with echocardiographically assessed left ventricular ejection fraction < 45 %.

The exclusion criteria included:

1. Clinically suspected primary hyperparathyroid states
2. Patients with renal failure, uremia
3. Lithium therapy, aluminium intoxication
4. Clinical suspicion of malignancy: Multiple myeloma, lymphoma, leukemia,tumours of lung, kidney, breast
5. Vitamin D related: intoxication, clinical suspicion of sarcoidosis & othergranulomatous diseases
6. Associated with high bone turn over: hyperthyroidism, thiazides, immobilisation,vitamin A intoxication.

Statistical analysis: Descriptive statistical analysis has been carried out in the present study.Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance isassessed at 5 % level of significance. p-value <0.05 is taken as significant.Chi-square test has been used to find the significance of study parameters oncategorical scale between two or more groups. Fisher's exact t-test has been used wherever Chi-square assumptions have failed.Pearson correlation co-efficient has been used to establish correlation betweenthe variables and its significance has been tested.Results are analysed using SPSS Software for Windows.Classification of Correlation Co-efficient (r):0.1-0.3 = Small correlation, 0.3-0.5 = Moderate correlation, 0.5-0.7= Large correlation, 0.7-0.9=Very large correlation, 0.9-1.0=Nearly perfect correlation and 1=Perfect correlation. Significant figures:p-value ≤ 0.01=Strongly significant, 0.01-0.05=Moderately significant and 0.05-0.10=Suggestive significance.

Results

Out of 50 patients studied, 50% (n=25) were males and 50%(n=25) were females.56%(n=28) of the study population were diabetic and hypertensive.90%(n=45) had duration of heart failure for ≥ 2 years.50%(n=25) were in NYHA functional classification Grade II and the other 50%(n=25) were in Grade III. 50%(n=25) of them had an Ejection fraction of ≤ 35%, 32%(n=16) of them between 35-40% and the remaining 18%(n=9) more than 40%. 56% (14 out of 25) of the patients with EF ≤35% had elevated serum PTH levels with a mean of 70.1±14.6 pg/ml. The meanserum PTH levels of the groups with EF 35-40% and > 40% were 53.4±13.2 pg/mland 41.4±9.3 pg/ml respectively. There was significant correlation between low EF (≤ 35%) andelevated serum PTH levels with p-value <0.001.56% (14 out of 25) in the NYHA functionalclassification Grade III had elevated serum PTH levels with the mean of 69.8±14.73 pg/ml. The mean serum PTH levels in the patients belonging to NYHA Grade II was49.4±13.53 pg/ml. There was a significant correlation between increasing NYHA grade and high serum PTH levels with a p-value < 0.001.Among the patients studied, 60.9% (14 out of 23) of patients with duration of heart failure >2 years had elevated serum PTH levels >72 pg/ml. There was asignificant correlation between the two variables with a p-value < 0.001 (Chi-square =22.8). Out of the study population, 56% (28 out of 50) were diabetics. 66.7% (14 out of 21) of patients with diabetes mellitus and EF ≤ 35% had elevated serum PTH levels witha mean of 74.01±7.68 pg/ml. The mean serum PTH levels in the patients with diabetes mellitus and EF > 35% (n=7) and the third group of non-diabetic population (n=22) were53.82±18.5 pg/ml and 47.64±13.5 pg/ml respectively. There was a significant correlation between the patients with diabetes mellitus and EF ≤ 35% with high serum PTH levels with p-value <0.001. Out of 50.56% (28)were hypertensives.

71.4%(10 out of 14) of patients with hypertension and EF ≤ 35% had elevated serum PTH levels with a mean of 75.27±7.06 pg/ml. The mean serum PTH levels in the patients with hypertension and EF > 35% (n=14) and the third group of normotensive population (n=22) were52.71±13.57 pg/ml and 53.97±18.2 pg/ml respectively. There was a significant correlation between the patients with hypertension and EF ≤ 35% with high serum PTH levels with p-value <0.001. There was a significant negative correlation between ejection fraction and serum PTH levels with r-value: -0.768 and significant positive correlation between duration of heart failure with serum PTH levels with r-value: 0.724.

Table 1: Comparison of Ejection Fraction and Serum Parathyroid Hormone among the study population

Ejection fraction (%)	Number of patients with serum PTH (>72pg/ml)	Number of patients with serum PTH (≤72pg/ml)
<35 (n=25)	14 (56.0%)	11(44%)
35-40 (n=16)	0 (0.0%)	16(100%)
>40 (n=09)	0 (0.0%)	9(100%)

Table 2: Comparison of serum PTH between NYHA grades

NYHA	Number of patients with serum PTH (>72 pg/ml)	Number of patientswith serum PTH (≤72 pg/ml)
Grade II (n=25)	0 (0.0%)	25 (100.0%)
Grade III (n=25)	14 (56.0%)	11 (44.0%)

Table 3: Relation of serum PTH with duration of symptoms

Duration	Number of patientswith serum PTH (>72 pg/ml)	Number of patients with serum PTH (≤72 pg/ml)
1-2 years (n =27)	0 (0.0%)	27 (100.0%)
≥ 2 years (n =23)	14 (60.9%)	9 (39.1%)

Table 4: Effect of diabetes and hypertension in patients with CHF and its relation to Serum PTH

	Number of patients with serum PTH (>72 pg/ml)	Number of patientswith serum PTH (≤72 pg/ml)
DIABETICS		
EF ≤35% (n=21)	14 (66.7%)	7 (33.3%)
EF >35%(n=7)	0 (0.0%)	7 (33.3%)
Non-diabetics (n=22)	0 (0.0%)	22 (100.0%)
HYPERTENSIVES		
EF ≤35% (n=14)	10 (71.4%)	4 (28.6%)
EF >35%(n=14)	0 (0.0%)	14 (100.0%)
Non-hypertensives(n=22)	4 (18.2%)	18 (81.8%)

Discussion

A total of 50 patients predominantly between46-60 years who were diagnosed to have congestive cardiac failure of different etiologies for a period of more than 1 year were studied. Among them, 90% had duration of heart failure for ≥ 2 years. Secondary hyperpara-thyroidism, defined as serum PTH levels higher than 48pg/ml, was associated with increased mortality and risk of hospitalization in elderly adults.[7] Normal serum PTH levels were defined as 14-72 pg/ml in our study. 56% of the patients with EF ≤ 35% had elevated serum PTH levels showing a significant correlation between low EF and elevated serum PTH levels. 56% patients in the NYHA functional classification grade III had elevated serum PTH levels suggesting significant correlation between increasing NYHA grade and high serum PTH. 60.9% of patients with duration of heart failure > 2 years had elevated serum PTH levels suggesting a positive correlation.Khouzam RN et al showed that, plasma PTH was elevated above the normal range(6-65 pg/mL) in both untreated and treated patients with CHF (204+/-60 and 134+/-14pg/mL, respectively). [8] Loncar G et al showed that CHF patients had markedly increased serum PTH levels (77 ± 33 vs 40 ± 11 pg/ml, p<0.0001).[9]Anderson et al included patients for an average of 2±1.5 years.[10] 50% were in NYHA functional classification Grade II and the other 50% were in Grade III. 50% of them had an Ejection fraction of ≤ 35%, 32% of them between35-40% and the remaining 18% more than 40%.Parathyroid hormone levels were defined as low (<15 pg/mL),normal (15-75 pg/mL), or elevated (>75 pg/mL).PTH >75 pg/mL predicted a greater likelihood of prevalent and incident disease,including mortality.Altay H et al showed that mean levels of PTH were 43±19,84±56,121±47, and 161±60 pg/ml in NYHA functional classes I, II, III,and IV, respectively (p<0.001)allowing rapid risk stratification in these patients.[11]T Sugimoto et al showed that Mean (SD) serum intact PTH levels significantlyincreased as NYHA classes increased (I: 40 (21), II: 55 (24), III:76 (46), IV: 131 (45) pg/ml) and could be taken as an independent predictor of hospitalisation for HF.[12]Persistent neurohormonal activation involving RAAS and ANS results inprolongedhypocalcemia. This results in the stimulation of release of calcitropichormones like serum PTH which in cardiomyocytes, simultaneously promote L-type Ca^{2+} channel activity leading to increased cytosolic free Ca^{2+} and, in turn,mitochondrial Ca^{2+} overloading with organellar-based oxidative stress and further myocardial damage, thus aggravating heart failure.[13]Our study results are comparable with the other study results showing high serum PTH levels correlating with increasing severity in terms of low EF and increasing NYHA functional grade.[7-11]Among the patients studied, there was a significant independent correlation between the diabetes mellitus and hypertension patients with EF ≤ 35% and high serum PTH levels with p-value <0.001. Smaller sample size was the limitation in our study. However, serum PTH can be used as an independent predictor of advancing heart failure both in terms of duration and the severity.

Conclusion

Serum-derived bio-markers of cardiomyocyte necrosis like serum PTH are associated with increased in-hospital and overall cardiac morbidity and mortality. Intensive therapy in such patients with calcium and vitamin D supplements have decreased the levels of serum PTH and resulted in improved left ventricular function. Insights into cellular and molecular pathways involved in ongoing cardiomyocyte necrosis are essential in developing novel cardioprotective strategies that would salvage them and prevent myocardial fibrosis.

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