Evaluation of malnutrition with blood ghrelin and fecal elastase levels in acute decompensated heart failure patients

Akut dekompanse kalp yetersizliği bulunan hastalarda kan ghrelin ve fekal elastaz düzeyi ile malnütrisyonun değerlendirilmesi

Mustafa Özcan, M.D., Güzin Zeren Öztürk, M.D., Murat Köse, M.D.,# Samim Emet, M.D.,*
Şengül Aydın, M.D., Kadem Arslan, M.D., Yücel Arman, M.D., Vakur Akkaya, M.D.,# Tufan Tükek, M.D.#

Department of Internal Medicine, Okmeydanı Training and Research Hospital, Istanbul;
#Department of Internal Medicine, Istanbul University, Istanbul Faculty of Medicine, Istanbul;
*Department of Cardiology, Istanbul University, Istanbul Faculty of Medicine, Istanbul

ABSTRACT

Objectives: Exocrine pancreatic dysfunction may contribute to malnutrition and lack of appetite in the advanced stages of heart failure. Nutritional assessment was carried out on patients diagnosed with mild or moderate/severe heart failure. Fecal elastase levels are an indicator of pancreatic exocrine function and ghrelin is an appetite hormone which is also investigated for its contribution to malnutrition.

Study design: This is an observational study. 52 patients (32 males, 20 females) aged over eighteen years and hospitalized for acute decompensated heart failure (ADHF) were included in the study. They were compared with 31 people (16 male, 15 female) of the same age as Control Group (C). Patients in New York Heart Association (NYHA) stages 1 and 2 were grouped as mild (miADHF), while those in NYHA stages 3 and 4 were grouped as moderate/severe ADHF (seADHF). Fecal and blood samples were taken at admission. In ADHF patients, exocrine pancreatic functions and their relationship with malnutrition were evaluated. Statistical analyses were performed using Tukey's test, the independent-sample t-test, the Kruskal-Wallis test, the Mann-Whitney U-test, the chi-square test and Pearson's bivariate correlation analysis.

Results: Significantly decreased fecal elastase levels were found when moderate/severe ADHF patients and the control group were compared. (C 278.9±144.8, miADHF 336.6±181.7, seADHF 168.7±153.6, p=0.002). 10 seADHF patients (50%) had severe, 4 (20%) moderate, and 6 (30%) mild pancreatic insufficiency. Ghrelin levels were higher in seADHF patients compared to C and miADHF patients (C 69.7±34.6, miCHF 82.5±48.2, SeADHF 105.0±78.1 p=0.361).

Conclusion: Fecal elastase and ghrelin hormone levels can contribute to the determination of malnutrition in ADHF patients.

ÖZET

Amaç: Ekzokrin pankreas fonksiyon bozukluğu ileri kalp yetersizliği durumlarında malnütrisyon ve iştahsızlığa neden olabilir. Çalışmamızda beslenme değerlendirmesi hafif veya orta/şiddetli kalp yetersizliği tanısı bulunan hastalar üzerinde yapıldı. Pankreasın ekzokrin fonksiyonunun bir göstergesi olan fekal elastaz ve yine bir iştah hormonu olan ghrelin düzeylerinin kalp yetersizliğinde malnütrisyonla ilişkisi değerlendirildi.

Çalışma planı: Gözlemsel çalışmaya akut dekompanse kalp yetersizliği (ADKY) nedeniyle hastaneye yatırılan 18 yaş üstü 52 hasta (32 erkek, 20 kadın) dahil edildi. Aynı yaş grubunda 31 (16 erkek, 15 kadın) sağlıklı kişi de kontrol grubu olarak alındı. New York Kalp Derneği (New York Heart Association - NYHA) evre 1 ve evre 2 hastalar hafif ADKY, NYHA evre 3 ve evre 4 hastalar orta/şiddetli ADKY olarak gruplandırıldı. Dışkı ve kan örnekleri alındı. ADKY'li hastalarda ekzokrin pankreas fonksiyonları ve malnütrisyon ile ilişkisi değerlendirildi. İstatistiksel analiz Tukey testi, bağımsız örneklem t-testi, Kruskal-Wallis testi, Mann-Whitney U-testi, ki-kare testi ve Pearson çift değişkenli korelasyon analizi kullanılarak yapıldı.

Bulgular: Orta/şiddetli ADKY'li hastalarda kontrol grubu ile kıyaslandığında önemli ölçüde azalmış fekal elastaz düzeyleri bulundu (Kontrol 278.9±144.8, hafif ADKY: 336.6±181.7, orta/şiddetli ADKY: 168.7±153.6, p=0.002). Orta/şiddetli ADKY'li 10 hastada (%50) ağır, 4'ünde (%20) orta ve 6'sında (%30) hafif pankreas yetersizliği vardı. Ghrelin seviyeleri kontrol grubunda ve hafif ADKY'li hastalarda (69.7±34.6, 82.5±48.2) orta/şiddetli ADKY'li hastalardakine (105.0±78.1) kıyasla daha düşük idi ancak fark istatistiksel olarak anlamlı değildi (p=0.361).

Sonuç: Fekal elastaz ve ghrelin hormon düzeyleri ADKY'li hastalarda malnütrisyonun saptanmasına katkıda bulunabilir.

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Correspondence: Dr. Samim Emet. İstanbul Üniversitesi Tıp Fakültesi Kardiyoloji Anabilim Dalı, Çapa, İstanbul.
Tel: +90 212 - 414 20 00 e-mail: samim03@hotmail.com

Heart failure (HF) is a complex composition of symptoms and signs arising from hemodynamic, renal, and neurohormonal responses caused by dysfunction of the heart.[1] This syndrome is an important health problem which is increasing in incidence in the older population with serious morbidity, mortality and uniformly poor prognosis.[2] Insufficient blood flow to peripheral tissues causes ischemia which may result in loss of function in many organs such as kidney, liver, and pancreas.[3] As HF progresses, the patient becomes bedridden, and increasing dyspeptic complaints and decreasing appetite leads to malnutrition.[3]

In the present study, we investigated fecal elastase levels, which are an indicator of pancreatic exocrine function, and blood ghrelin levels, which affect eating, sleeping, cell proliferation, the cardiovascular system and carbohydrate energy metabolism in patients with HF.

PATIENTS AND METHODS

Study design

This observational study was approved by the local Ethics Committee. Written informed consent was obtained from the participants.

Study population

Patients aged over 18 years and diagnosed with mild (n=32) and moderate/severe (n=20) acute decompensated heart failure (ADHF) were enrolled in the study as the patient group. Thirty-one age- and sex-matched healthy volunteers were selected as the control group. The control group had no systemic disease, and was drawn from outside the internal medicine clinic. Patients with any malignancy, any endocrine or exocrine pancreatic disease, acute or chronic liver or renal disease, active infection, any gastrointestinal disease or any surgery in the gastrointestinal track were excluded from the study group. Demographic data were collected, detailed medical history and history of drug use taken, and physical examination performed on all study groups. Body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters). Patients were divided into four groups according to BMI: BMI < 18.5 (underweight), 18.5 ≤ BMI < 25 (normal/healthy), 25 ≤ BMI < 30 (overweight), and BMI > 30 (obese).

Study protocol

Abbreviations:

ADHF	*Acute decompensated heart failure*
BMI	*Body mass index*
EF	*Ejection fraction*
FE	*Fecal elastase*
HF	*Heart failure*
NYHA	*New York Heart Association*

Blood samples for blood chemistry, complete blood count and ghrelin levels were taken from all participants. HF stage and duration were classified according to New York Heart Association (NYHA) criteria. Patients in NYHA stages 1 and 2 were grouped as mild (miADHF), and those in NYHA stages 3 and 4 were grouped as moderate/severe ADHF (seADHF).

Twelve-lead electrocardiograms were taken and examined for previous myocardial infarction, pathological Q waves, bundle branch block, atrial fibrillation, ventricular arrhythmias, and changes in the ST segment and T waves. Standard transthoracic echocardiography parameters and ejection fractions (EF) were collected in all groups.

Fecal elastase (FE-1) levels were determined using the ScheBo BioTech pancreatic elastase-1 enzyme immunoassay micro-ELISA test kit. (Elastase-1 stool kit ScheBo Biotech, Wettenberg-Giessen, Germany). Fecal elastase (FE-1), shows pancreatic exocrine insufficiency when levels are less than 200 mg/g. A 100-200 mg/g stool is taken to show moderate insufficiency. Levels lower than 100 mg/g show severe insufficiency.[4]

Blood samples taken for ghrelin levels were centrifuged at 600 rpm/min and then treated with 20-30 ml (mg) of aprotinin, a protease inhibitor, for each ml of EDTA containing a serum sample to prevent fragmentation of peptides by cellular proteases. Samples were placed into Eppendorf tubes and stored at -80 C for 3 months. Ghrelin levels were determined using the Ray Bio Human/ Mouse /Rat Ghrelin Enzyme Immunoassay Kit ELISA method. Serum samples were allowed to thaw standing at room temperature. After centrifugation, 1/10 volume of 1 N HCl was added. Normal values for N-octanol ghrelin were in the range of 32.61 to 65.2 pg/ml.[5-8]

Statistical analysis

Numerical data was given as mean ± standard deviation, and categorical data as percent and frequency. The Kolmogorov-Smirnov test was used to assess data distribution, and equality of variances of numerical variables was checked. Descriptive analyses were

presented using means and standard deviations for normally distributed variables. One way ANOVA was used to compare these parameters among the groups. An overall p-value of less than 0.05 was considered a statistically significant result. When it was significant, pairwise post-hoc tests were performed using Tukey's test. The Kruskal-Wallis test was conducted to compare the groups for parameters that were not distibuted normally and for ordinal variables. Pearson's bivariate correlation analysis was used for the correlation between two numerical data. Statistical analysis was done using SPSS for Windows 20.0 (SPSS, Inc. Chicago, IL, USA).

RESULTS

83 patients participated in the study (48 men [57.8%] and 35 women [42.2%]; mean age, 67.5±9.7 years; range, 46-91 years).

The comparison of demographic data between the

Table 1. Baseline characteristics of study groups

	Control (n=31)	Mild ADHF (n=32)	Severe ADHF (n=20)	*p*
	Mean±SD	Mean±SD	Mean±SD	
Age (year)	67±10	67±8	68±7	0.23
Male gender, n (%)	16 (51)	20(62)	12 (60)	0.665
Duration of HF	–	7.3±5.9	14.4±7.8	**<0.0001**
Height (m)	1.6±0.1	1.7±0.1	1.7±0.1	0.358
Weight (kg)	72±13	72±13	62±10	**0.008**
Body mass index (kg/m^2)	26.7±4.6	25.8±4.8	22.3±3.9	**0.003**
Ejection fraction (%)	61±5	38±7	31±6	**<0.0001**
Glucose (mg/dl)	96±12	99±17	100±14	0.494
Urea (mg/dl)	40±17	51±19	55±30	0.026
Creatinine (mg/dl)	0.9±0.3	1.1±0.3	1.2±0.3	0.004
Uric acid (mg/dl)	5.7±1.4	7.7±2.0	8.1±2.6	**<0.0001**
Total Cholesterol (mg/dl)	198±45	157±46	14±36	**<0.0001**
High-density lipoprotein (mg/dl)	46±8	33±9	33±10	**<0.0001**
Low-density lipoprotein (mg/dl)	126±40	100±36	92±33	**0.003**
Triglyceride (mg/dl)	117±60	120±63	88±36	0.108
Aspartate aminotransferase (U/L)	23±8	49±103	129±454	0.264
Alanine aminotransferase (U/L)	23±11	32±53	188±732	0.246
Alkaline phosphatase (U/L)	59±26	87±39	91±45	**0.004**
Gamma-glutamyl transferase (U/L)	44±20	57±53	69±120	0.809
Lactate dehydrogenase (U/L)	218±48	288±205	278±182	0.218
Total protein (g/dl)	6.5±0.6	6.8±0.8	6.7±0.7	0.444
Albumin (g/dl)	4.2±0.5	3.7±0.6	3.4±0.3	**<0.0001**
White blood cell (10^3/mm^3)	7.5±3.0	8.1±3.4	8.7±4.6	0.484
Red blood cell (10^6/mm^3)	4.3±0.6	4.2±0.7	4.0±0.6	0.344
Hemoglobin (g/dl)	12.6±1.4	12.4±2.0	11.8±1.5	0.254
Hematocrit (%)	36.8±3.4	36.1±6.1	34.3±3.6	0.164
Platelet (10^3/mm^3)	249±52	224±71	213±64	0.105

Continuous variables were expressed as mean (standard deviation) and categorical variables were expressed as number (percentage). ADHF indicates acute decompensated heart failure.

control and patient groups (miADHF and seADHF) are shown in Table 1. The mean age and male/female distributions of the control group were similar to those of the patient group. Duration of heart failure was longer in the severe ADHF group, as expected. Heights were similar between groups, but weight was significantly lower in the severe ADHF group which, as the numerator of BMI calculations, also significantly decreased BMI compared to controls and mild ADHF groups (Table 1).

Comparison of hematologic and biochemical parameters are given in Table 2. Blood urea nitrogen, creatinine and uric acid and alkaline phosphatase were significantly higher in patient groups compared to controls. The parameters were higher in severe ADHF groups compared to mild ADHF group, without reaching statistical significance. Total cholesterol, HDL cholesterol, LDL cholesterol and albumin levels

Table 2. Comparison of ejection fraction, elastase, ghrelin, and body mass index among groups

	Control (n=31)			Mild ADHF (n=32)			Severe ADHF (n=20)			*p*
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	
Ejection fraction (%)			61±5			38±7			31±6	**<0.0001**
Elastase (μg/gr)			279±145			337±182			169±154	**0.002**
Ghrelin (pg/ml)			70±35			83±48			105±78	0.361
Body mass index (kg/m^2)										
≥25 and <30	21	67.7		20	62.5		3	15.0		0.001
≥18.5 and <25	9	29.0		7	21.9		11	55.0		
<18.5	1	3.2		5	15.6		6	30.0		

Continuous variables were expressed as mean (standard deviation) and categorical variables were expressed as number (percentage). ADHF indicates acute decompensated heart failure.

Table 3. Comparison of elastase levels between control and ADHF group according to body mass index

	Body mass index (kg/m^2)			
	≥25 and <30 (n=44)	≥18.5 and <25 (n=27)	<18.5 (n=12)	*p*
Controls (n=31)	325±137	196±110	–	0.019
ADHF (n=52)	395±141	233±172	79±97	**<0.0001**
P value	0.102	0.563	–	
All patients (n=83)	362±142	220±153	77±93	**<0.0001**

Elastase levels were expressed as mean ± standard deviation. ADHF indicates acute decompensated heart failure.

Table 4. Comparison of ghrelin levels between control and ADHF group according to body mass index

	Body mass index (kg/m^2)			
	≥25 and <30 (n=44)	≥18.5 and <25 (n=27)	<18.5 (n=12)	*p*
Controls (n=31)	66±38	79±26	70	0.359
ADHF (n=52)	86.±60	100±72	88±50	0.587
P value	0.417	0.900		
All patients (n=83)	76±51	93±61	86±48	0.225

Ghrelin levels were expressed as mean ± standard deviation. ADHF indicates acute decompensated heart failure.

Table 5. Comparison of groups according to stages of pancreatic insufficiency

	Control (n=31)		Mild ADHF (n=32)		Severe ADHF (n=20)	
	n	%	n	%	n	%
Elastase <100	6	19.4	4	12.5	10	50.0
Elastase ≥100 and <200	4	12.9	3	9.4	4	20.0
Elastase ≥200	21	67.7	25	78.1	6	30.0

were significantly higher in the controls compared to the patient groups. There was a trend for lower values in these parameters in seADHF compared to miADHF, without reaching statistical significance (Table 1).

A comparison of EF, fecal elastase levels, ghrelin, and BMI of all groups is shown in Table 3. Ejection fraction was significantly lower in patient groups compared to controls, with values still lower in seADHF compared to miADHF. Fecal elastase levels were lower in seADHF group compared to miADHF and controls. Mean ghrelin levels tended to be higher with increasing severity of ADHF, with the lowest values in controls and the highest values in seADHF groups, without reaching statistical significance. BMI distribution was similar in controls and miADHF, with patients mostly in the overweight group, whereas seADHF patients were mostly in the normal weight and malnutrition groups (Table 2).

A comparison of body mass index and elastase levels in all groups is given in Table 4. Fecal elastase levels were significantly lower with lower BMI range groups, irrespective of ADHF or control grouping. Fecal elastase levels were not significantly different between controls and ADHF groups in the same BMI range (Table 3). However ghrelin levels did not differ significantly according to BMI in any group (Table 4).

There were no significant correlations observed between EF values and fecal elastase. However, a significant inverse correlation was observed between ghrelin levels and EF (r=-0.32, p=0.04).

Table 5 shows the comparison of the control, miADHF, and seADHF groups according to stages of pancreatic insufficiency as assessed by fecal elastase levels. Whereas approximately two-thirds of the controls and miADHF patients had normal pancreatic function, 70% of the severe ADHF group had pancreatic exocrine insufficiency (Table 5).

DISCUSSION

The incidence of HF is increasing with an aging population, and rates of death or re-hospitalization within 1 year in patients admitted to a hospital have risen to 40%. Complications that occur due to this disease also play a large role in this increased rate of admission, which also increases national health care spending.[9]

One complication of ADHF is malnutrition, which is a lack of intake in energy, protein, and other nutrients. Therefore the status of nutrition and whether malnutrition is present is important for HF patients, but in the past had been dismissed as an unavoidable consequence of the evolution of the disease. However recent studies have shown that malnutrition is not only highly prevalent in these patients, but also was an important risk factor for mortality and morbidity.[3]

Indeed, both organ dysfunction associated with the reduction in cardiac output and dietary problems depending on age and severity of the disease severely increase mortality.

Malnutrition leads to thinning of myofibrils, causes further deterioration of cardiac contractility and increased weight loss, which in turn further reduces cardiac output. Bradycardia and hypotension are more common in severe ADHF patients, and debility and malnutrition contribute to electrolyte imbalances, arrhythmias, and progression to multi-organ deficiencies and death. In addition, protein-losing enteropathy, commonly caused by ADHF, accompanied by hypoalbuminemia and hypoproteinemia may cause progressive loss of muscular mass resulting in weakness and decrepitude. Although these patients may be overweight due to salt and water retention, they should be considered malnourished because of the loss of lean body mass due to pancreatic insufficiency, intestinal congestion, and protein loss.[10]

There is no gold standard for assessing the nutritional status of ADHF patients. A variety of assessment tests are available when many parameters are combined. Some of the tests used in ADHF are subjective global assessments and mini-nutritional assessments.[10]

Fecal elastase and serum ghrelin levels have recently been highlighted as indicators of pancreatic exocrine function. Fecal elastase levels in patients with chronic pancreatitis, trauma, or chronic renal failure have been assessed.[11,12] In one study, fecal elastase was used as an indicator of malnutrition, and low levels were found in patients with chronic renal failure.[13]

In our study, there was significant difference in fecal elastase levels between the control and mild ADHF groups versus the severe ADHF group. In patients with advanced ADHF, 10 patients (50%) had severe, and 4 patients (20%) had moderate pancreatic insufficiency, whereas two- thirds of the controls and mild ADHF groups had normal pancreatic function. It may be that the duration of disease, which was shorter in the mild ADHF group, caused the difference. However, more importantly, it seems that patients with low BMI also had lower fecal elastase levels in the ADHF groups. Low BMI, associated with low cholesterol and albumin can be taken as an indicator of the presence of malnutrition in the seADHF group, but this is not as obvious in controls or miADHF patients. It has been previously reported that protein calorie malnutrition causes pancreatic exocrine dysfunction, with decreased output of enzymes and bicarbonate in the basal period of pancreatic secretion, a normal but smaller rise in enzymes with stimulation due to lower baseline and a suggestion of early exhaustion after the stimulatory phase. It was also reported that lipase secretion was more deeply affected, with trypsin less and amylase the least with malnutrition.[14] It seems that elastase secretion can also be affected by malnutrition. Total enzyme synthesis in the pancreas is 13 times more than in the liver, and it is logical that lack of amino acids will have a greater effect on exocrine enzyme synthesis in the pancreas than on any other system. As controls with lower BMI had lower fecal elastase levels, some of these patients may have had subclinical malnutrition as well. It seems that fecal elastase may be a sensitive indicator of malnutrition that may give warning before conventional markers like BMI, cholesterol or albumin are affected.

Ghrelin, a recently discovered orexigenic hormone, has effects on eating, sleeping, cell proliferation, the cardiovascular system, and carbohydrate and energy metabolism as well as on pancreatic exocrine and endocrine functions. Secreted mostly from the stomach and the pancreas, ghrelin is synthesized from newly-defined islet cells in the pancreas. In our study, there was no statistically significant difference between controls and ADHF patients for ghrelin levels, although there was a trend for increasing ghrelin levels with severity of ADHF. However, mean ghrelin levels in the controls and ADHF groups were higher than standard ranges reported in the literature. Taken together with fecal elastase levels, it may be that the choice or nutritional status of a subgroup of control patients were suboptimal though they had BMI, cholesterol and albumin levels within normal limits.

In conclusion, fecal elastase may be a sensitive marker of the synthetic capacity of the pancreas, which may deteriorate in a protein calorie deficiency state before malnutrition becomes obvious. Ghrelin may be affected by different systems in a myriad of ways, causing it to be higher than expected in the control group, which may compromise our interpretation.

Nutritional deficiency and related complications frequently occur in patients with ADHF, and are a major cause of mortality and morbidity. We detected increased ghrelin levels and decreased elastase levels in patients with advanced HF. Although fecal elastase and ghrelin levels do not directly indicate exocrine pancreatic function and malnutrition, such information helps inform other tests, and provides the possibility of using both for diagnosis and treatment in patients with end-stage HF. Future studies of elastase and ghrelin levels in a larger group of patients and across multiple disciplines, such as internal medicine, cardiology, nutrition, and metabolism, will provide better results.

Study limitations

A major limitation of our study is the number of the study group. Thus, this study should be considered a pilot study and additional studies should be conducted in future.

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Key words: Body mass index; ghrelin; heart failure; malnutrition.

Anahtar sözcükler: Beden kütle indeksi; ghrelin; kalp yetersizliği; malnütrisyon.