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The role of parathyroid hormone (pth) in the 6-month prognosis of patients with chronic heart failure hospitalized in the cardiac unit of university hospitals of ahvaz city in 2015-2016

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Abstract

Background and aim: Chronic heart failure (CHF) syndrome is the most common cause of hospitalization in patients over 65 years of age. HF is a clinical disorder that occurs due to impairment in the structure or function of the heart as inherent or acquired, and causes clinical symptoms. Therefore, the purpose of this study was to evaluate the role of parathyroid hormone (PTH) in the 6-month prognosis of patients with chronic heart failure hospitalized in the cardiac unit of university hospitals of Ahvaz city in 2015-2016. **Materials and methods:** This study is a descriptive epidemiologic study. In this study, a total of 202 people were enrolled in the study, of which 126 (62.3%) were male and 76 (37.6%) were female, and patients classified for HF according to Framingham criteria and in the subgroup of systolic HF (with an ejection fraction of less than or equal to 40%) and hospitalized in the heart unit of Imam Khomeini Hospital in Ahvaz during the year 2015-2016 were enrolled in the study. **Findings:** The results showed that the chance of stroke and death in people with a PTH of more than 39 pg/ml is 5.85 times more than those with PTH of less than 39 pg/ml, and with the rise in the NYHA, PTH has also increased. **Discussion and Conclusion:** According to the evaluations conducted in this study, it was found that PTH is related to the severity of heart failure and subsequently its short-term prognosis. Therefore, it seems that during the first hospitalization of patients with heart failure, measurement of PTH can play a significant role in clarifying patients' clinical condition and predicting their short-term prognosis, and subsequently changing of the therapeutic route.

Keywords: Heart failure, NYHA class, PTH



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Introduction

Chronic heart failure (CHF) is the most common cause of hospitalization in patients over 65 years of age (1). Heart failure is a serious health problem, which its prevalence has been increasing and 1-2% of the general population is affected by it, and its prevalence in the world is estimated at 25 million people annually (2). Heart failure leads to a decrease in the quality of life more than other chronic diseases, such as diabetes, chronic pulmonary disease and arthritis (3). Despite the recent evidence that prognosis is improving after the first hospitalization of these patients, drug therapy has no effective role in reducing the incidence and mortality of CHF and despite the new pharmacological treatments, episodes of exacerbation are common (4, 5). The number of hospitalization due to heart failure has tripled in the last three decades, and this number is increasing due to increased life expectancy, improved survival after myocardial infarction and access to effective treatment to prevent sudden death (1). Today, heart failure is considered to be a serious and growing public health problem. This disease is not only caused by damage to the heart cells, but also a combination of genetic, hormonal, inflammatory and biochemical changes with direct and indirect effects on the heart can increase the risk of heart failure (6).

The diagnosis of HF is done based on the clinical judgments and according to biography, examination and other essential tests. Accordingly, HF patients are classified into 4 classes, according to their functional capacity based on the New York Heart Association (NYHA) classification. This classification is useful in determining the extent of the patient symptoms in order to assess the adequacy of treatment and determine the prognosis of HF patients and their mortality and morbidity over time (1). Considering the importance of reduction in the life quality of HF patients, determining the population of HF patients who require heart transplantation or newer therapies, such as dual-chamber pacemakers and insertion of mechanical support devices, as well as the identification of patients with HF who are at higher risk for death or rehospitalization are of special importance (4, 7).

Over the past half century, there have been significant changes in both the causes and the therapeutic methods of heart failure (8).

Several biomarkers have been introduced as the predictive factors of risk in patients with cardiovascular diseases including HF, of which troponin I and T, NT-Pro BNP and hs CRP are easily measured (9). These bio-markers can be a useful guide to the treatment of acute and chronic episodes of the disease by providing prognostic information in HF, and clinically useful markers have unique characteristics, including: accuracy, accessibility and providing information that is not gained by the evaluation. These biomarkers also help to make the right decisions for treatment (10). One of these bio-markers is parathyroid hormone. Parathyroid hormone (PTH) is one of the main hormones regulating bone metabolism and minerals in the body. PTH 1-84, a biological active form of the hormone in the body, is produced by the parathyroid gland and is introduced into the systemic circulation of the body, and exerts its effect through the binding of its first 34



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amino acids to the PTH receptor (11). PTH receptors are present at the heart surface, and increased levels of this hormone increase the strength of the contraction of the heart and cause myocardial hypertrophy and interstitial fibrosis (12, 13). PTH activates the protein kinase C in myocytes, which this activation of this protein leads to hypertrophication of myocytes (14). Increased level of PTH is associated with hyperlipidemia and impaired glucose tolerance and leads to exacerbation of the atherosclerosis process (15, 16).

Since the presence of secondary hyperparathyroidism has been proven in patients with heart failure, measurement of PTH can be appropriate in classifying the risk factors and choosing effective therapeutic methods (17, 32, 33). The aim of this study was to evaluate the role of PTH in the 6-month prognosis of patients with chronic heart failure hospitalized in the cardiac unit of university hospitals of Ahvaz city, in order to achieve a suitable criterion for evaluation of short-term prognosis (6 months) of these patients, including the response to treatment, hospitalization, the need for a dual-chamber pacemaker, sudden death and mortality.

Materials and methods

This study was an epidemiologic study and was conducted on patients with heart failure and hospitalized in the cardiac unit of Imam Khomeini hospital of Ahvaz during the years 2015-2016.

In this study, patients who had HF according to Framingham criteria and were in the subgroup of systolic HF (with an ejection fraction of less than or equal to 40%) were included in the study. Patients with known chronic obstructive pulmonary disease (characterized by limited air flow in the airways that is not completely reversible, including emphysema and chronic bronchitis), primary valvular heart disease (including calcification changes of the valve due to age, hereditary or congenital conditions such as bicuspid aortic valve or myxomatous mitral valve diseases), infections, chronic inflammatory diseases such as sepsis, malignancy, arthritis, connective tissue diseases, severe liver diseases, and pregnancy were excluded from the study. After obtaining the biography and the clinical examination in the first referral, clinical information, vital signs, used drugs, as well as angiographic and echocardiographic information (performed by the plan executor and with the vivid device) were recorded in the information form. Initial tests including: ALT, AST, Lipid profile, FBS, and the biomarker (PTH) were requested for the patient. In order to obtain the fasting blood sample, the patient was placed in a fasting state for 10 hours, and samples were sent to the reference laboratory for carrying out the tests. The methods of doing each of the tests are: FBS: glucose oxidase/oxidase, TG: lipase/oxidase (colorimetry), chol: cholesteroxidase/oxidase, LDL: direct homogeneous, HDL: direct homogenous, AST: AST/MDH (without PLP), ALT: ALT/MDH (without plp), PTH: ECL.

Each patient referred every two months for 6 months, and in case of not referring, they were contacted and followed up (a total of 3 times). During these 6 months, when symptoms were worsening, patients referred and if necessary hospitalized, and ECG is taken at each visit, and the



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adequacy of the drug therapy was evaluated in them, and if necessary, the necessary measures, including introduction for heart transplantation, biventricular pacing, etc. were performed, and correlation between the levels of PTH biomarker and cardiovascular events and prognosis of these patients were evaluated. The calculation of statistical indexes was used for descriptive statistics. The chi-square test was used for evaluating the correlation between qualitative variables, and T-test was used for evaluating the correlation in quantitative variables and correlation test and for comparison of quantitative data in both genders of male and female.

Findings

In this study, 202 people were enrolled in the study, of which 126 (62.3%) were male and 76 (37.6%) were female. The base information for the participants is presented in Table 1.

Table 1. Baseline Patients Characteristics

Variables	All percentage		After 6 months follow up Dead Heart Attack		P-value
Age					Age(0.652)
30-39yrs	16	7.9%	2	2	
40-49yrs	23	11.38%	4	3	
50-59yrs	67	33.16%	12	16	
60-69yrs	43	21.2%	8	9	
70-79yrs	36	17.83%	4	12	
80yrs<	17	8.4%	4	3	
Gender					Gender(0.934)
Male	126	62.4%	19	30	
Female	76	37.6%	15	15	
Functional Class					FC(0.064)
I	67	33.1%	10	10	
II	49	24.2%	7	10	
III	50	24.7%	11	9	
IV	36	17.8%	7	16	
Angiography					Angiography(0.066)
Normal	9	4.5%	1	1	
Minimal CAD	10	5%	2	6	
SVD	33	16.3%	2	5	
2VD	17	8.5%	7	9	



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3VD	41	20.3%	3	3	
Not done	92	45.5%	19	21	
Risk Factors					
Smocking	52	25.7%	8	12	0.811
HTN	97	47%	17		0.715
DM	87	43%	21		0.063
HLP	56	27.7%	17		0.772
Positive family history	30	14.8%	23		0.218
Addiction	11	5.4%	6		0.408
Anemia	108	53.4%	15		0.026
No risk factors	32	15.85%	3	5	
Echocardiography			0	3	
10-15%	6	2.9%	18		
15-20%	13	6.4%	32		
20-25%	28	13.8%	3	8	Echocardiography(<0.001)
25-30%	31	15.3%			
30-35%	50	24.7%	6	0	
35-40%	74	36.4%	3		PTH(<0.001)
Biomarker			8		
PTH	202		9	8	
Mean(0.1-490)= 44.2	100%		3	8	
			9	12	
			4	9	

The ROC curve was used to determine the cutting point. Cutting point of 39 was selected for PTH hormone with a sensitivity of 63.29 and a specificity of 77.24. The area under the surface of the ROC curve obtained as 0.711 with a 95% confidence interval (0.773, 0.644), which indicates the accuracy of the selected point.



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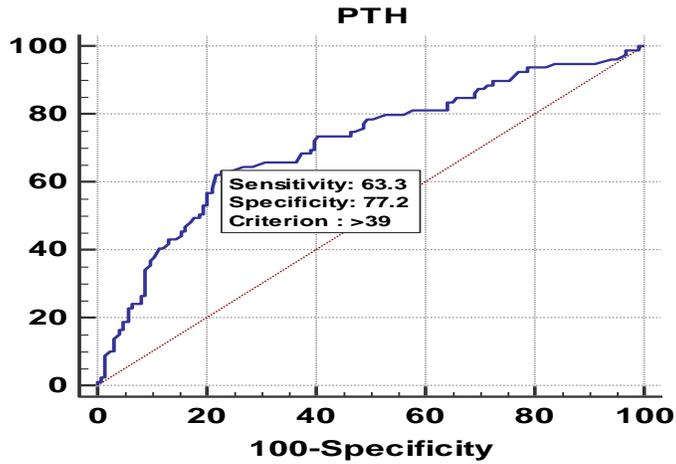


Chart 1: The ROC curve for determining the PTH cutting point

The difference in mean PTH level in functional class groups was investigated. Considering the absence of normality, the Kruskal-Wallis test was performed and $p\text{-value} < 0.001$ showed that the mean PTH level is different in at least two levels of functional class. The results of this study are presented in Chart 2.

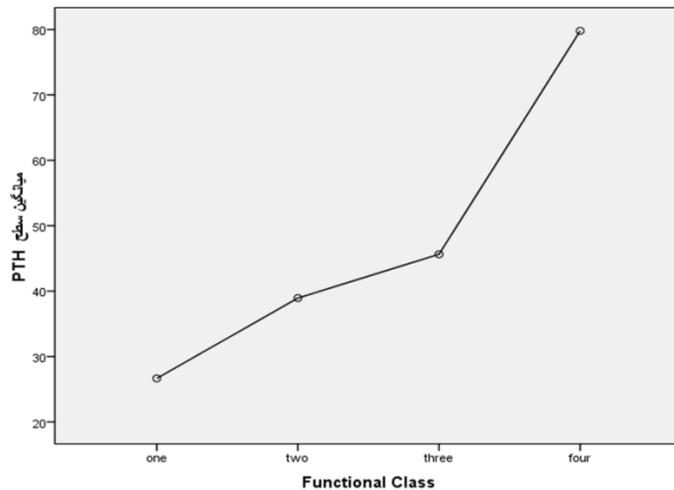


Chart 2: The difference between the mean values of PTH in different functional class groups

In this study, the history of previous hospitalization due to heart problems (before entering the study) was present in 134 people in the study (66.33% of the subjects). Of the total number of subjects in the study, 92 had no angiography at the start of the study, of which at least 69 were candidates for angiography in the past, which due to reasons such as lack of follow-up or dissatisfaction, this has not been done for them. For all patients when hospitalized, ejection fraction



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(EF) was estimated by the echocardiography machine. According to the main criteria for inclusion, the ejection fraction of less than or equal to 40%, the patients were divided into 6 groups, with the highest number of patients in the category of 35-40%.

16.8% of the participants in the study passed away. 22.27% of the participants in the study suffered a heart attack. 44% of the participants in the study were hospitalized at least one occasion due to the exacerbation of symptoms associated with heart failure. 6.93% of the subjects participated in the study underwent the embedding of pacemaker. 8.4% of the participants in the study received the flu vaccine and pneumococcal vaccine after the first time of hospitalization. According to the results of statistical analyzes, the mean Hb was different between the living and dead individuals with 95% confidence. For other variables with 95% confidence, there was no significant difference between the two groups. The chance of death or stroke was 90% for people with diabetes mellitus compared to people without diabetes mellitus. The chance of death or stroke for people who did not have pacemakers was 6 times higher than those who had it. The chance of stroke and death in the group that had no angiography was 9.21 times higher than that of normal subjects. The chance of stroke and death in the FC 4 group was evaluated as 3.18 times more than the group 1, 3.06 times more than the group 2, and 2.55 times more than the group 3.

Discussion and conclusion

The highest number of people with heart failure was in the age group of 50-59 years, indicating a high incidence of this disease in this age group. In the study by Razzolini (2015), it was suggested that the incidence of heart failure in ages older than 40 years was higher in men, but this proportion is reversed in ages older than 80 years (18). In the age group of 50-59, most subjects were men which was consistent with the results of the Razzolini study, but at the age of over 80 years, most of the patients were males, which was not consistent with the result of the mentioned study, which can be due to the smaller sample size of the present study compared to the mentioned study.

In the study by Bauters et al., the prevalence of diabetes mellitus in patients with heart failure was reported to be about 20% (19). Diabetes mellitus increases the risk of heart failure and death as a result of its association with cardiovascular risk factors such as high blood pressure, dyslipidemia and atherosclerosis (20). Diabetes mellitus with a prevalence of 43%, after high blood pressure, is the most common underlying risk factor in the study population, which is much higher than what it is reported in other studies, which may indicate a wrong way of living and lack of awareness of patients about diabetes prevention methods. The logistic regression was used to determine the effect of diabetes on prognosis of patient, which showed that the chance of stroke or death in people with diabetes increases by 90% compared to those without diabetes. This reveals the need for strict and precise control of diabetes in patients with heart failure.



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Anemia is present in about one third of patients with heart failure. Long-term anemia - for any reason - with the mechanism of causing cardiac hypertrophy and death of myocytes, exacerbates heart failure and worsens its prognosis (22, 21). According to conducted studies, the prevalence of anemia in patients with heart failure with reduced ejection fraction varies from 4% to 61% (23). In this study, 53.4% of the participants had anemia, in which 46% of patients with anemia suffered stroke or death after a 6-month follow-up, and this rate was 30% in the group without anemia, which was consistent with other studies. These findings reveal the significant role of anemia in the prognosis of patients with heart failure and the importance of controlling and treating it.

In patients with heart failure, the long-term prognosis of patients has a direct relationship with the severity of CAD that is revealed by angiography (25). In this study, the chance of stroke and death in people who did not undergo angiography was 9.21 times higher than those who had normal angiography. The results obtained show that in the group that angiography was not performed, there may have been some advanced degrees of CAD, but no proper treatment has been selected due to the uncertainty of its severity, and given that most people who did not undergo angiography were candidates for this procedure, but for some reason, such as dissatisfaction, they were not willing to undergo it, this shows the need for informing patients with heart failure about the dangers of not doing angiography.

The chance of stroke and death had increased with rising of NYHA Class, which was consistent with other studies (26).

The main goal of the design and implementation of this study was to determine a cut off point for the PTH hormone to measure the 6-month prognosis in patients with heart failure.

In similar studies, increased PTH levels have been reported in patients with heart failure, which is associated with a reduction in the survival of patients (27, 28).

In other studies, different values have been reported as the PTH cutoff point, varying from the wide range of 47 to 96.4 (2, 28, 29, 30, 31). In this study, by statistical analysis on PTH values obtained from 202 patients with a sensitivity of 63.29% and a specificity of 77.24%, 39 pg/ml was determined as the cut-off point, and it was estimated that the chance of stroke and death in people with a PTH of more than 39 pg/ml is 5.58 times more than people with a PTH of less than 39 pg/ml. This difference with other studies can be due to the difference in the number of participants, the severity of heart failure and the duration of follow-up.

In similar studies, with the rise of the NYHA class, the mean PTH has increased (4, 28, 31). In this study, a direct correlation was found between the rise in the NYHA Class and the increase in PTH levels, but due to the lack of normality among the number of individuals in each group of the NYHA classes, it was not possible to obtain a specific mean value for each group.



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According to the evaluation conducted in this study, it was determined that PTH is related to the severity of heart failure, and subsequently its short-term prognosis. Therefore, it seems that during the first hospitalization of patients with heart failure, in addition to performing basic and other usual and essential examinations, measuring the PTH can play an important and significant role in clarifying the clinical status of patients, predicting their short-term prognosis, and subsequently redirecting of therapeutic route to more useful and effective methods.

Suggestions

It is recommended that in subsequent studies, after the initial measurement of PTH level, if it is higher than the risk range, the therapeutic modalities of patients should change to more effective methods, and then their 6-month prognosis would be evaluated and its result would be compared to previous studies.

Reference:

1. Bonow, Mann, Zippes. Braunwald's heart disease. 2012; chap 27; p-517.
2. Shuang Z , et al. Correlations between serum intact Parathyroid Hormone (PTH) and N-terminal-Pro brain Natriuretic Peptide levels in elderly patients with Chronic Heart Failure (CHF). Archives of Gerontology and geriatrics. 2015; 60: 359-365.
3. Stewart AL , et al. Functional status and well-being of patients with chronic conditions: results from the medical outcomes study. JAMA. 1989; 262 :907–13.
4. McMurray JJ, Stewart S. The burden of heart failure. Eur Heart J. 2003; 5(suppl):3–14.
5. Ford I , et al. Top ten risk factors for morbidity and mortality in patients with chronic systolic heart failure and elevated heart rate : the shift risk model. International journal of cardiology .2015 ; 184 : 163-169.
6. Braunwald E. Biomarkers in heart failure. N Engl J med. 2008; 358: 2148-59.
7. Stevenson LW, et al. Target heart failure populations for newer therapies. Circulation. 1995; 92((suppl II)):174–181.
8. Braunwald E, Bristow MR. Congestive heart failure: fifty years of progress. Circulation. 2000; 102: 14-23.
9. Sabatine MS, et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndrome: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. Circulation. 2002; 105: 1760–1763.
10. Bonow, Mann, Zippes. Braunwald's heart disease. 2012; chap 26; p-509.
11. Gruson D, Ahn S, Rousseal M. Multiple biomarker strategy based on Parathyroid hormone and Natriuretic peptides testing for improved prognosis of chronic heart failure. Peptides. 2015 ; 64 : 24-48.



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12. Smogorzewski M. PTH, chronic renal failure and myocardium. *Miner Electrolyte Metab* . 1995; 21:55-62.
13. Ogino K, Burkhoff D, Bilezikian JP. The hemodynamic basis for the cardiac effects of parathyroid hormone (PTH) and PTH-related protein. *Endocrinology*. 1995;136:3024-30.
14. Schluter KD, Piper HM. Cardiovascular actions of parathyroid hormone and parathyroid hormone-related peptide. *Cardiovasc Res* 1998;37: 34-41.
15. Liang K, Oveisi F, Vaziri ND. Role of secondary hyperparathyroidism in the genesis of hypertriglyceridemia and VLDL receptor deficiency in chronic renal failure. *Kidney Int*.1998; 53: 626-630.
16. Akmal M, Massry SG, Goldstein DA. Role of parathyroid hormone in the glucose intolerance of chronic renal failure. *J Clin Invest*. 1985;75:1037-44.
17. Gurson D, Buglioni A , Burnett Jr. PTH : potential role in management of heart failure. *Clinica Chimia Acta*. 2014;433 : 290-296.
18. Razzolini R, Dllin C. Gender differences in heart failure. *Italy gender specific med*. 2015; 1:15-20.
19. Bauters , et al. Influence of diabetes mellitus on heart failure risk and outcome. *Cardivascular Diabetology*2:10.
20. Jagasia D, McNulty PH. Diabetes mellitus and heart failure. *CHF*.2003;9(3).
21. Silverberg DS, Wexler D, Iaina A. The role of anemia in the progression of congestive heart failure: Is there a place for Erythropoietin and intravenous iron?. *J Neohrol*. 2004 ; 17(6): 749-761.
22. Coats AJ. Anemia and heart failure. *Heart*. 2004; 90(9) : 977-979.
23. Tang YD, Katz SD. Anemia in choronic heart failure. *Circulation*. 2006 ; 113: 2454-61.
24. Groenveld HF, et al. Anemia and mortality in heart failure patients. *Journal of the American collage of cardiology*. 2008; 52(10): 818-827.
25. Flaherty JD, et al. Acute heart failure syndromes in patients with coronary artery disease. *Journal of the American collage of cardiology*. 2009; 53(3) : 254-263.
26. Ahmed A, Aronow WS, Fleg JL. Higher Newyork heart association classes and Increased mortality and hospitalization in heart failure patients with preserved left ventricular function. *AM Heart J*. 2006 ; 151(2): 444-445.
27. Loncar G, et al. Association of increased parathyroid hormone with neuroendocrine activation and endothelial dysfunction in elderly men with heart failure. *J Endocrinol Invest* 2011; 34: 78-85.
28. Sugimoto T. Serum Intact Parathyroid Hormone levels predict hospitalization for heart failure. *Heart*. 2009; 95: 395-98.



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Revista Publicando, 5 No 17. 2018, 149-159. ISSN 1390-9304

29. Bansal N, et al. Serum Parathyroid hormone and 25-hydroxy vitamin D concentrations and risk of incident heart failure : The multi-ethnic study of atherosclerosis.JAHA . 2014 ; 3 : e001278doi .10.1161/JAHA.114.001278.
30. Wu Gy , et al. Serum parathyroid hormone levels predict hospitalization in outPatients of heart failure : a preliminary study. Zhonghua Yi Za Zhi.2013; 28 : 2205-2208.
31. Altay H, et al. Relation of serum parathyroid hormone level to severity of heart failure. AM J Cardiology. 2012; 109(2) : 252-260.
32. ALEKSEEVA E.M., CHERNOV A.V., Implicit Features of Associating Life Situations with Mental States, Astra Salvensis, Supplement No. 2, 2017, p. 619.
33. OKRIASHVILI T.G., The State of Private Law in the Modern Legal Society, Astra Salvensis, Supplement No. 2, 2017, p. 539.