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Investigation of serum copeptin levels in patients with congestive heart failure

Zülfiye Kuzu[1], Oğuz Kaan Kaya[2], Arzu Neslihan Akgün[3], Hatice Solmaz[4]
Mesut Karataş[5], Mustafa Ferzeyn Yavuzkır[6]

[1]Department of Cardiology, Kayseri City Hospital, Kayseri, Turkiye
[2]Department of Cardiology, Antalya Training and Research Hospital, Antalya, Turkiye
[3]Department of Cardiology, Ankara Etlik City Hospital, Ankara, Turkiye
[4]Department of Cardiology, İzmir City Hospital, İzmir, Turkiye
[5]Department of Cardiology, University of Health Sciences, Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital, İstanbul, Turkiye
[6]Department of Cardiology, Fırat University Hospital, Elazığ, Turkiye

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Corresponding Author: Zülfiye Kuzu, zulfiyekuzu07@hotmail.com

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ABSTRACT

Aims: Congestive heart failure (CHF) is characterized by symptoms and signs of volume overload and tissue perfusion insufficiency and accompanied by neurohormonal activation. Copeptin is a part of pre-pro-vasopressin and synthesized in equal molar amounts with vasopressin. We aimed to evaluate the sensitivity and specificity of copeptin in indicating the diagnostic value of CHF

Methods: This retrospective study included a total of 80 patients including 40 with heart failure and 40 healthy individuals. The groups were compared in terms of demographic features, laboratory findings including copeptin levels.

Results: There was no statistically significant difference between the groups in terms of gender ($p>0.05$). Age, hypertension, diabetes mellitus, smoking were statistically significantly higher in the heart failure group compared to the control group ($p<0.05$). In both groups, serum copeptin levels were higher in men than in women. Copeptin levels in the heart failure group were statistically significantly higher than in the control group ($p<0.05$). In the heart failure group, there was a negative correlation between serum copeptin levels and age, gender, hypertension, smoking, HDL cholesterol, hematocrit, creatinine levels.

Conclusion: Copeptin is a good indicator of the course of the disease in patients with heart failure.

Keywords: Congenital heart disease, risk factors, contemporary clinical practice

INTRODUCTION

Congestive heart failure (CHF) is a complex clinical syndrome that can be caused by any structural or functional disorder that impairs the ability of the ventricle to fill with and pump blood.[1] Heart failure is a physiopathologic condition defined as the inability of the heart to pump blood at a rate sufficient for the needs of metabolic tissues or to do so only with increased filling pressures. CHF, a complex syndrome characterized by symptoms and signs of volume overload and tissue perfusion insufficiency and accompanied by neurohormonal activation, is a biological disorder whose progression can be prevented.[1,2]

Copeptin is a part of pre-pro-vasopressin and synthesized in equal molar amounts with vasopressin. The advantage of copeptin is its long stability, rapid measurement from plasma and significance. It may remain stable for 14 days in plasma with EDTA and 7 days in plasma with heparin and citrate.[3] Copeptin is a 39 amino acid glycopeptide which is the C-terminal end of provasopressin.[4]

We aimed to evaluate the sensitivity and specificity of copeptin in indicating the diagnostic value of congestive heart failure (CHF) by comparing plasma copeptin levels in subjects with and without CHF (healthy volunteers), to demonstrate its diagnostic value at the bedside, and to define the relationship of copeptin levels with disease progression and recovery.

METHODS

This study was approved by Ethics Committee of Fırat University (Date:14/05/2010, Decision No: 23). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between May 2010 and April 2011, 40 patients [mean age 56.37±8.71 years; 55% (n=22) male; 45% (n=18) female] who were hospitalized in the Cardiology Clinic of Fırat University Medical Faculty between May 2010 and April

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2011 and who were diagnosed with heart failure based on anamnesis, physical examination, tele cardiography, electrocardiography, biochemical parameters and BNP levels and who had an ejection fraction (EF) of 40% or less measured echocardiographic ally by Simpson's method were included in the study; 55% (n=22) male; 45% (n=18) female] were included as heart failure group.

A total of 80 subjects, including 40 healthy individuals [mean age 51, 22±8.70 years; 50% (n=20) males and 50% (n=20) females; mean age 51, 22±8.70 years; 50% (n=20) males and 50% (n=20) females) with preserved ventricular function and an echocardiographic ejection fraction (EF) of 60% or higher as measured by Simpson's method, without symptoms and laboratory findings of heart failure on anamnesis and physical examination, were included as the control group.

Exclusion criteria from the patient and control groups were those with malignancy, those with problems in hematologic parameters, those who did not accept the study and individuals under the age of 18 years. Copeptin levels were measured using an automated immunoassay.

Statistical Analysis

Statistical analysis was performed using SPSS 12.0 (Statistical Package for Social Sciences) program. Parametric data were expressed as mean ± standard deviation and nonparametric data as (%). Oneway Anova test was used to compare parametric data and normality was evaluated by Kormogorov-Smirnov test. Logarithmic transformations were applied to parameters that did not exhibit normal distribution characteristics before statistical analysis. Results were evaluated at 95% confidence interval and significance was evaluated at p<0.05 level.

RESULTS

There was no statistically significant difference between the groups in terms of gender (p>0.05). Age, hypertension, diabetes mellitus, smoking were statistically significantly higher in the heart failure group compared to the control group (p<0.05)(Table 1). In the heart failure group, 15 patients (37.5%) had a history of acute myocardial infarction.

Table 1. Demographic characteristics of the groups

	Control group (n=40)	HF* group (n=40)	p
Age (year)	51; 22±8.70	56.37±8.71	<0.5 (p=0.010)
Female n (%)	20 (50%)	18 (45%)	>0.05 (p=0.823)
Male n (%)	20 (50%)	22 (55%)	>0.05 (p=0.823)
Hypertension n (%)	-	18 (45%)	<0.05 (p=0.001)
Cigarette n (%)	21 (52.5%)	8 (20%)	<0.05 (p=0.005)
Diabetes mellitus	-	14 (35%)	<0.05 (p=0.001)

HF: Heart failure

When serum copeptin levels were analyzed between men and women in our study, serum copeptin levels were found to be 569±176.28 in men and 458.89±155.48 in women in the heart failure group and 394±56.13 in men and 394±56.13 in women in the control group. In both groups, serum copeptin levels were higher in men than in women. The difference between them was not statistically significant (p>0.05).

According to laboratory data, there was no statistically significant difference between the groups in hemoglobin, hematocrit and triglyceride levels (p>0.05). Total cholesterol, HDL cholesterol and LDL cholesterol levels were significantly lower in the heart failure group compared to the control group (p<0.05), and urea, creatinine and copeptin levels were significantly higher in the heart failure group compared to the control group (p<0.05) (Table 2).

Table 2. Characteristics of the groups from laboratory data

	Control group (n=40)	CHF group (n=40)	p
Hemoglobin (g/dl)	13.57±1.27	13.80±1.20	>0.05
Hematocrit (%)	40.29±4.29	41.55±4.38	>0.05
Total cholesterol (mg/dl)	210.88±58.68	179.15±40.36	<0.05
HDL cholesterol (mg/dl)	50.28±10.61	44.20±9.84	<0.05
LDL cholesterol (mg/dl)	130.32±24.74	117.23±31.02	<0.05
Triglyceride (mg/dl)	136.88±52.92	141.32±58.19	>0.05
Urea (mg/dl)	33.60±9.13	50.95±19.44	<0.05
Serum kreatinin (mg/dl)	0.97±0.16	1.120±0.249	<0.05
Serum copeptin (pg/mL)	387.50±65.8	519.50±174.22	<0.05

CHF: Congestive heart failure, HDL: High density lipoprotein, LDL: Low density lipoprotein

The difference in copeptin levels between the groups was statistically significant (p<0.05). Copeptin levels in the heart failure group were statistically significantly higher than in the control group. The copeptin level was 519.50 ± 174.22 in the heart failure group and 387.50 ± 65.8 in the control group. The difference was statistically significant (p<0.05, p=0.002) (Table 2, Figure).In the heart failure group (n=40), there was a positive correlation between serum copeptin levels and urea, smoking, total cholesterol, LDL cholesterol, triglyceride, hemoglobin and total cholesterol levels. However, in this group, serum copeptin levels were statistically significant only with smoking and gender (r: 0.416 and p= 0, 004 for smoking, r: -0, 319 and p= 0, 023 for gender) (Table 3).

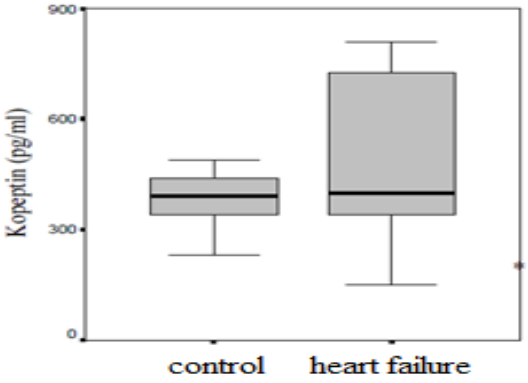

Figure. Serum copeptin levels

In the heart failure group, there was a negative correlation between serum copeptin levels and age, gender, hypertension, smoking, HDL cholesterol, hematocrit, creatinine levels.

In the control group (n=40), serum copeptin levels were negatively correlated with triglyceride, hematocrit, creatinine, urea, age, gender and smoking. In the control group (n=40), there was a positive correlation between serum copeptin levels and total cholesterol, HDL cholesterol, LDL cholesterol and hemoglobin (Table 4).

Table 3. Correlations of some parametric data with copeptin in the heart failure group

Heart failure group (n=40)	Copeptin (pg/ml)	
	r	p
Age (year)	-0.232	>0.05
Gender (male/female)	-0.319	<0.05
Cigarette	0.416	<0.05
Hypertension	-0.009	>0.05
Total cholesterol (mg/dl)	0.191	>0.05
HDL cholesterol (mg/dl)	-0.092	>0.05
LDL cholesterol (mg/dl)	0.011	>0.05
Triglyceride (mg/dl)	0.122	>0.05
Hemoglobin (g/dl)	0.024	>0.05
Hematocrit (%)	-0.043	>0.05
Urea (mg/dl)	0.036	>0.05
Serum kreatinin (mg/dl)	-0.254	>0.05

HDL: High density lipoprotein, LDL: Low density lipoprotein

Table 4. Correlations of some parametric data with copeptin in the control group

	Copeptin (pg/ml)	
	r	p
Age (year)	-0.138	>0.05
Gender (male/female)	-0.100	>0.05
Cigarette	-0.198	>0.05
Hypertension	-	-
Total cholesterol (mg/dl)	0.046	>0.05
HDL cholesterol (mg/dl)	0.160	>0.05
LDL cholesterol (mg/dl)	0.031	>0.05
Triglyceride (mg/dl)	-0.113	>0.05
Hemoglobin (g/dl)	0.124	>0.05
Hematocrit (%)	-0.071	>0.05
Urea (mg/dl)	-0.231	>0.05
Serum kreatinin (mg/dl)	-0.227	>0.05
Diabetes mellitus	-	-

HDL: High density lipoprotein, LDL: Low density lipoprotein

DISCUSSION

Chronic CHF, which is a consequence of many cardiovascular diseases, is one of the leading causes of morbidity and mortality.[5,6] Despite the progressive decrease in the mortality of coronary artery disease and hypertensive cardiovascular diseases, the incidence and prevalence of HF increases proportionally with aging. The main reasons for the increase in the prevalence of HF are the increase in the elderly population and the prolongation of life span due to the development of diagnostic and therapeutic methods in cardiovascular diseases.[5,6]

Although advances have been made in the pathogenesis and treatment of heart failure, we still lack important insights into the underlying disorders, especially those at the cellular level. Despite the shortcomings, ongoing research at both basic and clinical levels will allow clinicians to better understand and treat this clinical syndrome.[7] Expectations are that biochemical markers such as BNP, copeptin and short echocardiograms will be used to screen for heart failure and thus prevent the onset of the syndrome by starting treatment at an earlier stage.[8]

Vasopressin is an antidiuretic and vasoconstrictor hormone.[9,10] and has effects on free water absorption, body fluid osmolality, blood volume and vascular tone. It is also thought to cause cell proliferation. All these effects are regulated through V2 (renal) and V1a (vascular) receptors. There are data showing that vasopressin is related with the severity of heart failure and the course of the disease.[11,12] Vasopressin is a hormone that is difficult to measure because it is mostly bound to platelets and cleared rapidly from the blood.[3] Copeptin is part of pre-pro-vasopressin and is synthesized in equal molar amounts to vasopressin. The advantage of copeptin is that it has a long stability, is rapidly measured in plasma and is significant. It can remain stable for 14 days in plasma with EDTA and 7 days in plasma with heparin and citrate.3 Copeptin is a 39 amino acid glycopeptide, which is the fragment at the C-terminal end of provasopressin.[4] The value of this marker as an indicator has been demonstrated in patients with critical illness,[4,13] coronary artery disease 14 and advanced heart failure.

Copeptin has been shown to be at least as valuable a marker as BNP in showing the course of the disease in patients with advanced heart failure.[8] Indeed, studies have shown that vasopressin is not only elevated in heart failure but also associated with the severity of the disease.[6,15] Many studies on copeptin have shown that it is a reliable marker in heart failure.

In our study, we found that serum copeptin levels were significantly increased in the CHF group compared to the control group in accordance with the literature.

In the 2007 University of Leicester study of copeptin after acute myocardial infarction (LAMP), copeptin was found to be a strong indicator of death and CHF in patients with acute myocardial infarction.[8] It has been observed that this marker provides additional contributions in determining the prognosis together with clinical findings in the classification of patients into low, intermediate and high risk groups.[8] Again in the SAVE study analysis, vasopressin was shown as an indicator of cardiac events that may develop after myocardial infarction.[16]

In the Optimaal study, BNP and copeptin were compared. As a result of the study, it was reported that copeptin was a strong and new marker for mortality and morbidity in patients who developed CHF after acute myocardial infarction.[17]

In our study, serum copeptin levels were significantly higher in patients who developed CHF after acute myocardial infarction.

In the Gruppo di Ricerca GISSI Heart Failure Trial (GISSI-Heart Failure), plasma concentrations of 4 components of the neurohormonal system were measured in patients with chronic and stable heart failure and their relationship with outcome was evaluated. These were atrial natriuretic peptide (MR-proANP), adrenomedullin (MR-proADM), C-terminal pro-endothelin-1 (CT-proET-1) and C-terminal pro-vasopressin (CT-proAVP or copeptin). At the end of the study, copeptin was evaluated as one of the best biological markers for prognostic information and risk stratification.18Nakamura et al.[11] showed that vasopressin

increased in patients with NYHA (New York Heart Association functional classification) functional capacity 3 and 4.

In our study, we found a clinical increase especially in patients with high functional capacity according to NYHA. Kelly et al.[19] found that C-terminal provasopressin (copeptin) was associated with left ventricular dysfunction, remodeling, death and heart failure after acute myocardial infarction. Neuhold et al.[20] compared copeptin and BNP levels in heart failure patients at the Austrian Medical University in 2008. As a result of this study, it was found that the predictive value of copeptin was superior to BNP in determining 24-month mortality and was the strongest single predictor of mortality in patients with NYHA functional class II. More recent data also showed that copeptid levels are important indicators of heart failure, its severity and prognosis.[21-23]

5. CONCLUSION

In our study, we found that serum copeptin levels were significantly increased in the CHF group compared to the control group in accordance with the literature. In conclusion, in our study, serum copeptin levels were significantly increased in CHF patients and in patients with CHF after acute myocardial infarction compared to the control group. This shows that copeptin is a good indicator of the course of the disease in patients with heart failure.

Measurement of serum copeptin levels may be a predictor of mortality and morbidity in heart failure patients; however, randomized, prospective long-term follow-up studies are clearly needed for this. Our study is one of the pioneering studies on this subject and we believe that it will shed light on further studies on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Fırat University Medical Faculty Clinical Researches Ethics Committee (Date: 15.05.2010, Decision No23).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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