Res Cardiovasc Med. 2014 August; 3(3): e19321. DOI: 10.5812/cardiovascmed.19321
Published online 2014 July 28. **Research Article**

Hyper-Prolactinemia in Men With Idiopathic Dilated Cardiomyopathy: Does It Have any Prognostic Implications?

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Received: April 7, 2014; **Revised:** May 14, 2014; **Accepted:** May 24, 2014

Background: Prolactin (PRL) has increasingly been recognized to play a stimulatory role in inflammatory response. Recently, studies have reported an increase in prolactin level among patients with chronic heart failure, however, there is conflicting data about its role as a prognostic factor in these patients.
Objectives: We aimed to measure PRL level in male patients with idiopathic dilated cardiomyopathy (IDC) and its relationship with some prognostic factors.
Patients and Methods: Serum prolactin level was assessed in 33 men with a diagnosis of IDC, left ventricle ejection fraction (LVEF) less than 35% on standard medical therapy for heart failure and New York Heart Association class II-III. Serum NT-Pro BNP (N terminal pro brain natriuretic peptide), hs-CRP (High sensitive C reactive protein) and six-minute walk test (6MWT) were also measured. Our secondary endpoints were mortality, transplantation and hospitalization due to acute heart failure and all patients were followed for one year.
Results: The mean age was 33 ± 7 years (24-45 years) and the mean LVEF was 23% ± 6.5. The mean PRL level was 16 ± 7.7 ng/mL (95% confidence interval: 13.3-18.7 ng/mL), which was significantly higher than normal reference values (4.04-15 ng/mL) ($P < 0.0001$). There was no correlation between PRL levels and pro BNP, hs-CRP or 6MWT test, however, the serum PRL level was slightly higher among patients who died or were hospitalized or transplanted.
Conclusions: Considering our study results, prognostic implication of PRL should be questioned. However, it seems that the significant increase in serum PRL in the study population needs more consideration and may have its own pathophysiologic importance. Further studies are recommended for better addressing the role of PRL in chronic heart failure patients.

*Keywords:*Hyperprolactinemia; Cardiomyopathy, Dilated; Male; Prognosis

1. Background

Heart failure (HF) is a major cause of mortality and morbidity throughout the world. Despite the advances in research and its pathophysiology and management during the recent years, the prognosis of this dysfunction remains poor (1, 2). Neuroendocrine activation accompanies the development of the clinical syndrome of HF and is thought to contribute to the progression of cardiac dysfunction. Although the significance of the renin-angiotensin-aldosterone system and the sympathetic nervous system have been well understood, yet the possible involvement of immune-neuroendocrine interactions in the pathogenesis of cardiovascular disorders have also been supported by many new studies (2). Some studies show that prolactin is a major component of these interactions. Prolactin (PRL) represents a stimulatory link between the neuroendocrine and immune systems and recently a growing body of evidence indicates its involvement in the neuroendocrine adaptations to HF (3-7). Some reports show PRL is elevated in 25% of patients with HF and this may have functional and pathogenic implications (4).

2. Objectives

The aim of this study was to assess PRL level in patients with idiopathic dilated cardiomyopathy (IDC) and its relationship with biochemical and functional parameters in these patients.

3. Patients and Methods

3.1. Study Participants

A total of 33 patients with the diagnosis of HF according to the European Society of Cardiology Guidelines (1) who were admitted to the Heart Failure and Transplant Clinic between October and December 2012, were enrolled. The inclusion criteria were male gender, IDC with left ventricle ejection fraction (LVEF) less than 35% and New York Heart Association (NYHA) class II-III. All patients had to be on standard HF therapy with diuretics and neuro-hormonal blockers according to the latest guidelines on HF management (1). The exclusion criteria were acute HF state or overt fluid retention, history of ventricular arrhythmia treated by amiodarone, systemic hypertension, active myocarditis, history of significant endocrine disorder (including diabetes mellitus) or androgen use, NYHA class I and IV and inability to perform the six-minute walk test (6MWT). In addition, patients with significant hepatic, renal, hematologic, psychiatric disorders and history of treatment by any anti-psychotic, anti-anxiety or anti-depressant drugs were excluded. The study population was subsequently followed for a year and their hospitalization due to acute HF, transplantation or death was registered. No patient was lost during the follow up and HF medications were not changed unless an expected event occurred.

3.2. Data Acquisition and Laboratory Measurements

Primary evaluation, clinical history and physical examination were obtained from all patients, and demographic data and NYHA classification were recorded.

The NYHA class was evaluated, where class I indicates no limitations of physical activity, class II indicates slight limitation of physical activity, class III indicates limitation of physical activity and finally class IV indicates symptoms of dyspnea at rest (1).

The exercise tolerance and functional performance of patients were assessed by 6MWT according to the protocol of Guyatt and colleagues (8).

The levels of N terminal pro brain natriuretic peptide (NT-ProBNP) for neuro-homoral status (9-11) and high sensitive C-reactive protein (hs-CRP) as a pro-inflammatory marker (12, 13) have been recognized as important quantitative plasma biomarkers for the development of prognostic tools for IDC. Peripheral blood samples were collected for NT-ProBNP analysis using the ELISA method (Biomedia-Corp, Bratislava-Slovakia). Serum hs-CRP levels were measured via the slide agglutination method and immuneturbidimetry using a hs-CRP latex kit (Bionic-USA) for each sample.

Serum PRL was measured by the two-site immunoradiometric assay (IRMA) (Pathan, Iran). The reference range was 4.04-15.2 ng/mL. Thyroid stimulating hormone (TSH) was also measured by the radioimmunoassay (Autobio, China) in all patients with a reference range of 0.27-4.2 mU/mL. All blood samples were collected from the patients in a fasting state and sitting position, an hour after awakening from an overnight sleep.

3.3. Statistical Analysis

IBM SPSS Statistics 19.0 for Windows (IBM Corp. Armonk, NY, USA) was used for the statistical analysis. Data were expressed as mean ± standard deviation (SD) for the interval and count (percent) for the categorical variables. One-Sample Kolmogorov-Smirnov test was used to test the normal distribution of the interval variables. One-sample t-test was used to analyze differences in the mean values of hormonal concentrations between the patients and the normal reference values. Interval variables were compared between two groups, using Student's t test (for normally distributed data) or its non-parametric equivalent, Mann Whitney U test (for non-normally distributed data). Pearson's correlation coefficient (r) was also used to show linear correlations between interval variables. P values < 0.05 were considered significant. A logistic regression model was applied for multivariable analysis.

4. Results

4.1. Baseline Characteristics

There were 33 male patients with a mean age of 33 ± 7 (range = 24-45 years) with IDC. LVEF was 23% ± 6.5%. Concerning NYHA functional class, 22 (66.7%) of the patients were in class II and 11 (33.3%) were in class III. All patients were on standard recommended medical treatment for HF including angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blocker (ARB), beta-blockers, spironolactone, diuretics and digoxin. The mean body mass index was 23 ± 3.2 kg/m^2. The baseline clinical characteristics and laboratory test results of the study group are summarized in Table 1.

4.2. Serum Prolactin and Its Associations with NYHA Function Class and Other Prognostic Factors

The mean serum PRL level was 16 ± 7.7 (CI95%: 13.3-18.7) ng/mL, which was significantly higher than normal reference values (4.04-15 ng/mL) ($P < 0.001$).

Considering the TSH level, no one amongst the study population had hypothyroidism. As an important prognostic factor in these patients, the associations between NYHA function class, serum PRL and other prognostic factors were assessed specifically. The results are presented in Table 2. There were significant differences between NT-Pro BNP level, 6MWT and LVEF between NYHA FC II and III, which emphasized the better clinical condition and prognosis of the first group. However, despite of greater PRL serum levels in patients of the FC III group compared to FC II (17.3 ± 7.6 vs. 15.3 ± 7.8), this difference was not significant ($P = 0.5$).

The relationships between serum PRL level and other prognostic factors were also investigated. There were no correlations between serum prolactin level and NT-ProBNP ($r = 0.01$, $P = 0.5$) or hs-CRP levels ($r = 0.07$, $P = 0.3$). However there was a weak and marginally significant reverse correlation between 6MWT and prolactin level ($r = -0.33$ $P = 0.03$).

Table 1. Descriptive Statistics of Study Participants (n = 33) [a]

Variables	Mean ± SD (range)
Age, y	33 ± 7 (24-45)
LVEF, %	23 ± 6.5 (10-32.5)
BMI, Kg/m^2	23 ± 3.2 (18.5-31.1)
BSA, m^2	1.82 ± 0.2 (1.6-2.3)
6MWT, m	436 ± 116 (176-648)
Pro-BNP, ng/dL	1419 ± 1659 (23-5839)
hs-CRP, mg/dL	6.55 ± 15.01 (0.04-65)
TSH, mU/mL	2.44 ± 1.35 (0.4-5.9)
PRL, ng/mL	16 ± 7.7 (5.7-34.7)

[a] Abbreviations: PRL, prolactin; TSH, thyroid stimulating hormone; 6 MWT, six minute walk test; NT-Pro BNP, N terminal pro brain natriuretic Peptide; hs-CRP, high sensitive C reactive protein; LVEF, left ventricle ejection fraction; BMI, body mass index; BSA, body surface area.

Table 2. Comparison of Predictors between Groups of NYHA Function Class [a]

Predictor	NYHA Function Class		P value
	III (n = 11)	II (n = 22)	
PRL, ng/mL	17.28 ± 7.6	15.34 ± 7.8	0.502
TSH, mU/mL	2.9 ± 1.18	2.21 ± 1.4	0.171
6MWT, m	364.91 ± 132.6	471.5 ± 90.64	0.011
NT-Pro BNP, ng/dL	2715.28 ± 2080.77	770.88 ± 900.78	0.012
hs-CRP, mg/dL	8.66 ± 16.93	5.49 ± 14.25	0.576
LVEF, %	18.86 ± 9.18	24.89 ± 3.58	0.010

[a] Abbreviations: PRL, prolactin; TSH, thyroid stimulating hormone; 6MWT, six minute walk test; NT-Pro BNP, N terminal pro brain natriuretic peptide; hs-CRP, high sensitive C reactive protein; LVEF, left ventricle ejection fraction.

Table 3. Associations between the Predictors and Combined Events in the Patients Follow Up [a,b]

Predictor	Combined Event		P value
	Yes (n = 16)	No (n = 17)	
PRL, ng/mL	16.2 ± 8.2	15.8 ± 7.4	0.884
TSH, mU/mL	2.8 ± 1.3	2.1 ± 1.3	0.155
6MWT, m	431.8 ± 137.3	439.9 ± 96.3	0.846
NT-Pro BNP, ng/dL	1992.2 ± 1996.9	879.5 ± 1061.9	0.050
hs-CRP, mg/dL	7.7 ± 14.9	5.5 ± 15.4	0.676
LVEF, %	21 ± 7.4	25 ± 5.2	0.105
BMI, Kg/m^2	22.4 ± 2.7	23.5 ± 3.7	0.327
Age, y	32 ± 6.4	35 ± 7.2	0.213

[a] Abbreviations: PRL, prolactin; TSH, thyroid stimulating hormone; 6MWT, six minute walk test; NT-Pro BNP, N terminal pro brain natriuretic Peptide; hs-CRP, high sensitive C reactive protein; LVEF, left ventricle ejection fraction; BMI, body mass index.
[b] Any event including death, hospitalization due to heart failure and transplantation during one year.

4.3. Findings in the Patients' Follow Up

All the patients were followed for one year for events including mortality due to HF, hospitalization for acute HF and transplantation. During this follow up period, two patients (6%) died, 3 (9.1%) were transplanted and 11 (33.3%) were hospitalized at least once with a diagnosis of acute HF. Combined events (occurrence of death, transplantation or hospitalization) were observed in seven patients with NYHA FC II (31.8%) and in nine patients (81.8 %) with NYHA FC III (P = 0.007). Patients with events had higher NT-Pro BNP, hs-CRP, TSH level and lower LVEF and 6MWT; however except for Pro BNP, none of the differences were statistically significant. Also, the mean of PRL level was not different between those with or without events (Table 3).

A multivariable logistic regression model was applied to investigate the associations between the occurrence of combined events and PRL, adjusted for other predictors. No significant association was observed between PRL and event occurrence (β = -0.018, P = 0.744, OR [CI95%]: 0.98 [0.88-1.09]). However, the association between NYHA FC and the occurrence of events rose after adjustment (β = 2.27, P = 0.012, OR [CI95%]: 9.64 [1.63-56.92]), which meant that patients with FC III had greater probability of having events.

5. Discussion

In the present study we found a higher than normal serum PRL concentration among in 33 male patients with IDC and relatively stable medical conditions in an outpatient setting. There are several reports on measurement of serum PRL level in patients with HF. Opalinska et al. measured several hormonal levels including PRL in 27 HF males with a LVEF less than 35% and found hyperprolactinemia among these candidates (3). Limas et al. claimed that hyperprolactinemia is present in 25% of patients with HF (4) and in two recent studies, Landberg et al. (5) and Parissis et al. (6) showed elevated levels of serum PRL in different groups of patients with HF.

Nonetheless, despite the high frequency of hyperprolactinemia among patients with HF in these studies, there are conflicting findings about the role of PRL as a prognostic factor in patients with HF and its association with clinical and neuro-hormonal factors. In the present study we found no correlation between serum prolactin level and neuro-hormonal prognostic factors such as Pro BNP and hs-CRP. The serum PRL level also had no correlation with LVEF and there was no association between NYHA function class and serum PRL level in the present study. In our study the only prognostic factor correlated with serum PRL level was the 6MWT, however this correlation was relatively weak (r = 0.3, P = 0.03). On the other hand, the mean serum PRL level was not different among patients with and without HF related events, after the one-year follow up; even after adjustment for other predictors by multivariable analyses (Table 3). In Landberg et al. study similar findings were obtained. They measured

PRL level in 462 patients with mild to moderate HF mainly caused by ischemic heart disease and found no correlation between PRL level and LVEF; NT-Pro BNP and hs-CRP in HF patients with LVEF more or less than 50% and cardiovascular event after 10 years follow up were not higher among patients with higher serum level of PRL (5). Similarly, Wallaschofski et al. found no correlation between LVEF and the serum PRL level in 50 patients with chronic HF and concluded that there was no relevant association between PRL and immune responses in patients with HF (7). In contrast Limas et al. (4) and Opalinska et al. (3) found a significant correlation between LVEF and serum PRL level however their correlations were in opposite directions. Limas (4) found a positive correlation between PRL level and LVEF where the latter study showed greater increase in PRL level with decreasing LVEF.

In a recent large scale study, Parissis et al. showed that serum PRL is an independent predictor of prognosis in patients with advanced HF and is significantly correlated with NYHA class, LVEF, 6MWT, BNP and a number of proinflammatory markers such as IL-6 and IL-10 and tumor necrosis factor α (6). These results are in contrary with our study results which could be explained by differences in the study populations. Our study population was a group of male patients with IDC in an outpatient setting who were on an optimal standard therapy for at least three months whereas Parissis et al. (6) investigated patients hospitalized with acute HF who were older than our study population (65 ± 12 vs. 33 ± 7 years old); 17 % of patients were female and the prevalence of ischemic cardiomyopathy was about 60%. In addition, many of the cases had comorbid conditions such as chronic kidney disease and diabetes mellitus. Although their study population had a critical condition, considering the lower LVEF (22.9 ± 6.6% vs. 27 ± 7%) and higher Pro BNP level (1419 ± 1659 vs. 654 ± 658) in our study population, our patients seem to have experienced more advanced HF. Nonetheless, the mean of prolactin level was higher in our study than that of Parissis et al. (6) (16 ± 7.7 vs. 9 ± 5.5 ng/mL).

On the other hand, it is important to check TSH for the evaluation of thyroid function concomitant with checking PRL level. Parissis et al. (6) did not mention anything about concomitant measurement of TSH level in their study so the presence of thyroid dysfunction as a strong predictor of cardiovascular event in HF patients and a factor, which could influence PRL level, has not been addressed in their study.

One of the strengths of this study was the carefull selection of patients to reduce potential confounders. The serum PRL level could be affected by several medications, thus patients with a history of medications such as antidepressants or anti psychotics were excluded and the study population were chosen among patients with an uniform HF treatment protocol which was unchanged during follow up unless an event had occurred.

In conclusion, PRL as a multifunctional hormone plays an important role in immune-regulation, osmo-regulation, metabolism and angiogenesis (3-7) and there is substantial evidence in favor of its involvement in pathogenesis of peri-partum cardiomyopathy (14). However, considering the current and other studies results regarding the role of PRL in HF patients, this role could not simply be considered as a prognostic factor in HF and further investigations are needed to shed more light on the role of prolactin in pathophysiology of HF and its prognostic value.

Acknowledgements

The authors would like to thank Mr. Farshad Amouzadeh for his kind help with the English editing and preparation of the manuscript.

Authors' Contributions

Nasim Naderi participated in the research idea development, study design, data collection and manuscript writting. Hooman Bakhshandeh contributed to study design and writing the manuscript and performed the statistical analysis. Fatemeh Barzegari, Ahmad Amin and Sepideh Taghavi cooperated in data collection and preparation of the manuscript. Majid Maleki participated in the study design and supervised the research project.

Funding/Support

This research project was financially supported by the Rajaie Cardiovascular Medical and Research Center.

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