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NESFATIN-1: AS A NOVEL THERAPEUTIC AGENTS OF CONGESTIVE HEART FAILURE AND ANGINA PECTORIS

Zainab Samir Yahya Hammo[1], Zaid Mohammed Mubarak Almahdawi[2], Sahlah Khorsheed Abbas[3] , Suadat Mustafa Mohammed Al-Hermizy[4] and Noor Thahir Tahir[5]
Department of Physiology, College of Medicine, University of Tikrit, Iraq
zainabsamir1986@gmail.com [1]
Al-Imam University College, Tikrit, Iraq zaid.almahdawi@yahoo.com [2]
College of Science, University of Kirkuk, Iraq Sahlalmmuno@uokirkuk.edu.iq [3]
Department of Biology, College of Science, University of Tikrit, Iraq
Suadmustafa300@gmail.com [4]
National Diabetes center, Al- Mustansiriyah University, Baghdad, Iraq
dr.noorthair.ndc@uomustansiriyah.edu.iq [5]

Abstract

Background: Nesfatin-1, as an adipokine, has been shown to have a number of metabolic effects associated with a variety of inflammatory and cardiovascular diseases.

Objectives: The current study aimed at investigating the relationship of Nesfatin-1 levels with biochemical findings in patients with congestive heart failure and angina pectoris.

Methods: This study was carried out at Salah Al-Deen Hospital in Tikrit from the 1st of January 2022 to 30th of March 2022. The study included 70 males patients, 35 of them have congestive heart failure (G1) and 35 have angina pectoris (G2), range of the ages are between (40-70) years old. After checking their conditions throughout medical and clinical tests by specialist physician in this aspect. As well as choosing random group included 20 samples of healthy males of ages between (40-70) years old as a control group (C).

Results: Serum levels of Nesfatin-1 in patients groups (G1,G2) were significantly reduced, compared to the healthy subjects (C), (p P<0.01); however, there was no significant difference between patients groups. Additionally, this study further confirmed negative correlations between plasma Nesfatin-1 levels and CRP, cTnT, CK-MB, IL-6, IL-37 and AFABP-4, in patients with CHF. On the other hand, Nesfatin-1 negatively correlated with apelin in the same group.

Conclusion: this is, to our knowledge, the first report demonstrating a relationship between plasma Nesfatin-1 levels and CHF. Additionally, it possible promise new insights into the pathogenesis of heart disease. accordingly, at least in part, decreased levels of nesfatin-1 in CHF and angina pectoris groups as well as its association with several parameters, as mention above may indicate the potential role of Nesfatin-1 in the process of atherosclerosis, which requires further studies.

Abbreviation: CHF: Congestive Heart Failure; CRP: C-Reactive Protein; cTnT: Cardiac Troponin T; CK-MB: Creatine Kinase-MB; IL-6: Interleukin 6; IL-37: Interleukin 37; AFABP-4: Adipocyte Fatty Acid Binding Protein 4; CAD: Coronary Artery Disease.

Keywords: congestive heart failure, angina pectoris, adipokines, Nesfatin-1.

INTRODUCTION

Nesfatin-1 was discovered in 2006, it is an 82-amino acid polypeptide derived from the precursor protein nucleobindin 2 (NUCB2), whose processing also leads to Nesfatin-2 and -3, two peptides with so far unknown functions (Schalla and Stengel, 2019). Nesfatin-1 is a recently identified satiety-inducing adipokine found in hypothalamic regions that regulates energy balance. Later on, the 29-amino acid mid fragment of nesfatin-1, has been identified as the active core of nesfatin-1 also exerting an anorexigenic effect(Zegers, et al., 2021). It has to be noted that although full length Nesfatin-1 contains cleavage sites at the respective amino acids, cleavage has not been shown in vivo so far (Shimizu and Osaki, 2019). NUCB2/Nesfatin-1 – most antibodies do not distinguish between NUCB2 and processed nesfatin-1, therefore, the recent studies refer to the analyte as NUCB2/Nesfatin-1 – has first been detected in food intake-regulatory brain nuclei such as the paraventricular nucleus, arcuate nucleus and nucleus of the solitary tract , while subsequent studies extended this distribution to numerous other brain nuclei in rat and mouse. It is to note that NUCB2/Nesfatin-1 has been primarily detected in the soma and primary dendrites of neurons, whereas less immunoreactivity was observed in nerve fibers possibly pointing rather to an auto- or paracrine rather than an endocrine mode of action (Mori, et al., 2019).

Nonetheless, Nesfatin-1 was shown to cross the blood-brain barrier in both directions supporting a humoral route of signaling. Further corroborating this assumption, NUCB2/Nesfatin-1 has also been detected in the periphery, namely in the gastric mucosa, adipose tissue, pancreatic beta cells, testis, ovary, uterus, epididymis and cardiomyocytes (Angelone, et al., 2017; Alkanaani, et al.,2020). The stomach was identified as main source of peripheral NUCB2/nesfatin-1 with NUCB2 mRNA levels considerably higher than in other peripheral organs or the brain (Sun and Yang, 2018). There is growing evidence that nesfatin-1 may play an important role in the regulation of food intake and glucose homeostasis (Guo, et al., 2019). For instance, continuous infusion of Nesfatin-1 into the third brain ventricle significantly decreased food intake and body weight gain in rats. In previous studies, it was demonstrated that plasma Nesfatin-1 levels were elevated in patients with type 2 diabetes mellitus (T2DM) and associated with BMI, plasma insulin, and the homeostasis model assessment of insulin resistance (Kim, J. et al., 2016).

Angina Pectoris

Angina, also known as angina pectoris, is chest pain or pressure, a symptom of coronary heart disease. Myocardial ischemia comes about when the myocardium (the heart muscle) receives insufficient blood and oxygen to function normally either because of increased oxygen demand by the myocardium or because of decreased supply to the myocardium (Hemingway, et al., 2016). This inadequate perfusion of blood and the resulting reduced delivery of oxygen and nutrients are directly correlated to blocked or narrowed blood vessels. Angina is usually due to obstruction or spasm of the arteries that supply blood to the heart muscle. The main mechanism of coronary artery obstruction is atherosclerosis as part of coronary artery disease (Rayner-Hartley and Sedlak, 2020). There is a weak relationship between severity of pain and degree of oxygen deprivation in the heart muscle, where there can be severe pain with little or no risk

of a myocardial infarction (heart attack) and a heart attack can occur without pain. In some cases, angina can be quite severe. Major risk factors for angina include cigarette smoking, diabetes, high cholesterol, high blood pressure, sedentary lifestyle, and family history of premature heart disease (Choi, et al. 2020).

Congestive Heart Failure (CHF)

Heart failure (HF), also known as congestive heart failure (CHF) and congestive cardiac failure (CCF). Heart failure is not a disease but a syndrome, a cluster of signs and symptoms caused by the impairment of the heart's function as a pump to support the circulatory system, at rest or during exercise. It develops when the heart fails to properly fill up with blood during diastole leading to an increase in intracardiac pressures or in ejecting it during systole, thereby reducing cardiac output to the rest of the body. Filling dysfunction and high intracardiac pressure may result in the buildup of fluid in the veins and tissues. This manifests as water retention and swelling due to the buildup of liquid (edema), collectively referred to as congestion. Impaired ejection can cause inadequate perfusion of the body tissues with blood leading to ischemia(Lofthus, et al., 2015).

Pathophysiology of CHF

Heart failure is caused by any condition that reduces the efficiency of the heart muscle, through damage or overloading. Over time, these increases in workload, which are mediated by long-term activation of neurohormonal systems such as the renin–angiotensin system, lead to fibrosis, dilation, and structural changes in the shape of the left ventricle from elliptical to spherical (Blanco-Colio, et al., 2022). The heart of a person
with heart failure may have a reduced force of contraction due to overloading of the ventricle. In a normal heart, increased filling of the ventricle results in increased contraction force thus a rise in cardiac output. In heart failure, this mechanism fails, as the ventricle is loaded with blood to the point where heart muscle contraction becomes less efficient. This is due to reduced ability to cross-link actin and myosin filaments in over-stretched heart muscl (Aday and Ridker, 2020). The current study aimed at investigating the relationship of nesfatin-1 levels with biochemical findings in patients with congestive heart failure and angina pectoris

MATERIALS AND METHODS

This study was carried out at Salah Al-Deen Hospital in Tikrit from the 1st of January 2022 to 30th of March 2022. The study included 70 males patients, 35 of them have congestive heart failure (G1) and 35 have angina pectoris (G2), range of the ages are between (40-70) years old. After checking their conditions throughout medical and clinical tests by specialist physician in this aspect. As well as choosing random group included 20 samples of healthy males of ages between (40-70) years old as a control group (C) (Table 1).

The present study included 70 blood samples were collected from males who have angina pectoris and congestive heart failure and from healthy males their ages between (40-70) years old. Venous samples were taken early in the morning for the patient and control groups, after at least 12-hours of fasting and a 20- minute rest. The samples of blood were drawn from the median cubital vein or from another vein if this was not accessible. After cleaning the venipuncture site with iodine using concentric circles, the iodine

remained in contact with the skin until dried to ensure disinfection. After that 5 ml of blood was taken and put in the gel tube, gel tube has been put in the cool box (contained ice bag) till transport to the emergency unit laboratory and separated by centrifuging for 10 minutes at 6000 rpm. After separation of whole blood the serum was extracted by using micropipette, after that 2 ml of blood serum was put in three eppendorf tubes to make hormonal, immune, and biochemical tests. And then stored in a deep freezer (-20°C). The information of each participant was recorded through a questionnaire sheet include age, sex, weights, patient's residency and other information.

Detection of Nesfatin, AFABP-4, IL-37, IL-6, Apelin, CRP, cTnT and CK-MB levels in the serum were determined by an enzyme linked immunosorbent assay (ELISA) kits.

Table (1):- Demographic Distribution of Study Population

Groups	No. of Individuals	Age (years)
G1	35	
G2	35	(40-70) years old
C	20	

Statistical analysis

The statistical analysis was carried out by using statistical program (Minitab) and comparison between groups which were made by using one-way analysis of variance ANOVA and tried out the arithmetic means for parameters by using test of Duncan's multiple range test to delimitating significantly difference especially between groups. Pearson correlation coefficient (R) between nesfatin and other parameters was reported by using regression plots. The level of statistical significance was taken at ($P \leq 0.01$) and ($P \leq 0.05$) (Popović, 2021).

RESULTS

The results of this study revealed that the mean ± SD of adipokines levels for congestive heart failure, angina pectoris patients and control groups respectively were shown in table (2) and figures (1,2). Additionally, the mean ± SD of cytokines levels for congestive heart failure, angina pectoris patients and control groups respectively were shown in table (3) and figures (3,4). The mean ± SD of cTnT levels for congestive heart failure, angina pectoris patients and control groups respectively were (0.213±0.0957) ng/ml, (0.079 ± 0.02605) ng/ml and (0.028 ± 0.00767) ng/ml; in the view of mean of parity (p= 0.00002). The mean ± SD of CK-MB levels for congestive heart failure, angina pectoris patients and control groups respectively were (34.02±8.76) IU/L, (32.53 ± 8.73) IU/L and (14.22 ± 2.56) IU/L; in the view of mean of parity (p= 0.0009).

Table No. (2) Arithmetic average for Adipokines Concentrations in the studied groups

No. / Group	AFABP-4 (pg/ml)	Apelin (pg/ml)	Nesfatin-1 (pg/ml)	CRP (pg/ml)
	Mean ± S.D	Mean ± S.D	Mean ± S.D	Mean ± S.D
G1 n=35	109.27± 18.18 a	338.1 ± 35.0 b	53.81 ± 8.70 b	5.54 ±1.463 a

G2 n=35	108.59 ± 18.84 a	334.5 ± 31.2 b	47.38 ± 7.71 b	2.63 ±1.041 b
C n=20	43.73 ± 7.41 b	535.9 ± 36.7 a	97.53 ± 6.26 a	0.59 ±0.1982 c
P- value	P = 0.00003**	P =0.0007**	P = 0.00004**	P =0.00004**

Table (3) Arithmetic average for Cytokines concentrations in the studied groups

No. / Group	IL-6 (pg/ml)	IL-37 (pg/ml)
	Mean ± S.D	**Mean ± S.D**
G1 n=35	17.23 ± 5.519 a	35.19 ± 4.13 a
G2 n=35	14.06 ± 4.727 a	28.36 ± 4.05 a
C n=20	8.62 ± 2.27 b	15.92 ± 4.74 b
P- value	P = 0.00003**	P =0.0006**

Note: The similar letters mean that there are no significant differences between vertical groups and the different letters mean that there are significant differences between them at a potential level P ≤ 0.01(**).G1, Congestive Heart Failure patients; G2, Angina Pectoris patients; C, Healthy Individuals (Control).

In this current study, there was high significant difference (P ≤ 0.01) between the three groups (for Nesfatin-1) in the view of mean of parity (p= 0.00004). Nesfatin-1levels were significantly lower in patients groups than control group, on the other hand there was no statistically significant difference between CHF and angina pectoris patients. These current results are compatible with results for Dai, et al. (2019); Kadoglou et al. (2022) and Sivri, et al. (2022). However, the current results are incompatible with results for Tasatargil et al. (2017) and Ibe et al. (2021), they found Nesfatin-1 level was significant higher in patients groups than control group.

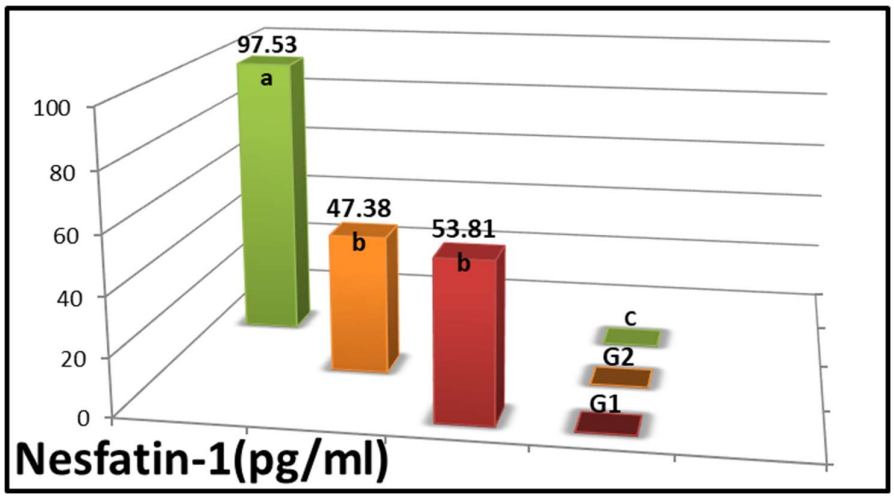

Figure (1): Levels of Nesfatin-1 pg/ml in patients and control groups

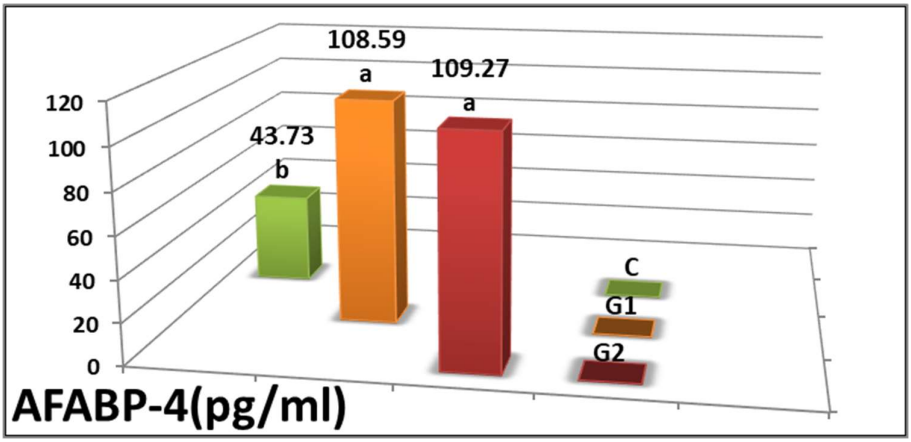

Figure (2): Levels of AFABP-4 pg/ml in patients and control groups

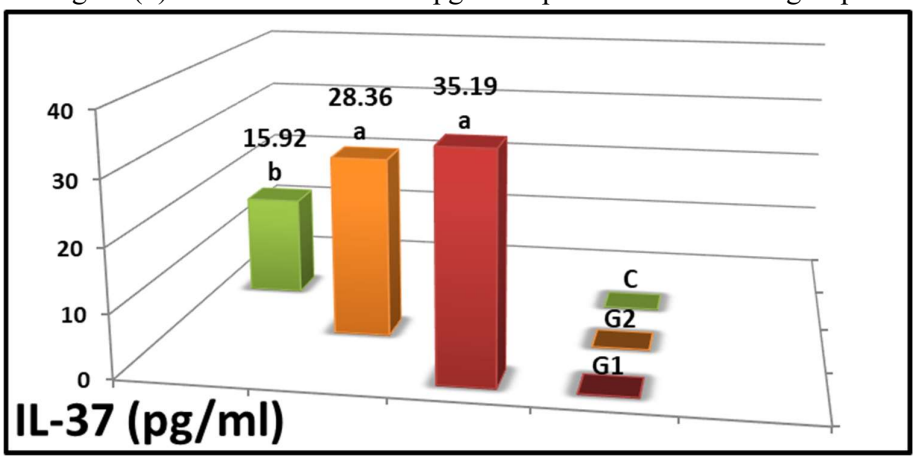

Figure (3): Levels of IL-37 pg/ml in patients and control groups

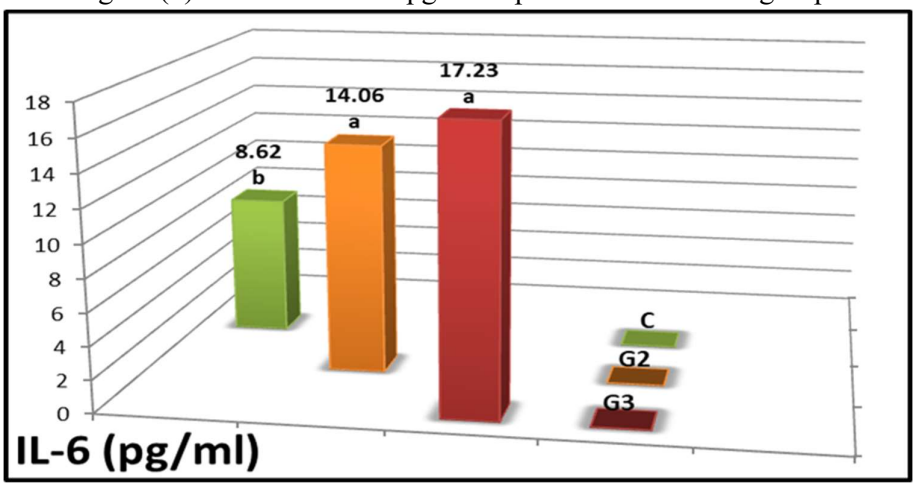

Figure (4): Levels of IL-6 pg/ml in patients and control groups

The results of Pearson's correlation demonstrated in tables (4,5) and Figures (5,6,7,8) observe that there is negative correlation between Nesfatin-1 level with CRP, cTnT, CK-MB, IL-6, IL-37 and AFABP-4, in patients with CHF. On the other hand, Nesfatin-1 negatively correlated with apelin in the same group; which confirmed current result of decrease level in patients compared with control groups.

Table 4: Correlation coefficient (R) between Nesfatin-1 with parameters in Congestive Heart Failure patients

parameters	Statistical variables	Nesfatin-1
IL-37	R	-0.536
	P	0.003**
AFABP-4	R	-0.124
	P	0.635ns
IL-6	R	-0.070
	P	0.788ns
CRP	R	-0.221
	P	0.394ns
Apelin	R	0.380
	P	0.033*
cTnT	R	-0.014
	P	0.956ns
CK-MB	R	-0.056
	P	0.830ns

Table 5: Correlation coefficient (R) between Nesfatin-1 with parameters in angina pectoris patients

parameters	Statistical variables	Nesfatin-1
IL-37	R	-0.328
	P	0.058*
AFABP-4	R	-0.135
	P	0.446ns
IL-6	R	0.248
	P	0.157 ns
CRP	R	-0.144
	P	0.417 ns
Apelin	R	0.366
	P	0.070*
cTnT	R	-0.277
	P	0.113 ns
CK-MB	R	-0.120
	P	0.499 ns

R: Correlation coefficient; P: p-value;* P≤0.05;** P≤0.01; ns :Not significant

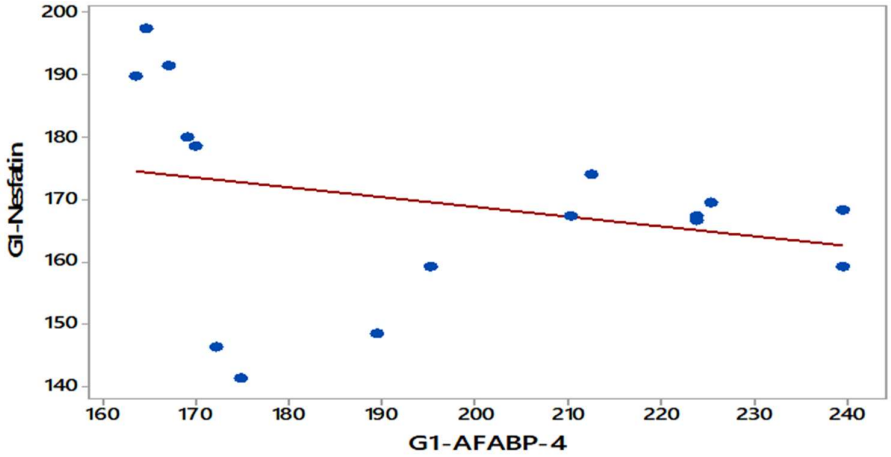

Figure (5) Correlation between AFABP-4 with Nesfatin-1 in congestive heart failure patients

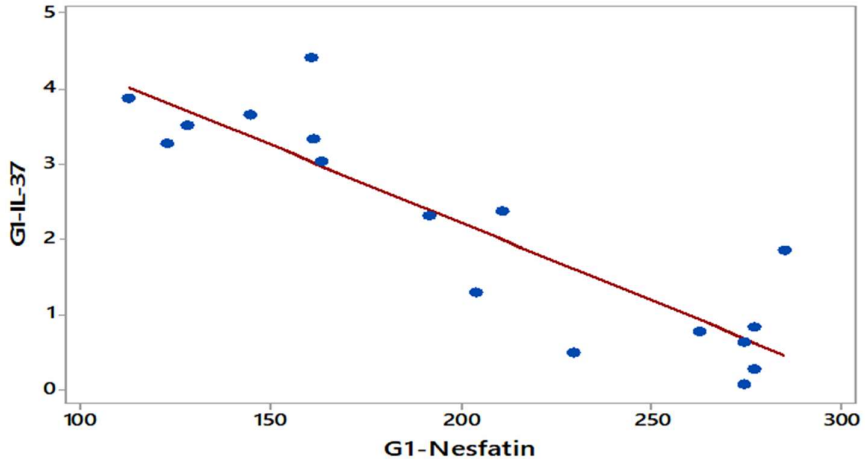

Figure (6) Correlation between IL-37with Nesfatin-1 in congestive heart failure patients

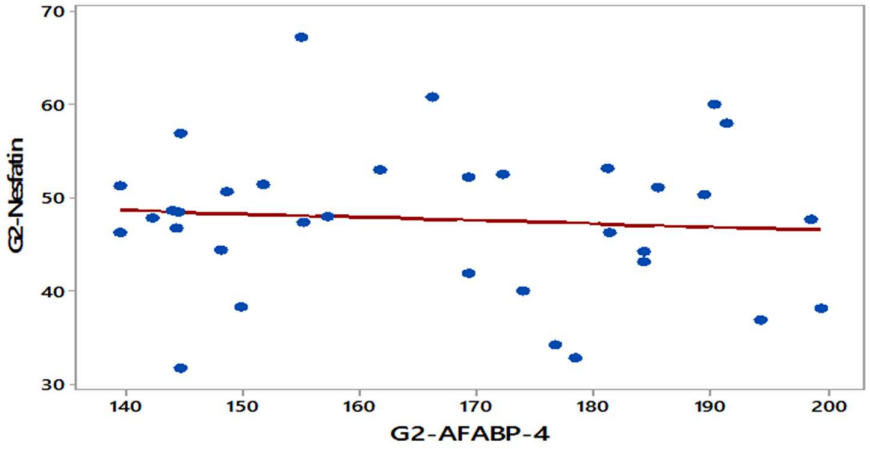

Figure (7) Correlation between AFABP-4with Nesfatin-1 in angina pectoris patients

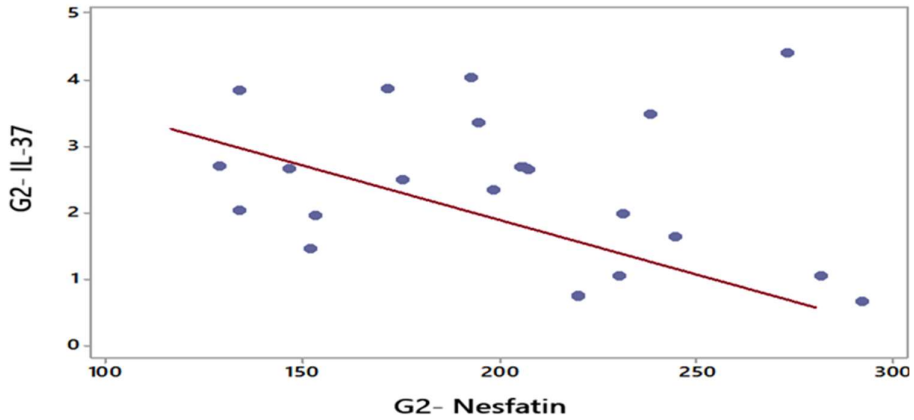

Figure (8) Correlation between IL-37with Nesfatin-1 in angina pectoris patients

DISCUSSION

Nesfatin-1 is a peptide with 82 amino acids that is produced as a result of the proteolysis of nucleobindin 2 (Oh, et al., 2006). Recently, the studies have revealed a close association of nesfatin-1 with CAD, mental disorders, neurological disease, diabetes, and polycystic ovaries syndrome (Schalla, et al., 2019). Tekin et al. indicated that nesfatin-1 is associated with metabolic syndrome and its components. The studies examining the relationship between obesity and nesfatin-1 have revealed that plasma nesfatin-1 levels are associated with BMI, body weight, and fat mass. The peripheral application of nesfatin-1 has been proven to have an antihyperglycemic effect on glucose metabolism. When the effects of nesfatin-1 on the cardiovascular system were examined, nesfatin-1 has shown to affect blood pressure, and it plays a role in the regulation of peripheral lipid accumulation and hepatic lipid metabolism. Therefore, nesfatin-1 plays several roles as a regulator in the metabolism and to has an effect on metabolic syndrome and its components (Tekin, et al., 2019; Abdulwahed, et al.,2020). Nesfatin-1 plays a role in the regulation of cardiovascular function. Nesfatin-1 distribution at the central level shows that it may play an important role in the regulation of cardiovascular functions and mechanisms that contribute to cardiovascular homeostasis (Yilmaz, et al., 2019). Nesfatin-1, which is localized with oxytocin in the paraventricular nucleus, stimulates the release of oxytocin by depolarization. It is also known that nesfatin-1 activates the melanocortin pathway through oxytocin. Therefore, the hypertensive effect is thought to be related to either central oxytocin or melanocortin pathways (Ramanjaneya, et al., 2020). Angelone et al. showed for the frst time that nesfatin-1 induces a dose-dependent reduction of contractility and relaxation in isolated rat heart preparations through mechanisms such as cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) pathway or the natriuretic peptide receptor A (NPR-A), which led to reduced infarct size; in goldfsh, a positive inotropic efect was associated with increased stroke volume and stroke work (Angelone, et al. 2020). In another study, it has been shown that high plasma nesfatin-1 levels may be associated with increased systolic and diastolic blood pressure values and increased heart rate in polycystic ovary syndrome (Şahin, et al., 2015). In an in vitro study, the mRNA of nesfatin-1 and its precursor NUCB2 were detected in rat hearts. In the same study, it was revealed that nesfatin-1 levels decreased in the heart tissue under an ischemia/reperfusion injury. Hence, it has been concluded that nesfatin-1 causes a significant decrease in infarction size against ischemia/

reperfusion injury and induces functional recovery after ischemic contraction (Angelone et al., 2017). Osaki et al. found that chemical sympathectomy using 6- hydroxydopamine could increase nesfatin/NUCB2 expression in the subcutaneous fat tissues (Osaki, et al. 2012). So, it may be plausible to say that high sympathetic activity could suppress nesfatin-1 expression. The elevated sympathetic activity induced by AMI may be one reason for the reduced expression of this peptide (Su, et al. 2022).

Dai et al. showed reduced plasma nesfatin-1 levels in patients with acute-MI. They also reported a significant negative correlation between Nesfatin-1 plasma levels and inflammatory factors, such as neutrophil percentage and C-reactive protein (Dai et al., 2019). Elevated levels of pro-inflammatory mediators, such as TNF-α, IL-6, and IL-1β, have been reported in both serum and heart tissue during MI (Kuyumcu et al., 2018). Inflammation is one of the most important mechanisms of myocardial infarction. The anti-inflammatory effects of nesfatin-1 have been reported in some studies (Dai et al., 2019). In the same line, Tasatargil et al. in an animal model of isoproterenolinduced MI, reported the anti-inflammatory effects of nesfatin-1 in preventing histopathological changes in cardiac tissue and increasing troponin T (Tasatargil, et al., 2017).

CONCLUSION

In conclusion, this is, to our knowledge, the first report demonstrating a connection between plasma Nesfatin-1 levels and CHF. Additionally, this study further confirmed negative correlations between plasma Nesfatin-1 levels and CRP, cTnT, CK-MB, IL-6, IL-37, AFABP-4, in patients with CHF. On the other hand, nesfatin-1 negatively correlated with apelin in the same group. It possible promise new insights into the pathogenesis of CAD. accordingly, at least in part, decreased levels of Nesfatin-1 in CHF and angina pectoris groups as well as its association with several parameters may indicate the potential role of nesfatin-1 in the process of atherosclerosis, which requires further studies. Finally, these associations could present with an additive prognostic value while evaluating high cardiovascular risk individuals. Further large-scale studies are necessary to establish these associations and determine the role of Nesfatin-1 in the pathogenesis, diagnosis and treatment of cardiovascular diseases.

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