

## Hormonal Profile in Patients With Dilated Cardiomyopathy

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**Background:** There is increasing evidence that endocrine system may be dysfunctional in patients with heart failure.

**Objectives:** In the present study, we investigated hormonal abnormalities in heart failure and the effect of disturbed hormonal balance on prognostic outcomes of patients with systolic heart failure.

**Patients and Methods:** Among patients followed in Heart Failure and Transplantation Clinic, 33 men with a diagnosis of idiopathic dilated cardiomyopathy receiving guidelines-directed medical therapies and with New York Heart Association Class II-III were enrolled. Serum concentrations of growth hormone (GH), insulin-like growth factor 1 (IGF-1), thyroid hormones, free testosterone, high-sensitive C-reactive protein (hs-CRP), and N-terminal pro-brain natriuretic peptide (NT Pro-BNP) were measured in all the patients. The physical performance of patients was assessed by six-minute walk test (6MWT). The patients were subsequently followed for a year and the data regarding their death, transplantation, or hospitalizations due to acute heart failure were recorded.

**Results:** Except for testosterone level, the levels of GH, IGF-1, T3, and T4 concentrations in the patients were significantly lower than the normal values ( $P < 0.05$ ). Among different hormone, only GH had correlation with NT Pro-BNP, hs-CRP, and 6MWT. There was no association between the occurrence of the combined events and different hormonal levels in multivariate analysis.

**Conclusions:** The hormonal levels were low in patients with idiopathic dilated cardiomyopathy. However, the prognostic significance of different hormonal deficiencies was not clear in our study populations who were receiving standard therapies for heart failure and had a relatively stable clinical condition.

**Keywords:** Heart Failure; Hormonal level; prognosis

### 1. Background

Heart failure (HF), a major cause of morbidity and mortality throughout the world, is responsible for a high rate of hospitalization and is a principal complication of all forms of heart diseases (1, 2). Although, the results of extensive investigations in this field have a great role in understanding HF pathophysiology and better management of patients, the prognosis of this disorder remains poor. The pathophysiology of HF is closely associated with neuroendocrine changes. The activation of neuroendocrine systems contributes to the progression of HF (3-5). Many neuroendocrine factors are changed in congestive HF (CHF). The neuroendocrine changes not only are a marker of the severity of cardiac dysfunction, but also directly worsen it. The cornerstone of HF therapy is modulating these neuroendocrine changes and decreasing their adverse effects (4-6).

It was suggested that growth hormone (GH) and its effectors, insulin-like growth factor 1 (IGF-1), may contribute to the regulation of the cardiovascular system (5-8). Overt hyperthyroidism and hypothyroidism have been reported to be common causes of HF and thyroid dys-

function is a modifiable risk factor in patients at risk of HF (9-12). In men with HF, serum levels of free testosterone are decreased in proportion to HF severity (5, 13, 14). The reduced level of testosterone in the advanced HF may contribute to catabolic and anabolic imbalance (13-15).

### 2. Objectives

The aim of this study was to assess hormonal level in patients with idiopathic dilated cardiomyopathy (DCM) and its association with certain prognostic factors and outcomes.

### 3. Patients and Methods

Among patients with HF presented to the Heart Failure and Transplantation clinic of Rajaie Cardiovascular, Medical, and Research Center, between October and December 2012, a total of 33 male patients with a diagnosis of idiopathic DCM, a left ventricle ejection fraction (LVEF)  $< 35\%$ , and New York heart association (NYHA) class of II or III were enrolled. All patients had to be on

optimal levels of guidelines directed medical therapies. The methods for patients selection, inclusion/exclusion criteria and prognostic variables have been explained in detail previously (16).

### 3.1. Hormonal Assays

The plasma levels of the following hormones were measured: thyroxine (T4), triiodothyronine (T3), and thyroid stimulating hormone (TSH) by radioimmunoassay (RIAS) (Autobio, China); free testosterone by RIAS (Monobid, USA); GH and IGF-1 by RIAS (Specteria, Finland); and serum prolactin by two-site immunoradiometric assay (IRMA) (Pathan, Iran). The blood samples were collected in the fasting state and sitting position just an hour after awakening from an overnight sleep. Table 2 depicts the normal reference values of hormonal level. Research and Ethics Committee of Rajaie cardiovascular medical and research center approved the study and informed consent was obtained from all the patients.

### 3.2. Patients' Follow-up

All the patients were subsequently followed for a year and their death, transplantation, and admissions for acute HF were recorded.

### 3.3. Statistical Methods

For all the statistical analyses, IBM SPSS statistics 19.0 for windows (IBM Corp, Armonk, New York, the United States) was used. Quantitative variables were presented as mean and standard deviation and categorical variables were expressed as number and percentage. One sample-Kolmogorov-Smirnov test was used to test normal distribution. For assessing the differences in the mean values of hormonal concentrations between the patients and the normal reference values, one-sample t test was used. Correlations between the indices were estimated using the Spearman Rho correlation coefficient and Pearson's correlation as appropriate. Binary logistic regression analysis was used for multivariate analysis. P values < 0.05 were considered statistically significant.

## 4. Results

There were 33 male patients with idiopathic DCM and a mean LVEF of  $22.87 \pm 6.5\%$ . Table 1 shows all the baseline data, clinical characters, and laboratory findings of the study group. The mean age was  $33.12 \pm 6.8$  year (range, 24 - 45 years). In addition, 22 patients (66.7%) were in NYHA class II and 11 (33.3%) were in class III. All patients were treated by guidelines-directed medical therapies including angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blocker (ARB), beta-blockers, spironolactone, and diuretics. The dosages of ACEI/ARB, beta-blockers, and spironolactone were at maximally tolerated doses and the diuretics dosages had not been changed significantly unless an event was occurred. Ap-

proximately 60% of patients received digoxin and 27% had intracardiac defibrillator (ICD) or cardiac resynchronization therapy (CRT).

### 4.1. Hormonal Levels Among Patients With Dilated Cardiomyopathy and Associations With NYHA Function Class and Other Prognostic Factors

Table 2 shows the values of hormonal level among the study population compared with normal reference values. As shown in Table 2, except for testosterone and TSH, the mean levels of most hormones were significantly different from their normal values. Table 3 shows the association between NYHA functional class, different hormonal levels, hs CRP, NT Pro-BNP, and six-minute walk test (6MWT). The NT Pro-BNP level, 6MWT, and LVEF were significantly different in NYHA class II and III, which emphasized the better clinical state in patients with NYHA class I. However, except for GH, there was no association between NYHA class and other hormonal levels. As shown in Table 3, the GH level is significantly higher among patients with a NYHA class III ( $1.5 \pm 2.5$  vs  $0.2 \pm 0.3$  ng/mL;  $P = 0.02$ ). Table 4 shows the correlations between prognostic predictors and hormonal levels.

**Table 1.** Descriptive Statistics in Thirty-Three Study Participants<sup>a</sup>

Variables	Values <sup>b</sup> (Range)
Age (y)	$33 \pm 7$ (24 - 45)
LVEF (%)	$22.9 \pm 6.6$ (10 - 32.5)
BMI (kg/m <sup>2</sup> )	$22.9 \pm 3.2$ (18.5 - 31.1)
BSA (m <sup>2</sup> )	$1.82 \pm 0.2$ (1.6 - 2.3)
6MWT (m)	$436 \pm 116$ (176 - 648)
NT Pro-BNP (ng/dL)	$1419 \pm 1659$ (23 - 5839)
hs-CRP (mg/dL)	$6.55 \pm 15.01$ (0.04 - 65)
T3 (nmol/L)	$1.8 \pm 0.4$ (1.1 - 2.6)
T4 (nmol/L)	$8.4 \pm 2.1$ (4.9 - 13.7)
TSH (mU/mL)	$2.44 \pm 1.35$ (0.4 - 5.9)
GH (ng/mL)	$0.62 \pm 1.55$ (0 - 8.2)
IGF1 (ng/mL)	$127.2 \pm 45.8$ (1.66 - 241)
PRL (ng/mL)	$16 \pm 7.7$ (5.7 - 34.7)
Testosterone (pmol/L)	$4.95 \pm 2.3$ (1.8 - 13.3)

<sup>a</sup> Abbreviations: 6MWT, six-minute walk test; BMI, body mass index; BSA, body surface area; GH, growth hormone; hs-CRP, high-sensitive C-reactive protein; IGF-1, insulin-like growth factor 1; LVEF, left ventricle ejection fraction; NT Pro-BNP, N-terminal pro-brain natriuretic peptide; PRL, prolactin; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

<sup>b</sup> Data are presented as Mean  $\pm$  SD.

**Table 2.** Values of Hormonal Level Among Thirty-Three Study Participants <sup>a</sup>

Hormones	Normal Values, Range	Patients (95% CI) <sup>b</sup>	P Value
GH (ng/mL)	0 - 4	0.62 ± 1.5 (0.07 - 1.1)	< 0.001
IGF-1 (ng/mL)	100 - 366	127.18 ± 45.82 (110 - 143)	< 0.001
Testosterone (pmol/L)	2.8 - 8	4.95 ± 2.33 (4.1 - 5.8)	0.2
T4 (nmol/L)	5.1 - 14.1	8.46 ± 2.10 (7.7 - 9.1)	0.004
T3 (nmol/L)	1.3 - 3.1	1.83 ± 0.37 (1.7 - 1.9)	< 0.001
TSH (mU/mL)	0.27 - 4.2	2.51 ± 1.31 (1.9 - 2.9)	0.2
PRL (ng/mL)	4.04 - 15.2	15.98 ± 7.67 (13.3 - 18.7)	< 0.001

<sup>a</sup> Abbreviations: CI, confidence interval; GH, growth hormone; IGF-1, insulin-like growth factor 1; PRL, prolactin; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

<sup>b</sup> Data are presented as Mean ± SD.

**Table 3.** Comparison of Predictors Between Groups of NYHA Function Class <sup>a,b</sup>

Variables	NYHA Function Class		P Value
	III (n = 11)	II (n = 22)	
PRL (ng/mL)	17.28 ± 7.6	15.34 ± 7.8	0.5
T3 (nmol/L)	1.8 ± 0.4	1.8 ± 0.4	0.8
T4 (nmol/L)	8.8 ± 2.4	8.2 ± 1.9	0.4
TSH (mU/mL)	2.9 ± 1.18	2.21 ± 1.4	0.1
Testosterone (pmol/l)	4.5 ± 1.7	5.2 ± 2.6	0.4
GH (ng/mL)	1.5 ± 2.5	0.2 ± 0.3	0.02
IGF1 (ng/mL)	128 ± 29.1	126.8 ± 52.9	0.9
6MWT (m)	364.91 ± 132.6	471.5 ± 90.64	0.01
NT Pro-BNP (ng/dL)	2715.28 ± 2080.77	770.88 ± 900.78	0.01
hs-CRP (mg/dL)	8.66 ± 16.93	5.49 ± 14.25	0.5
LVEF (%)	18.86 ± 9.18	24.89 ± 3.58	0.01

<sup>a</sup> Abbreviations: 6MWT, six-minute walk test; GH, growth hormone; hs-CRP, high-sensitive C-reactive protein; IGF-1, insulin-like growth factor 1; NT Pro-BNP, N-terminal pro-brain natriuretic peptide; PRL, prolactin; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

<sup>b</sup> Data are presented as Mean ± SD.

**Table 4.** Correlations Between Prognostic Predictors and Hormonal Levels <sup>a</sup>

	LVEF	6MWT	NT Pro-BNP	hs-CRP
<b>T3</b>				
r	0.1	0.2	0.04	0.14
P	0.4	0.4	0.8	0.4
<b>T4</b>				
r	0.05	0.09	0.14	0.2
P	0.7	0.6	0.4	0.1
<b>TSH</b>				
r	0.3	0.1	0.09	0.2
P	0.1	0.4	0.5	0.9
<b>GH</b>				
r	0.24	0.4	0.5	0.45
P	0.1	0.01	0.004	0.01
<b>IGF-1</b>				
r	0.1	0.04	0.04	0.1
P	0.4	0.7	0.8	0.5
<b>Testosterone</b>				
r	0.09	0.34	0.1	0.1
P	0.6	0.05	0.4	0.4
<b>PRL</b>				
r	0.03	0.3	0.08	0.1
P	0.9	0.07	0.6	0.4

<sup>a</sup> Abbreviations: 6MWT, six-minute walk test; GH, growth hormone; hs-CRP, high-sensitive C-reactive protein; IGF-1, insulin-like growth factor 1; LVEF, left ventricle ejection fraction; NT Pro-BNP, N-terminal pro-brain natriuretic peptide; P, P value; PRL, prolactin; r, Pearson or Spearman correlation coefficient; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

#### 4.2. Thyroid Hormones

The thyroid function test showed a normal TSH level and a significantly lower levels of T3 and T4 compared to normal reference values (1.7-1.9 vs 1.3-3.1 nmol/L,  $P < 0.001$  for T3; and 7.7-9.1 versus 5.1 - 14.1 for T4,  $P = 0.004$ ). However, there was no association between T3, T4, and TSH levels and LVEF, hs-CRP, NT Pro-BNP, and 6MWT distance (r range, 0.05-0.1;  $P > 0.05$ ).

#### 4.3. Growth Hormone and Insulin-like Growth Factor 1

As presented in Table 2, the mean of GH and IGF-1 levels were significantly lower than normal values. There was no association between IGF-1 level and LVEF, hs-CRP, NT Pro-BNP, and 6MWT; however, there was a significant moderate positive correlation between GH level and NT Pro-BNP ( $r = 0.5$ ,  $P = 0.004$ ) and hs-CRP ( $r = 0.45$ ,  $P = 0.01$ ). The 6MWT showed a relatively weak, but significant, reverse correlation with GH level (Table 4).

#### 4.4. Testosterone

The free testosterone level of our study population was within normal limits and there was no association between testosterone level and LVEF, NT Pro-BNP, and hs-CRP.

However, a weak but significant correlation was shown between 6MWT and testosterone level (Tables 2 - 4).

#### 4.5. Findings in the Patients' Follow-Up

All the study populations were followed for 12 months for death due to HF, hospitalization for acute decompensated HF, and heart transplantation. During the follow-up period, 11 patients (33.3%) were hospitalized at least once with a diagnosis of decompensated HF, 3 (9.1%) were transplanted, and 2 (6%) died. The combined event (occurrence of death, transplantation, or any admission for acute HF) was more prevalent in patients with NYHA class III than in those with NYHA class II (81.8% and 31.8%, respectively;  $P = 0.007$ ). Patients with such events had lower LVEF and 6MWT and higher NT Pro-BNP, hs-CRP, TSH, GH, and testosterone levels; however, none of the differences were statistically significant, except for NT Pro-BNP. Moreover, the mean of other hormonal levels were not different between those with and without combined events (Table 5).

To evaluate the associations between the combined events and different hormonal levels, multivariable logistic regression model, adjusted for other predictors, was applied. No significant correlation was seen between different hormonal levels and combined events (Table 6)

**Table 5.** Associations Between the Predictors and Study Combined Events in the Patients Follow-up <sup>a,b</sup>

Variables	Combined Event <sup>c</sup>		P Value
	Yes (n = 16)	No (n = 17)	
PRL (ng/mL)	16.2 ± 8.2	15.8 ± 7.4	0.8
T3 (nmol/L)	1.9 ± 0.4	1.7 ± 0.4	0.3
T4 (nmol/L)	8.6 ± 2.1	8.2 ± 2.2	0.5
TSH (mU/mL)	2.8 ± 1.3	2.1 ± 1.3	0.1
GH (ng/mL)	1 ± 2.2	0.24 ± 0.3	0.1
IGF-1 (ng/mL)	128.1 ± 42.7	126.3 ± 49.9	0.9
Testosterone (pmol/L)	5.2 ± 2.8	4.7 ± 1.9	0.5
6MWT (m)	431.8 ± 137.3	439.9 ± 96.3	0.8
NT Pro-BNP (ng/dL)	1992.2 ± 1996.9	879.5 ± 1061.9	0.05
hs-CRP (mg/dL)	7.7 ± 14.9	5.5 ± 15.4	0.6
LVEF (%)	21 ± 7.4	25 ± 5.2	0.1
BMI (kg/m <sup>2</sup> )	22.4 ± 2.7	23.5 ± 3.7	0.3
Age (y)	32 ± 6.4	35 ± 7.2	0.2

<sup>a</sup> Abbreviations: 6MWT, six-minute walk test; BMI, body mass index; GH, growth hormone; hs-CRP, high-sensitive C-reactive protein; IGF-1, insulin-like growth factor 1; LVEF, left ventricle ejection fraction; NT Pro-BNP, N-terminal pro-brain natriuretic peptide; PRL, prolactin; r, Pearson or Spearman correlation coefficient; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

<sup>b</sup> Data are presented as Mean ± SD.

<sup>c</sup> Any event including death, hospitalization due to heart failure, and transplantation by a year.

**Table 6.** The Adjusted Relationship Between Hormonal Levels and Prognostic Factors <sup>a</sup>

Variables	Beta	P Value	Odd Ratio (95% CI)
Age	-0.173	0.05	0.841 (0.7 - 1)
LVEF	0.004	0.9	1.004 (0.7 - 1.3)
6MWT	-0.001	0.8	0.99 (0.9 - 1)
NT Pro-BNP	0.001	0.4	1.001 (0.9 - 1)
hs-CRP	0.037	0.3	1.04 (0.9 - 1.1)
T3	-0.03	0.1	0.99 (0.9 - 1.1)
T4	-0.558	0.2	0.6 (0.2 - 1.3)
TSH	0.885	0.07	2.4 (0.9 - 6.4)
GH	0.683	0.4	1.9 (0.2 - 13.8)
IGF1	0.003	0.7	1.003 (0.9 - 1.02)
PRL	-0.048	0.5	0.95 (0.8 - 1.1)
Testosterone	-0.240	0.3	0.8 (0.4 - 1.3)

<sup>a</sup> Abbreviations: 6MWT, six minute walk test; GH, growth hormone; hs-CRP, high sensitive C-reactive protein; IGF-1, insulin-like growth factor 1; LVEF, left ventricle ejection fraction; NT Pro-BNP, N-terminal pro-brain natriuretic peptide; PRL, prolactin; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

## 5. Discussion

The investigators indicated that the neuroendocrine abnormalities are closely associated with HF. It has also been shown that many hormonal molecules including GH, IGF-1, T3, T4, TSH, and free testosterone are down-regulated in the setting of cardiac dysfunction (4, 5, 13). In the current study, we measured these hormonal levels in a group of patients with a diagnosis of idiopathic DCM in an outpatient setting. Our study population had relatively stable clinical condition (NYHA class II to III), were treated with guidelines-recommended therapies at optimal level, and their diuretic dosage did not change during the follow-up period unless they developed an event.

### 5.1. Thyroid Hormones

T3 increases cardiac output by affecting all the determinants of cardiac performance (10, 11). An important effect of T3 is inducing the relaxation of the vascular smooth muscle cells (10). In the presence of normal or near-normal T4 and TSH levels, the patients with HF might have reduced T3 levels (11, 12). In some reports, about one-third of patients with severe HF had low-T3 syndrome (5, 12, 17). A similar prevalence rate (34%) was reported in another study of 132 patients with HF (11). Similar to the previous studies, our study demonstrated that the T3 and T4 levels were lower in patients with DCM than in the normal population, while the TSH level was nearly normal. The value of low T3, as a predictor of poor prognosis in HF, has been suggested by many investigators (5, 10, 11, 17-19). In a similar studies, after a 12-month follow-up period, cardiac and all-cause-mortality was higher in the low-T3 group, and free T3 was the strongest and an independent predictor of death in a multivariate analysis (5, 17, 19). In our study, neither was an association found between the T3, T4, TSH

levels and combined endpoints during 12-month follow-up nor were there any correlations between all the thyroid hormones and 6MWT, NT Pro-BNP, and hs-CRP. The possible explanation for this finding could be that all of patients in our study were on optimal guideline-recommended medical therapies for HF and had stable clinical condition; therefore, longer follow-up period might be needed to assess them. It should be addressed in another study whether the optimal medical therapies for HF can modify the influence of low level of thyroid hormones on HF's outcomes and how it exerts this modification.

### 5.2. Growth Hormone and Insulin-Like Growth Factor 1

Several clinical and experimental studies suggest that GH and IGF-1 may act as a modulator in cardiovascular system (5, 8, 20). An acquired resistance to GH in patients with HF who are cachectic has been suggested (8, 21, 22). Therefore, patients with lower lean body mass and those who are cachectic tend to have an abnormal GH-IGF-1 axis (5, 21-23). There are also several reports that suggest a proportion of patients with HF may be resistance to the treatment with GH (23-28). However, there are contradictory data regarding the treatment of patients with HF with GH. In an investigation, seven patients with idiopathic DCM received GH therapy for three months and after three months, the left ventricular wall thickness increased and the patients had impressive improvement in clinical status (7). Cittadini et al. suggested that short term GH therapy in patients with HF could be accompanied by improvement in exercise tolerance and cardiac performance (25). However, Isgaard et al. investigated the effects of three-month GH therapy in patients with CHF

and reported no significant effects on ejection fraction, left ventricular mass, functional capacity, and exercise performance (26).

In our study, both GH and IGF-1 levels were significantly lower than the normal values (Table 2). There was no association between LVEF and GH and/or IGF-1. However, regardless of normal body mass index (BMI) in our patients, the level of GH was significantly higher among patients with a NYHA class III ( $1.5 \pm 2.5$  ng/L in NYHA III vs  $0.2 \pm 0.3$  ng/dL in NYHA II), which may suggest an acquired resistance to GH in those who had worse clinical condition. On the other hand, the presence of moderate association between prognostic factors (NT Pro-BNP, hs-CRP, and 6MWT distance) and GH level, which indicated higher GH levels in patients with shorter 6MWT distance and higher pro-BNP and CRP, may be suggestive for resistance to GH among patients with more critical condition. These results are similar to those of Cittadini et al. and Adamopoulos et al. that showed the treatment with GH can reduce the NYHA class, pro-BNP, and the circulating proinflammatory cytokines in patients with HF (24, 25, 28). The lower IGF-1 level in current study could be considered as another sign for this resistance to GH; however, we found no significant association between any of prognostic factors and IGF-1 level.

Numerous studies have suggested an abnormal GH/IGF-1 axis in cachectic patients with HF and offered GH therapy in these patients (8, 23-25, 27, 28). However, although GH therapies might reduce the pro-BNP level and improve the clinical condition of patients (24, 25, 27, 28), to our knowledge, the influence of GH level and GH therapy on long-term outcomes of patients with HF have not been investigated yet. In current study, GH and IGF-1 levels were not different in patients with and without combined event. Despite higher event rate in patients with NYHA class III and higher NT Pro-BNP level, multivariable logistic regression analysis showed no association between the occurrence of combined event and GH or IGF-1 level after adjustment for other variables. These results could be explained by the fact that none of our patients were cachectic and their clinical condition were stable; therefore, follow-up for a duration of a year might not be enough to assess prognostic value of GH in HF. Another study with larger sample size should be conducted for this purpose.

### 5.3. Testosterone

In men with HF, serum levels of free testosterone may be decreased in proportion to the severity of HF (5, 27, 29-31). The prevalence of testosterone deficiency in all ages was 43%. In male patients with HF, low testosterone level is an independent predictor of death (5, 27). In patients with advanced HF, reduced testosterone level is one of the features contributing to the anabolic or catabolic imbalance (27, 29-31). In the present study, the testosterone level of patients with DCM was within normal limits. The mean level of testosterone was not different among

patients with or without combined events. Although, the testosterone level may be decreased proportional to the illness severity in HF, the good clinical condition of our patients can be a possible explanation for this finding. However, among all the studied prognostic indices, 6MWT and the free testosterone level had a weak negative correlation, which indicated that patients with lower level of testosterone might have poor functional capacity. Following the patients for longer duration may be needed for better defining the role of testosterone levels in the prognosis of patients with HF who are receiving optimal guideline-based medications.

### 5.4. Study Limitation

The careful selection of patients to reduce confounders was the strengths of this study. However, the study sample was limited.

In conclusion, we showed some hormonal levels were expectedly low in comparison to other similar studies. However, the prognostic significance of different hormonal deficiencies was not clear in our study populations who were receiving standard HF therapies at maximally tolerated doses and had a relatively stable clinical condition. Other studies should investigate whether using the standard treatments for HF can modify and postpone the effects of abnormal hormonal effects. Investigation of these associations may shed some fresh light on pathogenic pathway underlying the development and progression of CHF.

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### Authors' Contributions

Nasim Naderi: Leader of the project, clinical examination of the case and treatment; Mona Heiadrili: Scientific writing; Fateme Barzegari: Case finding; Behshid Ghadrdoost: analysis; Ahmad Amin: Clinical examination of the case and treatment; Sapideh Taghavi: Clinical examination.

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