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Research Article

Leptin secretion and NT-proBNP levels in overweight and obese patients with chronic heart failure with or without atrial fibrillation

Alexandra Dădârlat, Dana Pop, Dumitru Zdrenghea, Gyorgy Bodisz, Florina Fringu, Diana Gurzau, Silvana Susca-Hojda, Anca D. Buzoianu

"Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Abstract. Introduction and scope. Leptin, an important citokine secreted in the adipose tissue, known for its central role in regulation of appetite and body weight, represents an important hormone for the cardiovascular pathology. There are investigators showing leptin's deleterious effects on the cardiac function, by increasing blood pressure and oxidative stress, but also there are alternative hypotheses regarding leptin's protective effects in heart failure patients are found in the literature. The aim of the study was to investigate the possible relationship between leptin secretion and NT-proBNP levels in obese heart failure population, stratified by the presence of atrial fibrillation. Material and methods. We recruited 88 patients with overweight or obesity hospitalised in Rehabilitation Hospital, Department of Cardiology, Cluj-Napoca in 2016–2018 for worsening heart failure. Blood samples for laboratory assessments were obtained from the patients on the day of the arrival. Leptin was measured using the ELISA method (Human Leptin BioVendor kit). NT-proBNP was measured using the chemiluminescence method. Patients were stratified by the presence of atrial fibrillation into two groups. Results.The mean age was 69 ± 9 years and 51% were females. Median BMI was 36 (27–48) kg/m2. Among the patients included in the study, 46 patients (52%) had atrial fibrillation. The most common aetiology of heart failure in our patients was ischaemic. NT-proBNP median value was 1342 pg/mL (923-3076 pg/mL). NT-proBNP levels were not significantly influenced by the presence of atrial fibrillation 1579 pg/mL (963-3600 pg/mL) vs. 1120 pg/mL (893-2700 pg/mL) with a P = 0.1, diabetes mellitus or age in heart failure patients. An inverse relationship was found between NT-proBNP values and creatinine clearance estimated by Cockcroft-Gault equation. Also, NT-proBNP values negatively correlated with BMI.Median serum leptin levels were 25 ng/mL (10-41 ng/mL). Leptin median levels were not significantly different in patients with atrial fibrillation 26 (12.9-44.2 ng/mL) in comparison with patients in sinus rhythm 24 (6.5-39.6 ng/mL) – P=0.68. NT-proBNP levels did not significantly vary with leptin serum levels (correlation (Spearman R) = -0.101, p=0.35), regardless of the presence of atrial fibrillation. Conclusion. NT-proBNP levels were significantly lower in patients with higher BMI. More advanced renal impairment correlated with higher NT-proBNP levels. Leptin levels directly correlated with BMI. Leptin levels were not influenced by sex, age, left ventricle ejection fraction. We found no significant association between leptin levels and NT-proBNP values in obese heart failure patients with or without atrial fibrillation.

Key Words: leptin, NT-proBNP, obesity, atrial fibrillation, heart failure

Corresponding Author: A. Dadarlat, email: dadarlat.alexandra@yahoo.ro

Introduction

Obesity has reached pandemic proportions worldwide and is a common finding in people with heart failure. The risk of heart failure increases by 5 % in men and 7 % in women for every 1 kg/m2 increment in body mass index (BMI) (Mathew et al 2008). Natriuretic peptides are cardiac hormones secreted at the atrial or ventricular level due to myocardial parietal stress, known as important tools in the diagnosis, prognosis and management of heart failure. The physiological effects of the BNP are vasodilatation, enhancement of natriuresis and diuresis and renin-angiotensin-aldosterone system suppression (Wirth et al 2014). NT-proBNP levels are influenced by age, renal function, atrial fibrillation, arterial hypertension and other cardiac or non-cardiac conditions which can weaken their diagnostic and prognostic value. There is now overwhelming evidence that obesity is associated with lower levels of B-type natriuretic peptides (BNP) in patients with CHF (Ponikowski et al 2016). But, despite all the research made in this area, the exact mechanism of natriuretic peptide suppression in obese patients with heart failure is still unknown. A plausible explanation is the attenuation of natriuretic peptides synthesis or secretion in patients with obesity due to a reduced cardiac distensibility (Gruden et al 2014; Madamanchi et al 2014).

The existing link between obesity and heart failure is at least partially explained by the secretion of various adipokines. Adipokines are cytokines released by the adipose tissue that have various physiological effects. There are over 50 adipocytokines which have been described, some of which are produced almost exclusively by adipocytes. One of them is leptin, a peptide hormone consisting of 167 amino acids. Leptin levels are elevated in obesity, but they are also influenced by cardiac diseases (Jong et al 2018). Although leptin is mainly expressed in white adipose tissue, it was also found in the heart (Hall et al 2015). There still are controversies regarding

leptin's cardio-protective effects in obese heart failure patients (Dadarlat et al 2018). There is evidence incriminating leptin, a satiety adipokine that increases proportionally with the BMI as one of the most important hormones implicated in heart failure development. Hyperleptinemia, which is commonly found in obese patients, leads to endothelial dysfunction, pro-inflammatory effects, oxidative stress, cardiomyocyte hypertrophy and proliferation of vascular smooth muscle cells (Jong et al 2018; Pop et al 2015). On the other hand, there are studies showing the deleterious effects of the deletion of leptin receptors in the heart, which was associated with a decreased myocardial contractile function and glucose metabolism. Therefore, the lack of cardiac leptin receptors increases mortality and morbidity in patients with coronary heart disease (Hall et al 2015). In the heart, leptin is responsible for fatty acid and glucose metabolism modulation and also has anti- steatosis and apoptosis effects (Hall et al 2015).

The aim of this study was to investigate the association between leptin and the N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) in obese heart failure population, stratified by the presence of AF.

Materials and methods

We conducted a cross-sectional study of 88 patients with overweight or obesity hospitalised in the Rehabilitation Hospital, Cardiology Department, Cluj-Napoca in 2016–2018 for worsening heart failure. The selected patients were informed about the study protocol and gave their signed informed consent. The institutional ethics committee of "Iuliu Hatieganu" University of Medicine and Pharmacy approved the study protocol.

We categorised participants according to body mass index (BMI). BMI was calculated according to the following formula: weight in kilograms divided by the square of the height in meters. Clinical history, ECG, laboratory data and current medications were recorded. The NYHA classification was used to assess functional capacity. Hypertension (HTN) was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or current use of antihypertensive medication. Echocardiographic measurements were performed.

All patients received optimal heart failure therapy according to current guidelines.

Blood samples for laboratory assessments were obtained from the patients on the day of the arrival. Serum was separated by centrifugation at 1500 g for 10 minutes at 4°C, then was transferred into 1 mL cryotubes, and stored at −70°C for later analysis. Leptin was measured using the ELISA method (Human Leptin BioVendor kit). Calibration of the assay was performed according to the manufacturer's recommendations. The limit of detection for leptin was 0.2 ng/ml. NT-proBNP was measured using the chemiluminescence method. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault Equation.

Statistical Analysis

Statistical analysis was carried out using MedCalc (v 10.3.0.0, MedCalc Software, Ostend, Belgium) and SPSS Statistics for Windows (v 16.0, IBM Corporation, Armonk, NY, USA) software programs. Normal distribution was assessed using the Kolmogorov–Smirnov test. The results regarding categorical variables are presented as numbers and percentages. For numerical data, mean, standard deviation and median values were calculated (depending on distribution's normality). Baseline characteristics were stratified by the presence of atrial fibrillation. Mann-Whitney U test was used in order to compare numerical variables with non-normal distribution, after normality assessment with Wilk test. Inter-group differences were tested using the Student's t-test. Both raw data (using Spearman's coefficients) and log-transformed data (using Pearson's coefficient) were computed.

A two-sided P-value of <0.05 was determined to be statistically significant.

Results

Out of all patients, 46 patients (52%) had permanent atrial fibrillation. In the overall population the mean age was 69 ± 9 years and 51% were females. Median BMI was 36 (27–48) kg/m2. The most common aetiology of heart failure in our patients was ischaemic. Seventy-three percent of the participants were hypertensive, 38% had diabetes mellitus, 34% were current smokers and 18% had a positive history of myocardial infarction. The clinical characteristics of the studied groups are presented in Table 1, stratified by the presence of atrial fibrillation. Obesity grade 3 was found in 24% of patients with atrial fibrillation in comparison with patients without AF where grade 3 obesity was seen only in 14%. Overweight was found twofold more frequently in patients in sinus rhythm. The left ventricle ejection fraction was not significantly different between the two groups of patients (45 ± 11 in patients with AF vs 45 ± 12; p =0.9). We found a significant difference between HDL-cholesterol levels between the two groups, patients with atrial fibrillation presented significant lower levels (37 ± 10 mg/dl vs 44 ± 11 mg/dl; P-value = 0.004).

NT-proBNP median value was 1342 pg/mL (923-3076 pg/mL). NT-proBNP levels were not significantly influenced by the presence of atrial fibrillation 1579 pg/mL (963-3600 pg/mL) vs. 1120 pg/mL (893-2700 pg/mL) with a P = 0.1 in heart failure patients with overweight or obesity.

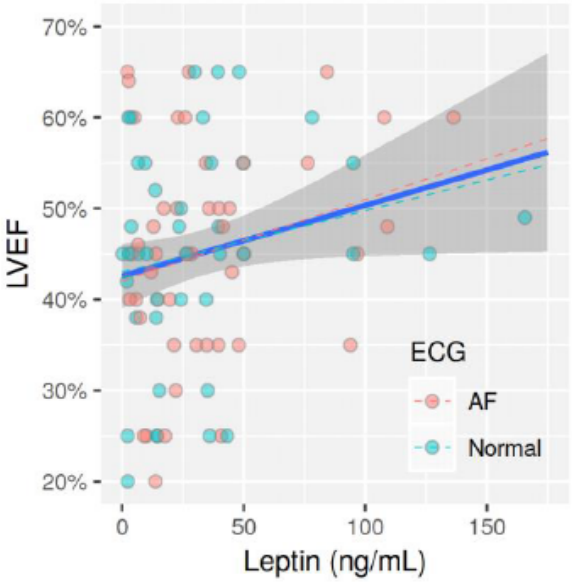


Fig 1. Correlation between leptin levels and left ventricle ejection fraction in overweight or obese heart failure patients with or without AF

Table 1. Baseline demographic characteristics in patients with heart failure and overweight or obesity, stratified by the presence of atrial fibrillation.

Overweight and obese patients with chronic heart failure:	with AF	without AF	P
Demographics			
Patients- No (%)	46 (52.2%)	42 (47.7%)	1
Age, mean years ± standard deviation	69.48 ± 8.81	69.38 ± 10.15	0.962
Female sex – No (%)	24 (57.1 %)	21 (50%)	0.9
Aetiology			
•Ischaemic heart disease	20 (43.5%)	26 (56.5%)	0.101
•Dilated cardiomyopathy	10 (21.7%)	5 (10.9%)	0.029
•Valvular	10 (21.7%)	6 (13.0%)	0.120
•Tachyarrhythmias	14 (30.4%)	2 (4.3%)	0.000
• Others	5 (10.9%)	6 (13.0%)	0.828
NYHA functional class I- II- No (%)	13 (28.2%)	19 (45%)	0.098 OR=2.1
NYHA functional class III-IV- No (%)	33 (71.7%)	23 (54.7%)	
Smoking status – No (%)	12 (26.1%)	18 (39.1%)	0.072
Laboratory			
HDL-cholesterol mg/dl (mean ± SD)	37.31 ± 10.42	44.14 ± 11.46	0.004
LDL-cholesterol mg/dl (mean ± SD)	107.91 ± 44.62	99.43 ± 30.53	0.298
Triglycerides- mg/dl (mean ± SD)	142.55 ± 43.80	127.84 ± 51.21	0.15
Glycemia- mg/dl (mean ± SD)	119.71 ± 40.25	115.91 ± 38.86	0.654
Creatinine (mg/dl)	1.16 ± 0.39	1.09 ± 0.46	0.432
NT-pro-BNP- pg/dl median (IQR)	1579 (963-3600)	1120 (893-2700)	0.1

An inverse relationship was found between NT-proBNP values and creatinine clearance estimated by Cockcroft-Gault equation (r=-.35, p=0.001). Also, NT-proBNP values negatively correlated with BMI (r=-.3, p=0.04).

Moderate and severe mitral regurgitation were found more frequently in patients with atrial fibrillation (p-value=0.01). We found no significant differences in terms of other valvular diseases (aortic insufficiency, aortic stenosis) between the two groups.

Left atrial dilatation was significantly more common in patients with atrial fibrillation compared with patients without AF, with a mean anteroposterior diameter of 47 ± 9 mm vs. 42 ± 10 mm; P= 0.01 and an area of 31 ± 7 cm2 vs 27 ± 10 cm2; P=0.01.

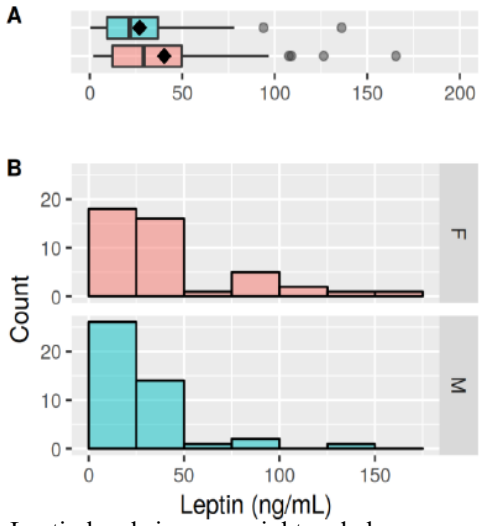


Fig. 2. Leptin levels in overweight and obese women and men with heart failure.

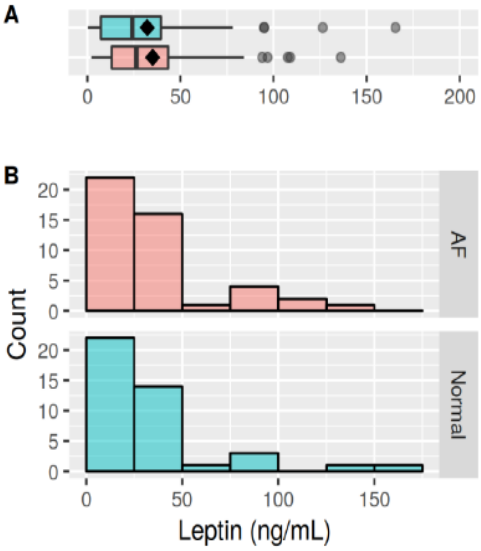
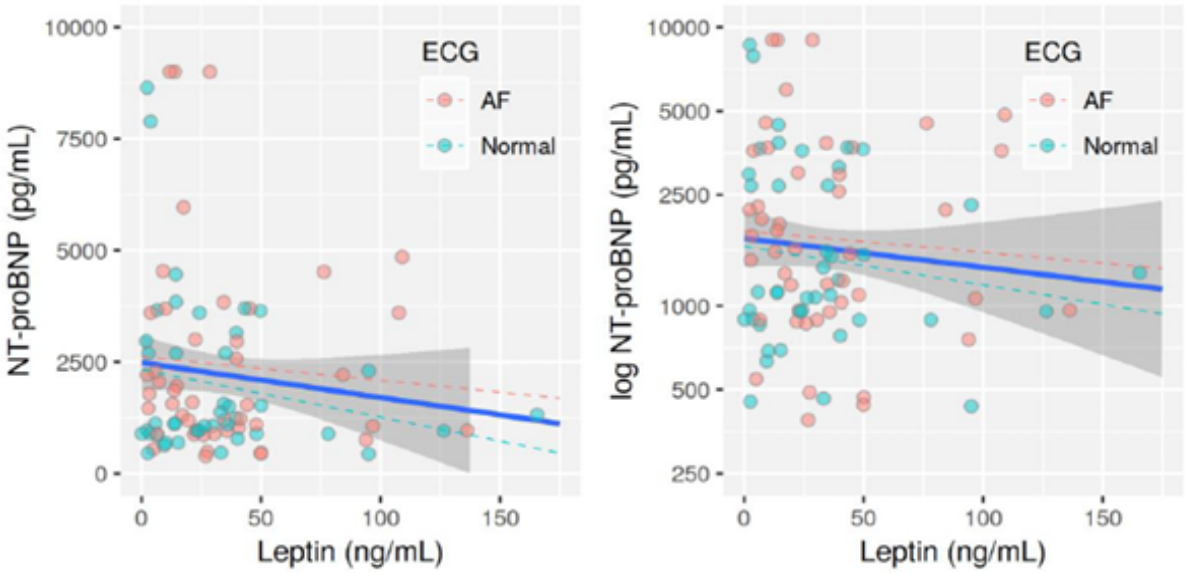


Fig. 3. Leptin levels in patients with atrial fibrillation vs patients in sinus rhythm.

Median leptin value was 25 ng/mL. A positive correlation (r= 0.347, p= 0.001) was found between leptin concentrations and BMI. No correlation was found between leptin serum levels and left ventricle ejection fraction (r= 0.183, p=0.08), regardless of the presence of AF- figure 1. Leptin levels were not significantly higher in women compared with men (40.3 ± 38.2 vs. 27 ± 26.2, p = 0.06) - figure 2. Leptin levels were not significantly different in patients with atrial fibrillation (35 ± 32 ng/mL), median value 26 ng/mL in comparison with patients in sinus rhythm (32 ± 34 ng/mL), median value 24 ng/mL, p=0.68 - figure 3. We found no relationship between NT-proBNP levels and leptin serum levels in overweight or obese heart failure patients with or without AF, as you can see in figure 4.

Discussion

There is robust data showing that patients with obesity have lower NT-proBNP values (Horwich et al 2018), limiting its prognostic and risk stratification value in this subgroup of patients. Moreover, a recent study showed that excluding heart failure with preserved ejection fraction in patients with overweight and



Raw data: Correlation (Spearman R) = -0.101, p=0.35. After log transfomations: Correlation (Pearson R) = -0.098, p=0.365.

ECG	Spearman R (raw data)	p	Pearson R (log-transformed data)	p
All	-0.101	0.35	-0.098	0.365
AF	-0.16	0.287	-0.16	0.287
Sinus Rhythm	-0.037	0.817	-0.037	0.817

Fig. 4. Correlation between leptin and NT-proBNP levels in overweight and obese heart failure patients, stratified by the presence of AF.

obesity based solely on NT-proBNP determination is strongly discouraged, recommending the use of lower NT-proBNP diagnostic thresholds (Buckley et al 2018). Although, the exact pathophysiological mechanism is not fully understood, the reduced cardiac distensibility is a possible explanation (Madamanchi et al 2014). Also, there are many other conditions that affect NT-proBNP levels in a patient, such as atrial fibrillation and renal disease. There is evidence that NT-proBNP values are elevated in AF, with implications in prognostic stratification and therapeutic decisions. In the current study, higher NT-proBNP levels were not registered in overweight and obese patients with atrial fibrillation compared with their counterparts without AF. Other studies had also similar results (Zheng et al 2014). So, it is possible that the presence of obesity in AF patients has similar effects on NT-proBNP levels as in heart failure patients in sinus rhythm.

Also, an inverse relationship is described between NT-proBNP levels and renal function impairment (Ponikowski et al 2016). In the present study, in accordance with existing data, an inverse relationship between NT-proBNP and creatinine levels, respectively estimated glomerular filtration rate (eGFR) was found.

Overweight and obese patients are usually hyperleptinemic, serum leptin levels being strongly correlated with BMI. Also, females usually have higher leptin levels than men (Lieb et al 2009). In our study female patients did not present statistically significant higher leptin levels. In the current study, the median serum leptin level was 25 ng/mL in overweight and obese heart failure patients. Serum leptin levels in patients with chronic heart failure have shown previous conflicting results. There are studies correlating hyperleptinemia found in obese patients with a favourable prognosis in heart failure (Van Berendoncks et al 2013; Szabó et al 2014). Other studies suggest that increased leptin may predict progression to HF in patients at high risk (Barbosa-Ferreira et al 2013). In the current study there was no significant relationship between leptin levels and left ventricle ejection fraction. Also, high leptin levels were predictors of HF independent of BMI in patients without pre-existing coronary heart disease. Therefore, the association between obesity and HF may in part be mediated by leptin in patients without pre-existing ischaemic heart disease. On the other hand, other studies have shown decreased leptin levels in patients with HF, especially those with cardiac cachexia or advanced HF. In addition, leptin levels also correlate with the functional class of HF. Richartz et al. demonstrated increased levels of leptin in patients with functional class II and decreased levels in patients with functional class III and IV (Richartz et al 2001).

In the current study leptin was not associated with NT-proBNP. This finding is in line with existing data which shows that only

adiponectin, but not leptin is independently associated with NT-proBNP (Allison et al 2015). But, there are studies showing that leptin remains an important diagnostic and prognostic marker for HF. So, in a population where NT-proBNP levels are highly influenced, leptin may represent an efficient alternative tool for heart failure diagnosis and prognosis.
We have to acknowledge that the relatively small cohort of patients is a major limitation of our study.

Conclusion

NT-proBNP levels in patients with heart failure and overweight or obesity are not significantly influenced by atrial fibrillation. Lower levels of NT-proBNP were found in patients with higher BMI. Moreover, leptin levels were strongly correlated with BMI. But, we found no significantly association between leptin serum levels with NT-proBNP values in overweight and obese patients with or without AF. Even though, leptin doesn't correlate with NT-proBNP levels in this subgroup of patients, it still may represent an important prognostic tool in heart failure patients.

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References

Allison MA, Criqui MH, Maisel AS, Daniels LB, Roberts CK, Polak JF, Cushman M. Adiponectin is independently associated with NT-proBNP:The Multi-Ethnic Study of Atherosclerosis. Nutr Metab Cardiovasc Dis 2015 Aug;25(8):780-6.

Barbosa-Ferreira JM1, Fernandes F, Dabarian A, Mady C. Leptin in heart failure. Expert Opin Med Diagn 2013;7(1):113-7.

Buckley LF, Canada JM, Del Buono MG, Carbone S, Trankle CR2, Billingsley H, Kadariya D, Arena R, Van Tassell BW, Abbate A. Low NT-proBNP levels in overweight and obese patients do not rule out a diagnosis of heart failure with preserved ejection fraction. ESC Heart Fail 2018 Apr;5(2):372-378.

D. Pop, P. Peter, A. Dădârlat, A. Sitar-Tăut, D. Zdrenghea. Serum ghrelin level is associated with cardiovascular risk score. ROM. J. INTERN. MED., 2015, 53, 2, 140–145.

Dadarlat A, Pop D, Procopciuc L. , Buzoianu A. Links between Renin-Angiotensin System Genetic Polymorphisms and Leptin Secretion in Obese Heart Failure Patients. Acta Endo (Buc) 2018 14(2):274-279.

Gruden G, Landi A, Bruno G. Natriuretic peptides, heart, and adipose tissue:new findings and future developments for diabetes research. Diabetes Care 2014;37(11):2899-908.

Hall ME, Harmancey R, Stec DE. Lean heart:Role of leptin in cardiac hypertrophy and metabolism. World J Cardiol. 2015;7(9):511–524.

Horwich TB, Fonarow GC, Clark AL. Obesity and the Obesity Paradox în Heart Failure. Prog Cardiovasc Dis 2018;61(2):151-156.

Jong CJ, Yeung J, Tseung E, Karmazyn M. Leptin-induced cardiomyocyte hypertrophy is associated with enhanced mitochondrial fission. Mol Cell Biochem 2018.

Lieb W, Sullivan LM, Harris TB, Roubenoff R, Benjamin EJ, Levy D, Fox CS, Wang TJ, Wilson PW, Kannel WB, Vasan RS. Plasma leptin levels and incidence of heart failure, cardiovascular disease, and total mortality in elderly individual. Diabetes Care. 2009;32(4):612-6.

Madamanchi C, Alhosaini H, Sumida A, Runge MS. Obesity and natriuretic peptides, BNP and NT-proBNP:mechanisms and diagnostic implications for heart failure. Int J Cardiol 2014;176(3):611-7.

Mathew B, Francis L, Kayalar A, Cone J. Obesity:effects on cardiovascular disease and its diagnosis. J Am Board Fam Med 2008;21(6):562-8.

Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure:The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;27:2129-200.

Richartz BM, Lotze U, Krack A, Gastmann A, Küthe F, Figulla HR. Leptin:a parameter for metabolic changes in heart failure. Z Kardiol. 2001;90(4):280-5.

Szabó T, Scherbakov N, Sandek A, Kung T, von Haehling S, Lainscak M, et al. Plasma adiponectin in heart failure with and without cachexia:catabolic signal linking catabolism, symptomatic status, and prognosis. Nutr Metab Cardiovasc Dis. 2014;24(1):50-6.

Van Berendoncks AM, Garnier A, Ventura-Clapier R, Conraads VM. Adiponectin:key role and potential target to reverse energy wasting in chronic heart failure. Heart Fail Rev. 2013;18(5):557-66.

Wirth J, Buijsse B, di Giuseppe R, Fritsche A, Hense HW, Westphal S, et al. Relationship between N-terminal pro-brain natriuretic peptide, obesity and the risk of heart failure in middle-aged German adults. PLoS One 2014;25;9(11):e113710.

Zheng LH, Wu LM, Yao Y et al. Impact of body mass index on plasma N-terminal ProB-type natriuretic peptides in Chinese atrial fibrillation patients without heart failure. PLoS One 2014;9(8):e105249.

Authors

•Alexandra Dădârlat, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 8 Victor Babeş street, 400012, Cluj-Napoca, Romania, email: dadarlat.alexandra@umfcluj.ro

•Dana Pop, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Clinical Rehabilitation Hospital, 46-50 Viilor street, Cardiology Department, 2nd floor, room 222, Cluj-Napoca, Romania, e-mail: pop67dana@gmail.com

•Dumitru T. Zdrenghea, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Clinical Rehabilitation Hospital, 46-50 Viilor street, Cardiology Department, email: dzdrenghea@yahoo.com

•Gyorgy Bodisz, Clinical Rehabilitation Hospital, 46-50 Viilor street, email: gbodizs@yahoo.com

•Florina Fringu, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 8 Victor Babeş street, 400012, Cluj-Napoca, Romania, email: florina.fringu@yahoo.ro

•Diana Gurazau, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 8 Victor Babeş street, 400012, Cluj-Napoca, Romania, email: gurzaudiana@yahoo.com

•Silvana Susca-Hojda, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, 8 Victor Babeş street, 400012, Cluj-Napoca, Romania, email: hojda.silvana@umfcluj.ro

•Anca D. Buzoianu, "Iuliu Haţieganu" University of Medicine and Pharmacy, Dept. of Pharmacology, Toxicology and Clinical Pharmacology, 23 Marinescu street, Cluj-Napoca, Romania, email: abuzoianu@umfcluj.ro.

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