ORIGINAL RESEARCH

Bagcilar Med Bull 2023;8(2):127-134
DOI: 10.4274/BMB.galenos.2023.2022-11-096

Predictive Value of Nesfatin-1, Galectin-3, Ghrelin, and Leptin Expressions in Patients with Metabolic Syndrome who Underwent Coronary Artery Bypass Graft (CABG) Surgery

Koroner Arter Bypass Grefti (CABG) Ameliyatı Yapılan Metabolik Sendromlu Hastalarda Nesfatin-1, Galektin-3, Ghrelin ve Leptin Ekspresyonlarının Prediktif Değeri

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Abstract

Objective: This study aims to investigate the expression of Nesfatin-1, Galectin-3, Ghrelin, and Leptin in mediastinal adipose tissue and their relationship with postoperative complications in patients with and without metabolic syndrome who underwent on-pump coronary artery bypass graft (CABG) surgery.

Method: Fifty patients who underwent CABG surgery and who were in sinus rhythm were included in the study. The patients were divided into two groups according to whether they had metabolic syndrome or not. All patients' age, gender, weight, height, postoperative intensive care unit length of stay, total hospital stay, and post-operative complications (Low cardiac output synd. Inotropy-IABP requirement, insulin-dependent diabetes mellitus, arrhythmia, kidney failure, respiratory failure) were recorded. In the histopathological evaluation, the expression density of Nesfatin-1, Galectin-3, Ghrelin, and Leptin in the the adipose tissue samples were mainly examined.

Results: There was no statistically significant difference between the expression of Galectin-3, Ghrelin, and Leptin with post-operative complications, length of stay in the intensive care unit, and body mass index in patients with and without metabolic syndrome. However, there is a significant difference between Nesfatin-1 expression and the risk of

Öz

Amaç: Bu çalışmanın amacı, on-pump koroner arter bypass grefti (CABG) ameliyatı yapılan metabolik sendromu olan ve olmayan hastalarda mediastinal yağ dokusunda Nesfatin-1, Galectin-3, Ghrelin ve Leptin ekspresyonlarını ve postoperatif komplikasyonlarla ilişkisini araştırmaktır.

Yöntem: Çalışmaya CABG cerrahisi uygulanan ve sinüs ritminde olan 50 hasta dahil edilmiştir. Hastalar metabolik sendromu olanlar ve olmayanlar olarak iki gruba ayrıldı. Tüm hastaların yaşı, cinsiyeti, kilosu, boyu, postoperatif yoğun bakım yatış süreleri, total hastane yatış süreleri ve post-operatif komplikasyonlar (düşük debi send. İnotropi-IABP ihtiyacı, insüline bağımlı diabetes mellitus, aritmi, böbrek yetmezliği, solunum yetmezliği) kayıt altına alınmıştır. Histopatolojik değerlendirmede incelenen mediastinal yağ doku örneklerinde adiposit ve lenfosit nükleusunda Nesfatin-1, Galectin-3, Grehelin and Leptin ekspresyonu yoğunluğu değerlendirilmiştir.

Bulgular: Galectin-3, Ghrelin and Leptin ekspresyonu istatistiksel olarak metabolik sendromu olan ve olmayan hastalarda, post-operatif komplikasyonlar, yoğun bakım yatış süresi, vücut kitle indeksi ile anlamlı bir fark bulunmamaktadır (p>0,05). Bununla birlikte Nefsatin-1 ekspresyonu ile post-operatif komplikasyonlar, yoğun bakım yatış süresi ve metabolik sendrom riski ile anlamlı bir fark bulunmaktadır (sırasıyla, p=0,026, p=0,030, p=0,047).

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Cite this article as: Altun E, Dolapoğlu A, Solmaz Avcıkurt A, Avcı E. Predictive Value of Nesfatin-1, Galectin-3, Ghrelin, and Leptin Expressions in Patients with Metabolic Syndrome who Underwent Coronary Artery Bypass Graft (CABG) Surgery. Bagcilar Med Bull 2023;8(2):127-134

Abstract

postoperative complications, length of stay in intensive care unit and metabolic syndrome (respectively p=0.026, p=0.030, p=0.047).

Conclusion: Nesfatin-1 plays a role in glucose homeostasis as a negative regulator of glucose levels. In this study, it is thought that patients with low body mass index and high Nefsatin-1 expression may have a better postoperative clinical course.

Keywords: Adipose tissue, Galectin-3, Ghrelin, Leptin, metabolic syndrome, Nesfatin-1, open-heart surgery

Öz

Sonuç: Nesfatin-1, glikoz seviyelerinin negatif düzenleyicisi olarak glikoz homeostazında rol oynar. Bu çalışmada düşük vücut kitle indeksi ve Nefsatin-1 ekspresyonu yüksek olan hastaların daha iyi bir post-operative klinik seyir gösterebileceği düşünülmüştür.

Anahtar kelimeler: Açık kalp cerrahisi, Galektin-3, Ghrelin, Leptin, metabolik sendrom, Nesfatin-1, yağ dokusu

Introduction

Although there are many new innovations in coronary artery bypass graft (CABG) surgeries, patients may experience many physical, psychological, and social problems following surgery. In studies, patients undergoing CABG surgery have been reported to experience mild symptoms such as pain, wound infections, leg edema, numbness in the arms, constipation, nausea, vomiting, anorexia, sleep disturbance, fatigue, weakness, cognitive problems as well as life-threatening complications such as arrhythmia, low cardiac output syndrome and respiratory-renal failure (1).

Studies have shown that obesity and metabolic syndrome are very common and strong risk factors for operative mortality in patients undergoing CABG surgery. Interventions that may contribute to reducing the prevalence of metabolic syndrome in patients with coronary artery disease (CAD) can significantly improve survival in these patients (2,3). On the other hand, body mass index (BMI) has been shown to be an independent predictor of post-CABG pulmonary complications, although not mortality after CABG (4).

According to the definition of the World Health Organization (WHO), metabolic syndrome is characterized by a combination of metabolic abnormalities such as central (abdominal) obesity, low high-density lipoprotein, high triglycerides, high blood pressure, and hyperglycemia (5). It is known that the mortality and morbidity risk of CABG surgery is high in patients with obesity and/or metabolic syndrome. Accordingly, the multiple risk factors that drive patients with CAD to open-heart surgery are collectively found in metabolic syndrome.

In recent years, many obesity genes have been identified. The expression of Nesfatin-1 (nucleobindin-2 NUCB2/Nesfatin-1), an anorexigenic peptide, decreases with fasting (6). Studies have reported that Nesfatin-1 can cross the blood-brain barrier and be expressed in various peripheral tissues, indicating that Nesfatin-1 exhibits a wide range of physiological activities (7). Nesfatin-1 has been proven to be a new moderator in appetite, energy and glucose homeostasis, and insulin secretion, with important implications for the etiology of metabolic diseases including diabetes and obesity (8). Leptin and ghrelin, on the other hand, are two hormones that are considered to have a major impact on energy balance. Leptin is a mediator in the long-term regulation of energy balance by suppressing food intake and thereby inducing weight loss. Ghrelin release increases appetite and acts as an eating initiation signal (9). The net effect of leptin is to reduce food intake and increase energy expenditure. Galectin-3 is a lectin that plays an important regulatory role in cardiac fibrosis and remodeling, mechanisms that contribute significantly to the development and progression of heart failure. Galectin-3 has been found to increase in patients with acute decompensated and unstable heart failure (10).

Within this scope, this study aims to investigate the expression of Nesfatin-1, Galectin-3, Ghrelin, and Leptin in mediastinal adipose tissue and its association with postoperative complications in patients with and without metabolic syndrome who underwent CABG.

Materials and Methods

In this prospective study, 50 patients who presented to the cardiovascular surgery clinic, were diagnosed with CAD after coronary angiography, were between the ages of 53-85, underwent adult CABG surgery, and were in sinus rhythm were included. Patients who used immunosuppressive drugs and had a history of oncological and hematological diseases were excluded.

Surgical technique: All CABG surgeries were performed under general anesthesia with standard median sternotomy. Cardiopulmonary bypass was used in all operations with crossclamped aorta under cardioplegic arrest and moderate hypothermia. Multidose cold blood cardioplegia was administered intermittently through the aortic root in all patients and retrogradely

through the coronary sinus for myocardial protection. CABG was performed using conventional techniques, and complete revascularization was achieved in all the patients. In the presence of total occlusion of coronary vessels, endarterectomy was performed. After surgery, the patients were transferred to the intensive care unit. The patients were then extubated providing they breathed spontaneously, achieved adequate blood gases, and had stable hemodynamics.

Adipose tissue sampling: Following sternotomy, the anterior mediastinum was exposed and pre-pericardial adipose tissue was dissected to create better exposure and then the pericardium was opened. This mediastinal adipose tissue material that was removed during other routine procedures was fixed in 10% formaldehyde solution for 48 hours. The samples were turned into paraffin blocks after fixation and conventional tissue processing protocols. Histopathological evaluation was performed on hematoxyline-eosin stained slides. Sections of 3 µm thick were taken from the prepared blocks on a slide using a microtome (Leica 2245, Nussloch, Germany). Hydrogen peroxide receptor blockade was performed after all samples were washed with phosphate-buffered solution (PBS) in immunohistochemical procedures. The samples were then incubated by primary anti-Leptin (Rabbit polyclonal, Human specific, Abcam), anti-Ghrelin (Mouse monoclonal, Human specific, Abcam), anti-Galectin-3 (Mouse monoclonal, Human specific, Abcam), and anti-NUCB2/Nesfatin-1 antibodies (Mouse monoclonal, Human specific, Abcam). This was followed by washing in PBS and incubation with universal secondary antibody. Paraffin blocks were taken for immunohistochemical staining. The preparations obtained in the immunohistochemical studies were examined under the light microscope (Nikon, Eclipse Ci, Tokyo, Japan) by the pathologist in a blinded manner.

Nesfatin-1, galectin-3, leptin and ghrelin immunoreactivity was localized in nucleus of the cells. To assign an objective score, a histogram profile of each image, i.e., the number of pixels of a given intensity value relative to a given intensity value, was created using the standard program feature of Nis Elements 4.30 (Nikon, Imaging Software, Tokyo, Japan). It is noteworthy that we excluded the pixel intensity values corresponding to non-specific staining. The image analysis system that was used to acquire and analyze images consisted of a PC with hardware and software, a spot insight camera, and an optical microscope. This necessitates preliminary software procedures including spatial calibration (on a micron scale) and color segmentation adjustments for quantification. The brown staining intensity of the nucleus indicated the presence of Nesfatin-1, Galectin-3, Ghrelin, and Leptin expression. The positivity ratio was estimated. That is, the number of pixels shows the expression level of the detected antigen and may also be expressed as a percentage of the total number of image pixels. <80 pixels reflects: Weak (1+), 80-200 pixels reflects: Moderate (2+) or >200 pixels reflects: strong (3+). A score of 1 was considered negative, while the scores of 2 and 3 were positive (11).

The length of stay in the intensive care unit, total hospital stay, and post-operative complications (Low Cardiac Output syndrome, Insulin-Dependent DM, Arrhythmia, Kidney Failure, Respiratory Failure) of all patients were recorded.

BMI was calculated for each patient according to WHO categorization. All patients included in the study were evaluated consistently with the International Diabetes Foundation 2005 Metabolic Syndrome (MetS) diagnostic criteria (5). Accordingly, the patients included in the study were divided into two groups: MetS (-) and MetS (+).

Statistical Analysis

Before the study, "Power analysis" was performed to determine the number of subjects to be used in the study. To find a significant difference between the group means, the required minimum number of subjects in each group was determined as 8 (type 1 error =0.05, power of the test =0.80). G*Power version 3.1.9.4 was used for power analysis. SPSS v.24.0 package program (SPSS Inc, Chicago, Illinois, USA) was used in the statistical analysis of the data obtained from the study. In statistical analysis, the Mann-Whitney U test was used to compare metric or categorical variables between patients and controls. p-values of <0.05 were considered statistically significant.

Ethics committee approval: In this study, the investigation protocol was in accordance with the Helsinki Committee requirement and approved by the Ethical Committee of Balıkesir University (decision no: 2017/47).

Results

Descriptive data about the patients have given in Table 1. When evaluated in terms of nefsatin-1 expression, 32 patients were observed as nefsatin-1 positive (Figure 1a, 1b). The results showed that there was a statistically significant difference between Nefsatin-1 positive and negative patients according to postoperative status, BMI,

metabolic syndrome, and length of hospital stay ($p<0.05$). Patients with high nefsatin-1 expression stayed in the intensive care unit shorter (Table 2) and had less metabolic syndrome (Table 3). It was observed that 68.4% of patients with a BMI of 25 and below showed high expression of Nefsatin-1 (Table 3). While 40.6% of Nefsatin-1 positive patients did not have a post-operative complication, at least one complication was observed in 88.9% of Nefsatin-1 negative patients (Table 4).

Considering Leptin, Ghrelin, and Galectin-3 expressions, there was no statistically significant difference in terms of postoperative status, BMI, metabolic syndrome, and hospital stay ($p>0.05$).

On the other hand, considering the operative conditions of the CABG patients such as CPB time, X-clamp time, and endarterectomy bypass count, there was no statistically significant difference in terms of Nefsatin-1, Leptin, Ghrelin, and Galectin-3 expressions ($p>0.05$) (Table 5).

Discussion

In this study, immunohistochemical expression of Nesfatin-1, Galectin-3, Ghrelin, and Leptin was investigated in pericardial adipose tissue and inflammatory cells that infiltrate the adipose tissue in patients undergoing CABG. Additionally, its relationship with the postoperative status, BMI, metabolic syndrome, and length of hospital stay was examined. Increased nefsatin-1 expression was associated with fewer post-operative complications, shorter intensive care unit length of stay, and lower metabolic syndrome risk. Patients with low BMI and high Nefsatin expression had a better post-operative clinical course.

Ghrelin is a 28 amino acid polypeptide hormone released from the fundus of the stomach. Clinical studies have reported that ghrelin has potentially beneficial cardiovascular effects such as reduction of mean arterial

Table 1. Descriptive information and postoperative conditions of the patients

	n	%
Gender		
Male	36	72
Female	14	28
Body mass index (BMI)		
BMI above 25	31	62
BMI below 25	19	38
Post-operative status		
Insulin dependent diabetes mellitus	16	32
Arrhythmia	11	22
Renal failure	1	2
Respiratory failure	1	2
Atrial fibrillation	2	4
Low cardiac output syndrome	9	18
Mortality	1	2
None	16	32
Length of stay in hospital (days)		
Length of stay in intensive care	3.1±1	
Total length of stay	9.2±3	
Metabolic syndrome (MetS)		
MetS (-)	32	64
MetS (+)	18	36

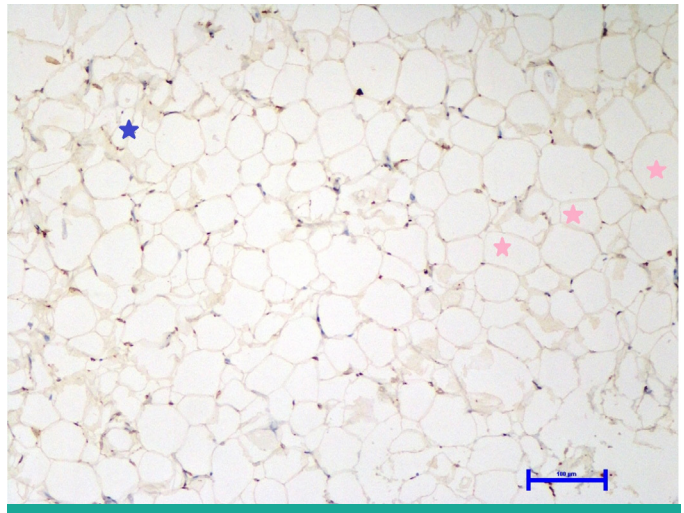

Figure 1a. Low Nesfatin expression in pericardial adipose tissue (pink stars) and inflammatory cells (blue stars), (Nesfatin-1 antibody, 100x)

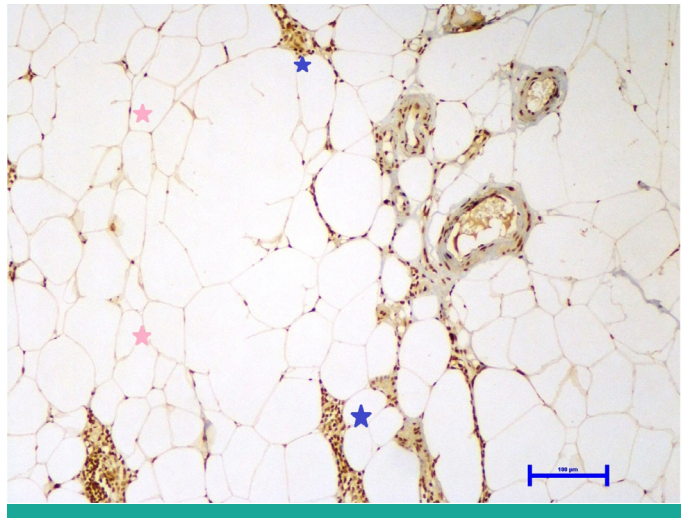

Figure 1b. High Nefsatin expression in adipocytes and inflammatory cells (Nesfatin-1 antibody, 100x)

blood pressure, increase in myocardial contractility, protection of endothelial cells, and improvement of energy metabolism of myocardial cells (12). Clinical studies have shown that the administration of exogenous ghrelin results in improvement in coronary flow, heart rate, dilatation of peripheral blood vessels, narrowing of the coronary arteries, and ventricular and endothelial function. Exogenous ghrelin administration has also been reported to reduce muscle wasting in heart failure, improve exercise capacity, inhibit cardiomyocyte apoptosis, inhibit sympathetic nerve activity, and protect against heart failure induced by myocardial infarction (12).

Table 2. Comparison of Nesfatin-1, Leptin, Ghrelin and Galectin-3 expressions in terms of length of stay in intensive care and hospital

	Length of stay in intensive care (mean/SD)	Total length of stay (mean/SD)
Nefsatin-1 positive	**2.6 days*/1.4**	8.4 days/3.4
Nefsatin-1 negative	4.1 days/1.4	10.8 days/3.5
Leptin positive	2.9 days/1.4	8.8 days/3.3
Leptin negative	3.3 days/1.3	9.6 days/3.3
Ghrelin positive	3.1 days/1.3	9.1 days/3.4
Ghrelin negative	3.2 days/1.4	9.7 days/3.4
Galectin-3 positive	3 days/1.5	8.5 days/3.7
Galectin-3 negative	3.1 days/1.4	9.3 days/3.4

*Statistically significant, SD: Standard deviation

Table 3. Comparison of Nefsatin-1 expression positive patients in terms of metabolic syndrome and comparison of Nefsatin-1 expression and BMI in patients

	Nefsatin-1	
	Positive	**Negative**
BMI above 25	19 (61.3%)	12 (38.7%)
BMI below 25	**13 (68.4%)***	6 (31.6%)
MetS (-)	**20 (76.9%)***	6 (23.1%)
MetS (+)	12 (50%)	12 (50%)

*Statistically significant, BMI: Body mass index, MetS: Metabolic syndrome

Table 4. Comparison of Nefsatin-1 expression and post-operative complication of the patients

	Post-operative complication	
	Yes	**No**
Nefsatin-1 positive	19 (59.4%)	**13 (40.6%)***
Nefsatin-1 negative	**16 (88.9%)***	2 (11.1%)

*Statistically significant

Table 5. Comparison of Nesfatin-1, Leptin, Ghrelin, and Galectin-3 expressions in terms of operative conditions of the coronary artery bypass graft patients

	Operative conditions										
	All patients	**Metabolic syndrome n (%)**		**Nefsatin -1 n (%)**		**Leptin n (%)**		**Ghrelin n (%)**		**Galectin-3 n (%)**	
	Average	MetS (-) 32 (64%)	MetS (+) 18 (36%)	Positive 32 (64%)	Negative 18 (36%)	Positive 20 (40%)	Negative 30 (60%)	Positive 41 (82%)	Negative 9 (18%)	Positive 4 (8%)	Negative 46 (92%)
CPB time	52.4	52.8	52.6	51.4	51.1	56.5	49.1	53.4	52.2	51.1	53.2
X-clamp time	33	32.9	33.4	32.3	34.4	31	30.8	33.2	32.3	33.2	33.6
Endarterectomy	5 patient	3 patient	2 patient	1 patient	4 patient	3 patient	2 patient	4 patient	1 patient	1 patient	4 patient
By-pass count	2.6	2.6	2.6	2.6	2.5	2.5	2.4	2.6	2.4	2.4	2.6

Leptin, a major regulator of fat and energy storage in mammals, on the other hand, acts on hypothalamic receptors to increase energy expenditure and decrease food intake. Plasma leptin levels are closely associated with fat mass and decrease with weight reduction (13).

Galectin-3 is a carbohydrate-binding protein with a molecular weight of 29-35 kDa, depending on the type. It is similar to Bcl-2 protein, which has an anti-apoptotic role in cells. Due to its structural similarity with Bcl-2, galectin-3 has also been reported to have anti-apoptotic properties (4). Galectin-3 is a pro-inflammatory protein and plays a role in T-cell mediated inflammation. Studies have shown that Galectin-3 plays a role in the emergence of acute coronary syndromes such as myocardial infarction. Therefore, an increased galectin-3 amount may be a determinant in the prognosis and diagnosis of the disease, since increased inflammation in acute coronary syndromes adversely affects the prognosis (14,15).

Nesfatin-1 is very commonly expressed in peripheral tissues, including the adipose tissue, pancreas, kidney, liver, and gut. Nesfatin-1 has important metabolic functions such as gastrointestinal function, glucose homeostasis, water intake, temperature regulation, water intake, and sleep (16). Nesfatin-1 is an anorexigenic factor. Satiety triggers are drug targets of weight loss to reduce obesity-related diseases. Nesfatin-1 is thought to be post-translationally processed into the bioactive Nesfatin-1 peptide, which induces satiety, induces weight loss, and thus improves insulin sensitivity (16). Studies have shown that chronic intracerebroventricular injection of Nesfatin-1 reduces body weight in rats, while animals gain body weight following intracerebroventricular injection of antisense morpholino oligonucleotide against the gene encoding Nesfatin-1 (17). Yang et al. (18) found that Nesfatin-1 knockout mice exhibited low insulin secretion and late-onset blood glucose elevation as well as elevated blood glucose in the glucose tolerance test, revealing the role of pancreatic β-cell-produced nesfatin-1 for the automatic maintenance of insulin secretion by pancreatic β-cells. In their study, Ravussin et al. (16) showed that following a high-fat diet, loss of Nesfatin-1 exacerbated metabolic inflammation in adipose tissue macrophages in an NFkB-dependent manner without inducing classical M1 or alternative M2-like macrophage polarization. They also found that deletion of Nesfatin-1 did not affect food intake or adiposity and instead caused insulin resistance in mice fed a high-fat diet (16).

Slow coronary flow (SCF) is an important coronary angiographic phenomenon characterized by delayed progression of angiographic contrast agent in coronary arteries in the absence of obstructive CAD. A study showed that serum Nesfatin-1 level was lower in the SCF group than in the normal coronary flow group. Nesfatin-1 may play a role in the pathogenesis of the SCF phenomenon by mechanisms such as inflammation and endothelial dysfunction (19). In a study, myocardial infarction was induced in rats by subcutaneous injection of isoproterenol, and then the intraperitoneal administration of Nesfatin-1 revealed a significant cardioprotective activity by reducing cardiac troponin-T and pro-inflammatory cytokine levels, and thus the protective effect of Nesfatin-1 against isoproterenol-induced MI was demonstrated (20).

Recent studies have revealed that Nesfatin-1 expression in peripheral tissues including the heart, spinal cord, pancreas, islets, stomach and adipose tissue has crucial physiological roles in body weight and also contributes to the pathophysiology of insulin resistance and associated metabolic problems such as obesity and diabetes (8,21,22).

The anorexigenic and anti-hyperglycemic properties of Nesfatin-1 significantly affect both food intake and glucose metabolism in the body's metabolic regulation (8). Studies examining the relationship between obesity and Nesfatin-1 have shown that plasma Nesfatin-1 levels are associated with BMI, body weight, and fat mass. Peripheral administration of Nesfatin-1 has been proven to have an antihyperglycemic effect on glucose metabolism (23). Nesfatin-1 has a role in glucose homeostasis as a negative regulator of glucose levels and is also important in energy expenditure by increasing thermogenesis (24). Nesfatin-1 is thought to be a pioneer in the diagnosis and treatment of diseases such as metabolic syndrome, obesity, diabetes, and cardiovascular disease (23). Although there exist several studies on the issue, additional studies on Nesfatin-1 in the management of metabolic diseases, especially for type-2 diabetes and obesity, are needed.

In most people, the body weight is maintained in a balanced state and can remain the same for many years. To have a stable weight, there must also be a balance of energy. Energy intake should equal energy expenditure. However, when the energy balance is disturbed, as in obesity, constant weight problems may emerge. The obese and overweight population has been increasing rapidly as one of the important consequences of a high-energy diet that is rich in fat. An increasing number of people, including children, are becoming obese (25). Obesity adversely affects cardiac

hemodynamics, structure, and function. Furthermore, it causes systolic and especially diastolic left ventricular dysfunction. Therefore, it is not surprising that obesity significantly increases the prevalence of heart failure (9). Studies have shown that the most effective treatment is provided by a combination of diet and exercise (26). Since diet and exercise have important effects on energy homeostasis, the use of therapeutic drugs alone does not seem sufficient to treat obesity.

Conclusion

Recent years have witnessed a huge increase in our knowledge of the effects of Nesfatin-1 and the mechanisms underlying them. Finally, the therapeutic potential of Nesfatin-1 in these diseases should be further explored to encourage further studies. On the other hand in this study, we aimed to show the importance of Nesfatin-1 in CABG patients. Further studies can research biochemical or epigenetic changes. Identification of the as yet unknown Nesfatin-1 receptor will enable us to better explore the effects underlying its different actions, which will be a major step forward in understanding the physiology of Nesfatin-1.

Ethics

Ethics Committee Approval: In this study, the investigation protocol was in accordance with the Helsinki Committee requirement and approved by the Ethical Committee of Balıkesir University (decision no: 2017/47).

Informed Consent: Informed consent was obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: E.A., A.S.A., E.Av., Design: E.A., A.S.A., E.Av., Data Collection or Processing: E.A., A.D., Analysis or Interpretation: E.A., A.D., Drafting Manuscript: E.A., A.S.A., E.Av., Final Approval and Accountability: E.A., A.S.A., E.Av., A.D., Technical or Material Support: E.A., A.D., E.Av., Supervision: E.A., A.D., Writing: E.A., A.S.A., A.D., E.Av.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: This study was supported by the Scientific Research Projects Unit of Balıkesir University (BAP 2017/202).

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