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Relationship between Parathyroid Hormone Level and Early Remodeling Heart Failure after Acute Myocardial Infarction

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ABSTRACT

Background: Previous studies have indicated that parathyroid hormone (PTH) has been linked to post-myocardial infarction (MI) development. The aim of this cross-sectional study was to evaluate the relationship between PTH level and heart failure due to post infarction remodeling during the first 72 hours of hospitalization.

Methods: Seventy patients with a diagnosis of acute MI (age ≥18 years, 22 females and 48 males) were enrolled. Patients were admitted to the Imam Raza Educational, Research and Treatment Center, Mashhad University of Medical Sciences, Iran between July 2014 to September 2015. We measured PTH and vitamin D level. Blood samples were taken after 24 hours and 72 hours.

Results: During the first 72 hours, the PTH level significantly increased in patients with Post-MI heart failure. 68% of the subjects had an inappropriate vitamin D level at the time of admission. Mean levels of vitamin D and PTH increased compared with the baselines (95% CI, 0.15 to 10.03, P: 0.044), (95% CI, 6.5 to 24.8, P:0.001) respectively.

Conclusion: Acute elevations of serum PTH levels increased early remodeling heart failure after MI. Serum vitamin D status was independent of high serum PTH level. Based on the current evidence, PTH excess may be a risk factor for heart failure, so early treatment and omitting risk factors are the most effective strategies for the patients with acute myocardial infarction.

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Introduction

The most common cause of heart failure is myocardial infarction. Heart muscle cells die or lose some of their contractile ability which leads to reduced contraction of the heart (1). Because of the limited capacity of heart cells to regenerate after injury, the dead cells are replaced by a fibrotic scar. This is caused by manipulation of the surrounding myocardium which is called remodeling. Remodeling process includes hypertrophy and fibrosis of the left ventricular wall. Remodeling process results in the impaired cardiac function (2). Heart failure develops and its complications like remodeling can be tracked through biomarkers of disease status (3-5). One of these markers which is studied here in this study, is parathyroid hormone (PTH). Information on myocardial infarction biomarkers can provide useful data to predict the consequences of the disease, and reduce mortality and morbidity in patients (6).

Hyperparathyroidism is subdivided into primary and secondary hyperparathyroidism. It seems that both primary and secondary hyperparathyroidism are associated with an increased risk of cardiovascular diseases. Hyperparathyroidism is associated with a reduction in arterial pressure and myocardial contractility, which can cause apoptosis, fibrosis, and vascular smooth muscle cell

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hypertrophy as well as left ventricular hypertrophy (7).

Remodeling after MI can be seen in two periods: early remodeling in the first 72 hours after acute MI and late remodeling one year after MI (8). The possible mechanisms for this effect are listed here: increasing neovascularization and cell survival and angiogenesis or increasing migration of CD45/CD34 stem cells to the ischemic heart tissue and reducing ischemic cardiomyopathy (9). In most recent studies, patients were followed for a long time and the effects of late remodeling after MI and heart failure have been studied. It was reported that in patients with heart failure, parathyroid hormone serum level increased. But its exact time is unknown, if the increase of parathyroid hormone occurs just after myocardial infarction or after a while.

The association between PTH level and the risk of MI has been reported. But this study has an important novelty. It is the first study that measured PTH level immediately after MI in two time intervals. First, when the patient was hospitalized due to MI (in the first 24 hours of hospitalization) and the second, 72 hours after admission just when early remodeling happens. Especially in our population, due to racial differences and traditional risk factors among major Iranian ethnic groups (10), it was urgently needed to investigate the levels of this hormone and its relation to future events after heart attack.

On one hand, after a heart attack PTH causes angiogenesis to re-establish blood supply to the damaged cells, and on the other hand, the change of heart tissue or remodeling has been seen following this increase (11-13). Therefore, this preliminary study was designed to investigate the level of PTH as a cardiac biomarker in patients with MI and its relevance to heart failure.

Methods

This study was a cross-sectional study base on convenience sampling method. All patients with acute MI were enrolled in this study between July 2014 and March 2015 at the Department of Cardiology, Imam Reza Hospital, Mashhad University of Medical Sciences.

To detect an intragroup difference of six points in vitamin D level and PTH from baseline to follow-up with a statistical power of 80%, a type I error risk of 5%, and an estimated standard deviation (SD) of 6.5%, a total of 78 patients were estimated to be needed for enrollment in the study (14).

The inclusion criteria consisted of confirmation of the diagnosis of acute MI based on medical history, physical examination, clinical presentation, and laboratory data. Patients who had a history of respiratory, hepatic, or renal dysfunction, bone diseases or took daily calcium, received vitamin D injections, or used drugs such as phosphates, anticonvulsants, steroids, isoniazid, lithium, and rifampin that affect the levels of PTH were excluded from the study. The study protocol was approved by the local ethics committee of the Mashhad University of Medical Sciences and informed consent was obtained from all patients.

All patients underwent a detailed clinical examination. Demographic characteristics, medical history, physical examination findings, medication use, treatment details, and outcomes were recorded and computerized prospectively. Vitamin D and intact PTH levels were measured from serum samples by using gamma kit and the effects of parathyroid hormone on the occurrence of early heart failure in patients with MI was assessed during the first 72 hours of hospitalization. The primary outcome of the study was the change of the PTH level at 72 hours from baseline and the occurrence of heart failure at 72 hours (determined by echocardiogram). A definitive diagnosis of cardiac failure was made by the cardiologist.

Within the first 24 hours of hospitalization, medical information was collected from parents or guardians through a standardized questionnaire. In each patient, blood samples were collected after the first and third day of admission. The samples were obtained within 72 hours after arrival at the emergency department. Immediately, routine hematological and chemical parameters including plasma glucose, total cholesterol (TC), triglycerides, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), serum calcium and phosphorus, blood sugar and serum electrolyte were analyzed and then, samples were centrifuged at 2500 rpm, 4 centigrade for 15 minutes and serum was separated. Centrifuged plasma was filtered and serum samples were stored at -70°C before analysis of vitamin D and PTH. Vitamin D and PTH were measured with an enzyme-linked immunosorbent assay (ELISA) kit. Patients were classified and compared based on PTH level. Patients with PTH <65pg/ml were considered as normal and PTH levels above 65pg/ml were considered as hyperparathyroidism.

Continuous data were given as mean ± standard deviation. We used paired t-test to compare the changes in serum concentrations of vitamin D and PTH between admission and day 3. All numeric variables were tested for normality of distribution by the Kolmogorov–Smirnov test, and if necessary, Wilcoxon sum rank test was used. The results were considered significant if the p-value was <0.05. Correlation between the changes in vitamin D and PTH was tested by the Pearson correlation test. The Statistical Package for Social Sciences (version 20.0; SPSS Inc., Chicago, USA) was used for all analyses.

Results

A total of 69 participants (47 men and 22 women) from 140 evaluated patients were enrolled in the study during 8 months. The average age and body mass index (BMI) of the patients were 61.86 ± 13.3 years and 25.08 ± 3.60 kg/m2, respectively. No significant difference was found in demographic data and vitamin D status between the two time points. Majority of the patients (65.2%) had vitamin D insufficiency (52.2%) or deficiency (13%). Subgroup analysis based on vitamin D status revealed that there was a significant difference in gender distribution in three groups of patients (P: 0.007). However, no significant difference

was found related to age (P:0.24) and BMI (P: 0.15) between different vitamin D status subgroups.

In this study, the effect of PTH on early remodeling in patients who were hospitalized due to MI was investigated. Based on the findings of this study, 86% of the subjects had an inappropriate vitamin D level at admission. Also 53% of the patients had vitamin D insufficiency and 33% had vitamin D deficiency. Characteristics of the patients on the basis of vitamin D status are summarized in Table 1. Mean levels PTH increased compared with the levels on the first day (95% CI, 0.15 to 10.03, P:0.044), (95% CI, 6.5 to 24.8, P:0.001) respectively (Table 2). The data showed that by increasing PTH levels in patients with MI, the chance of early remodeling occurrence increases accordingly.

Table 1. Characteristics of the patients on the basis of vitamin D status.

NO:69	Vitamin D status*			P- value
	Vitamin D deficient[a]	Vitamin D insufficient[b]	Vitamin D sufficient[c]	
Age (year± SD)	58.22±14.79	63.22±12.73	65.20±11.35	0.08
Sex (male/female)	14/9	31/6	3/7	0.63
Body mass index (kg/m^2)	25.71±3.97	24.94±3.09	23.96±4.3	0.32
Weight (kg)	72.56±14.20	71.19±10.48	62.90±9.53	0.05

*Vitamin D status at the first day of admission in acute MI patients

a: Vitamin D deficient :25(OH)D3≤ 15 ng/ml

b: Vitamin D sufficient: 25(OH)D3> 30 ng/ml

c: Vitamin D Insufficient: 15 <25(OH) D3≤ 30 ng/ml

Table 2. Serum concentrations of PTH after 3 days in acute MI patients with heart failure due to early remodeling

	Just after MI (mean+-SD)	72 hours after MI (mean+-SD)	95% Confidence Interval of the Difference		p-value
			Lower	Upper	
PTH	30.98	46.65	6.5	24.8	0.001

An increasing PTH trend was observed in 64.3% of patients after 3 days, while vitamin D levels decreased in 14% of these patients. The changes in PTH levels were significantly correlated with the changes in vitamin D levels (Pearson correlation coefficient r = -0.416, P< 0.001).

Discussion

The incidence of heart failure after MI shows that although the increase in PTH compensates the damage to the heart and helps the survival of cells, it increases the risk of developing heart failure over time. In the present study, we investigated whether elevated PTH can affect cardiomyocytes to cause post-MI events such as hypertrophy or not. Many studies have shown that PTH can improve cardiac function after MI through neovascularization and increasing cell survival. We studied this correlation by measurement of serum PTH level in patients after MI. This is the first study that measured PTH level immediately after MI with 72 hours' intervals.

Recently, many studies have been done to investigate the effects of PTH on the cardiovascular system. Some inconsistent results such as improving the recovery process and increasing the mortality have been reported. For instance, the relationship between increasing levels of PTH and mortality in patients with HF has been reported in a few studies (11, 12).

It is clear that PTH facilitates stem cell release into the blood circulation, which leads to the recovery of damaged heart after MI (13). Therefore, PTH is an effective factor for improving tissue injuries.

The results of a study which was done in mouse models by Zaruba et al., showed that PTH therapy improved post-MI survival and myocardial function significantly. PTH therapy was correlated with increased migration of angiogenic CD45+/CD34+ progenitor cells to the ischemic heart tissue. They found that the infarcted hearts of PTH-treated mice increased the up-regulation of VEGF-A mRNA which is an important angiogenesis factor (13).

To compare the effects of G-CSF and PTH on cardiac tissue perfusion, several mice with MI were followed and received PTH (80µg/kg) and G-CSF (100µg/kg) for 5 days. The data of stimulation and tracking stem cells from bone marrow concentrate (BMC) at days 6 and 30 post-MI were analyzed. It was found that PTH increased the infarct size by increasing BMC migration to the heart muscle which could be considered as a therapeutic application for PTH in ischemic heart disease (15).

In one study, Gupta et al. showed that serum level of PTH in patients with the deficiency of vitamin D was 37.56±19.02pg/

ml, in patients with vitamin D insufficiency was 23.70±9.85 pg/ml, and in myocardial infarction patients with vitamin D sufficiency was 42.0±30.52 pg/ml. Although the relationship between vitamin D and PTH level is significant (P =0.037), serum level of PTH increased in all patients regardless of the vitamin D levels (16). In this study, 86% of the patients with myocardial infarction were in the vitamin D deficient and insufficient groups and PTH level was high in both groups.

In a study by Kolaszko et al., similar results were obtained which confirmed that PTH increased in patients with heart failure and correlated with left ventricular ejection fraction (LVEF), while 25(OH) D levels were not different among the study groups (17).

Also, the results of a study by Bansal et al., on patients without cardiovascular disease demonstrated that increased serum PTH levels were associated with an increase in left ventricular mass and also risk of HF events (18). The association between high serum PTH levels and heart failure necessitates more studies to be done to determine the benefits of PTH suppression after acute MI (within 72 hours) to prevent the occurrence of heart failure.

However, the detailed pathophysiological mechanisms remain unclear. Our study confirms that PTH excess is associated with heart failure. There are still no accurate data on related molecular mechanisms. It is thought that PTH has some effects on the cardiovascular system directly through the renin□angiotensin□aldosterone system (19).

Knowing the precise molecular mechanism of this hormone helps in controlling its harmful effects on the cardiovascular system. But it is more important to control serum PTH levels. Attention should be paid to the control of serum PTH levels in cardiovascular patients.

The main limitation of this study is that the participants' gender, place of living, social class, race and age over 18 years make differences in diet and exposure to sunlight which consequently cause differences in the levels of vitamin D and early PTH. These observations emphasize the need for additional research. Conducting more detailed studies with larger populations and a longer follow-up is recommended.

In conclusion, in recent years, much effort has been made to regenerate myocardial damaged tissues and researchers are still looking for possible mechanisms of hormones and trace elements on the heart during and after a heart attack. Based on the current evidence, PTH excess may be a risk factor for heart failure, so early treatment and omitting risk factors are the most effective strategies for the patients with acute myocardial infarction.

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