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Original Article

Neurotrimin and Syndecan-1 Biomarker Levels in Patients With Decompensated Heart Failure

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ABSTRACT

Background: Heart failure (HF) is a complex clinical syndrome estimated to have afflicted 23 million people worldwide. This study aimed to measure syndecan-1 and neurotrimin levels in patients with decompensated heart failure (DHF) admitted to the emergency department.

Methods: This study was conducted from November 2017 through June 2018 in Imam Khomeini Hospital, a referral center in Ahvaz, Iran. Baseline demographics were recorded. The Human Syndecan-1/CD138 (SDC1) ELISA kit for the measurement of syndecan 1 and the Human Neurotrimin ELISA kit for the measurement of neurotrimin (ZellBio GmbH, Berlin, Germany) were used. The detection range for syndecan 1 and neurotrimin was 1.5 to 48 ng/mL and 0.4 to 12.8 ng/mL, respectively.

Results: Seventy-two patients met the study inclusion criteria. The mean level of syndecan 1 and neurotrimin was 24.31 ± 8.27 ng/mL (11–37 ng/mL) and 0.52 ± 0.19 ng/mL (0–9 ng/mL), respectively. The results showed no correlations between the severity of illness and syndecan-1 and neurotrimin levels, nor were there any correlations between age, sex, blood urea nitrogen, creatinine, the estimated glomerular filtration rate, and B-type natriuretic peptide (in DHF >500 ng/mL) and the levels of syndecan 1 and neurotrimin (P >0.05).

Conclusions: The syndecan-1 level did not change in patients suffering from HF with reduced ejection fraction (EF). Further, patients in any EF classification had a low level of neurotrimin. However, no significant associations were found between the classes of the EF and the serum neurotrimin level. ***(Iranian Heart Journal 2021; 22(3): 88-94)***

KEYWORDS: Heart failure, Biomarker, Syndecan 1, Neurotrimin, Emergency department

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Heart failure (HF) is a complex clinical syndrome estimated to have afflicted 23 million people the world over. [1] The HF diagnosis is associated with an increased possibility of hospitalization and mortality risks. [2, 3] The prognosis of patients suffering from HF is still poor, and correct diagnosis is challenging even for expert clinicians. [4] Standard medical or interventional treatments are associated with a wide variety of side effects; hence, numerous programs have been applied to establish instant and appropriate diagnosis. One of the interesting aspects of this scenario is the evaluation of biomarkers. [5]

Although several biomarkers such as B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have been established, other biomarkers including syndecan 1 and neurotrimin may be valuable as prognostic and diagnostic markers. [6] The *Syndecan-1 gene* (OMIM: 186355) is a cell surface proteoglycan supposed to be responsible for cardiac fibrosis regulation. [7] Animal studies have demonstrated that tissue injuries and inflammatory responses lead to syndecan-1 expression. [8] Human studies have indicated that patients with a higher level of syndecan 1 have poor kidney function. [9] Some studies have described a greater risk of all-cause mortality in patients suffering from HF with doubled syndecan-1 levels. [10]

Neurotrimin is a glycosylphosphatidylinositol (GPI)-anchored cell that belongs to the IgLON family. Situated on chromosome 11q25, neurotrimin encodes a 39-kDa protein. In addition, neurotrimin (*the NTM gene*, OMIM: 607938) regulates the outgrowth of neurites; however, it inhibits neurite outgrowth in sympathetic neurons. [11]

Neurotrimin is a new biomarker in HF that may provide information regarding pathophysiological mechanisms and may be a predictive factor for the treatment outcome. [12] This study aimed to measure syndecan-1 and neurotrimin levels in patients with DHF admitted to the emergency department.

METHODS

Study Design

This study was conducted from November 2017 through June 2018 in Imam Khomeini Hospital, a referral center in the Iranian city of Ahvaz. The study protocol was approved by the appropriate ethics committees, and written informed consent was obtained from every patient or every patient's legal guardian.

All patients with chronic HF aged 18 years or above with a clinical diagnosis of HF according to the Framingham criteria and with a diagnosis of DHF at admission to the emergency department were primarily enrolled. In this study, patients suffering from HF with both preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) were entered. The cutoff point of the left ventricular EF to recognize HFpEF was predefined at greater than 40%. [13]

Patients with the following conditions were excluded from the study: a BNP level of less than 500 ng/L, pregnancy, chronic pulmonary obstructive disease (COPD) exacerbation, severe liver failure based on the Child-Pugh score, [14] end-stage renal disease undergoing maintenance dialysis, and hypothyroidism.

The following baseline demographics were recorded at the time of enrollment: age, sex, the severity of illness based on the New York Heart Association (NYHA) functional classification [15] and the EF percentage (mild =45%–55%, moderate =35%–44.99%, and severe >99%), a previous history of diabetes, hypertension, coronary artery disease, COPD, medication history, and laboratory data.

A peripheral venous blood sample was obtained immediately after the emergency department admission. The samples were centrifuged at about 4000 rpm for 6 minutes and were stored at −20 °C for later

measurement of syndecan 1 and neurotrimin.

The Human Syndecan-1/CD138 (SDC1) ELISA kit for the measurement of syndecan 1 and the Human Neurotrimin ELISA kit for the measurement of neurotrimin (ZellBio GmbH, Berlin, Germany) were used. The detection range for syndecan 1 and neurotrimin was 1.5 to 48 ng/mL and 0.4 to 12.8 ng/mL, correspondingly.

Statistical Analysis

The statistical analyses were performed with SPSS, version 20. Continuous variables were checked for normality; and if they were normal, they were compared by the application of the Student *t* test. The χ^2 test or the Fisher exact test was applied for categorical variables, as appropriate. A *P*-value of less than 0.05 was considered statistically significant in all the cases.

RESULTS

Eighty-one consecutive patients admitted to the emergency department were evaluated for eligibility, and 72 patients met the study entry criteria. Nine patients were excluded: 4 patients due to COPD exacerbation, 2 patients due to hypothyroidism, and 3 patients due to newly diagnosed HF.

The baseline demographic data and biochemical characteristics at the emergency department admission are presented in Table 1. The mean age was 67.07 ± 9.4 years, the mean EF was 28.48 ±10.71%, and the mean BNP level was 2187.24 ± 2045.82 ng/mL at admission. Among the 72 patients, 66 cases (91.6%) had HFrEF.

The severity of illness based on the NYHA classification in our patients was class II in 14 cases, class III in 35, and class IV in 23. The severity of illness according to the EF percentage was mild in 9 cases, moderate in 16, and severe in 47 (Table 2).

The mean level of syndecan 1 and neurotrimin was 24.31 ± 8.27 ng/mL (11–37 ng/mL) and 0.52 ± 0.19 ng/mL (0-9–ng/mL), respectively. The results showed no correlation between the severity of illness and the level of syndecan 1 or neurotrimin levels (Table 2). Further, no correlations were detected between age, sex, blood urea nitrogen, creatinine, the estimated glomerular filtration rate, and BNP (in DHF >500 ng/mL) and the levels of syndecan 1 and neurotrimin (*P* >0.05).

Table 1. Demographic data of the patients

Variables	*P*- value
Age, y (mean ± SD)	67.07 ± 9.4 (44-96)
Female gender, n (%)	52
Biological and Hemodynamic Conditions at Admission	
RR, cpm (mean ± SD)	25.52 ± 10.09 (13-49)
SBP, mm Hg (mean ± SD)	137.74 ± 41.83 (120.7-240.1)
DBP, mm Hg (mean ± SD)	
HR, bpm (mean ± SD)	83.45 ± 21.73 (2-143)
LVEF (%)	28.48 ± 10.71 (10-55)
Laboratory Data at Admission	
Serum creatinine, mg/dL (mean ± SD)	1.31 ± 0.7
BUN, mg/dL (mean ± SD)	25.54 ± 14.07
BNP, ng/mL (mean ± SD)	2187.24 ± 2045.82
Positive CRP (%)	59.7
Comorbidities n= (%)	
Chronic heart failure	69.4

Diabetes mellitus	45.8
Hypertension	52.8
Hyperlipidemia	38.9
Atrial fibrillation	9.7
Coronary artery disease	73.6
Chronic kidney disease	12.5
Drugs at admission n= (%)	
β-blockers	55.6
CCBs	6.9
ACE inhibitors	37.5
ARBs	8.3
Digoxin	16.7
Diuretics	23.6
Nitrates	44.4
Warfarin	8.3
Clopidogrel	23.6
Low-dose aspirin (80 mg)	59.7
Statins	55.6
Oral antidiabetic agents	20.3
Insulin	5.6

RR, Respiratory rate; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate; LVEF, Left ventricular ejection fraction; CCBs, Calcium channel blockers; ACE, Angiotensin-converting enzyme; ARBs, Angiotensin receptor blockers

Table 2. Correlations between syndecan-1 and neurotrimin levels and the severity of illness according to the ejection fraction percentage

Biomarkers	Severity of Illness				
	Total (N =72)	Mild (n =14)	Moderate (n =35)	Severe (n =23)	***P*- value**
Syndecan 1, mean ± SD (range)	24.31 ± 8.27 (11-37)	23.34 ± 7.98 (11-35)	25.68 ± 7.70 (14-35)	27 ± 10.61 (11-37)	0.36
Neurotrimin, mean ± SD (range)	0.52 ± 0.19 (0-9)	0.53 ± 0.21 (0.2-0.90)	0.53 ± 0.20 (0.2-0.9)	0.50 ± 0.17 (0.20-0.80)	0.89

DISCUSSION

In the present study, we found no significant relationships between syndecan-1 and neurotrimin biomarkers and the severity of DHF with EF classifications. The findings of this study are in line with the results of some previous studies. [10, 12, 16]

The syndecan family (syndecan 1, 2, 3, and 4) is a heparan sulfate proteoglycan, containing an extracellular domain with attached heparan sulfate or chondroitin sulfate, a short cytoplasmic tail. [17] Syndecans have a role in angiogenesis and the regulation of integrin-mediated cell adhesion and proliferation. Syndecan 1 is especially shown to be involved in many human pathophysiologic processes such as inflammation in the acute-phase post-myocardial infarction, [17-19] fibrosis, and the remodeling of angiotensin-II–induced HF. [18] In a previous study in a chronic HF setting, relationships were observed between inflammation markers and HFpEF, whereas relationships were detected between HFrEF and cardiac stretch markers. [10] Syndecan 1, as an inflammation marker, is a predictor of the clinical outcome in HFpEF, but not in HFrEF. [10] Because most of our patients had HFrEF, our results also showed that the

syndecan-1 level might not be increased in these patients and that syndecan 1 might be preserved in patients with HFpEF.

Neurotrimin, as an IgLON superfamily of cell adhesion molecules, participates in 70% of amino acid sequence homology. This subfamily of glycosylphosphatidylinositols is an immunoglobulin with 4 members: Neurotrimin/hNT/CEPU-1, OPCML/OBCAM, LAMP/LSAMP, and Kilon/NEGR1/Neurotractin. Their theorized function as cell adhesion molecules might be the adjustment of synaptogenesis and neurite outgrowth, [20-23] and they might also function as tumor suppressor genes. [24-27] To date, there have been no human studies on the neurotrimin level in patients with HF except one, which reported that patients having responded to angiotensin-converting enzyme inhibitors and beta-blockers had higher levels of this biomarker than non-responders and it could be an accurate predictor of treatment response in patients with HF. [12] Our results showed that the neurotrimin level in patients suffering from HF with any EF classification was low, but we could not find any significant relationships between the classes of the EF and this biomarker level.

Limitations

The limitations of our study were its small sample size, inability to follow up patients, and the lack of neurotrimin level assessment after treatment. Further studies on larger populations and with longer follow-ups are warranted to investigate the correlation between syndecan-1 and neurotrimin levels and DHF severity.

CONCLUSION

The syndecan-1 level did not change in our patients with HFrEF. Moreover, patients in any EF classification had a low level of neurotrimin; nonetheless, our results demonstrated no significant associations between the classes of the EF and the serum neurotrimin level. Consequently, neurotrimin may be a valuable biomarker for the recognition of the pathophysiological mechanisms of HF and the detection of these patients. More studies are required on HF populations with both HFpEF and HFrEF for the recognition of the role of syndecan 1 and neurotrimin.

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