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The effect of BMI, serum leptin, and adiponectin levels on prognosis in patients with non-ischaemic dilated cardiomyopathy

Wpływ BMI, stężenia leptyny i adiponektyny na rokowanie u pacjentów z niedokrwienną kardiomiopatią rozstrzeniową

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Abstract

Introduction: The recent studies demonstrated that obese heart failure patients have better prognosis — "obesity paradox". The aim of the study was to evaluate the relationship between body mass index (BMI), leptin and adiponectin concentrations and prognosis in patients with heart failure due to non ischeamic dilated cardiomyopathy (NIDCM).

Material and methods: 128 patients with NIDCM were included and followed-up for three years. Leptin and adiponectin were measured at baseline using commercially available ELISA tests. Clinical data, routine laboratory parameters, NT–proBNP were assessed as risk factors for reaching the study endpoints: urgent heart transplantation (B), death (C), or combined endpoint death or urgent heart transplantation (D).

Results: Patient with adverse outcome had lower BMI and higher NT-proBNP concentration. Leptin was significantly elevated in group C and adiponectin was higher in groups B and D than in survived patients. Patients with leptin concentration below median or with adiponectin concentration above median were more often transplanted in three years follow-up ($p = 0.029$, $p = 0.022$, respectively). The cumulative probability of death was greater in patients with concentration of leptin above median ($p = 0.024$). In the multivariable Cox proportional hazards analyses, increasing leptin and lower BMI were predictors of death. Adiponectin was associated with higher risk of heart transplantation. Both an inverse association of BMI and positive association of leptin and adiponectin with combined endpoint were discovered. Further adjustment to established risk factors abolished association between combined endpoint and BMI, and modestly attenuate with adiponectin and leptin concentration.

Conclusion: Evaluation of adiponectin and leptin concentrations was more useful than BMI in prediction of unfavourable outcome in patients with NIDCM. **(Endokrynol Pol 2017; 68 (1): 26–34)**

Key words: *leptin; adiponectin; BMI; dilated cardiomyopathy; heart failure*

Streszczenie

Wstęp: Badania ostatnich lat wykazały, że otyli pacjenci z niewydolnością serca mają lepsze rokowanie — „paradoks otyłości". Celem badania było określenie relacji między wskaźnikiem masy ciała (BMI) a stężeniami leptyny i adiponektyny w aspekcie rokowania u pacjentów z niewydolnością serca z powodu kardiomiopatii o etiologii innej niż niedokrwienna.

Materiał i metody: Do badania włączono 128 pacjentów z kardiomiopatią nie- niedokrwienną, których obserwowano przez trzy lata. Stężenie leptyny i adiponektyny oznaczono przy włączeniu do badania przy użyciu dostępnych komercyjnych testów ELISA. Dane kliniczne, rutynowe parametry laboratoryjne, NT-proBNP oceniano jako czynniki ryzyka dla osiągnięcia punktów końcowych: pilnej transplantacji serca (B), śmierci (C) lub złożonego punktu końcowego śmierci, lub pilnej transplantacji serca (D).

Wyniki: Pacjenci, którzy osiągnęli punkt końcowy z mieli niższe BMI i wyższe stężenie NT-proBNP. Stężenie leptyny było znacząco podwyższone w grupie C, a stężenie adiponektyny było wyższe w grupie B i D, w porównaniu z pacjentami którzy nie osiągnęli punktu końcowego. Pacjenci ze stężeniem leptyny poniżej mediany lub adiponektyny powyżej mediany częściej wymagali przeszczepu w trybie pilnym w ciągu trzech lat obserwacji ($p = 0.029$, $p = 0.022$, odpowiednio). Skumulowane prawdopodobieństwo zgonu było większe u pacjentów ze stężeniem leptyny powyżej mediany ($p = 0.024$). W wieloczynnikowej analizie proporcjonalnego ryzyka Coxa, wyższ e stężenie leptyny i niższe BMI były predyktorami zgonu. Adiponektyna była predyktorem transplantacji serca. Wykazano odwrotną korelację z BMI i pozytywną z leptyną i adiponektyną dla złożonego punktu końcowego. Uwzględnienie w analizie wieloczynnikowej ustalonych czynników ryzyka wyeliminowało BMI jako predyktor złożonego punktu końcowego a tylko nieznacznie wpłynęło na znaczenie prognostyczne adiponektyny i leptyny.

Wniosek: Oznaczenia stężeń adiponektyny i leptyny były bardziej użyteczne niż BMI w przewidywaniu niekorzystnych zdarzeń u pacjentów z kardiomiopatią rozstrzeniową. **(Endokrynol Pol 2017; 68 (1): 26–34)**

Słowa kluczowe: *leptyna; adiponektyna; BMI; kardiomiopatia rozstrzeniowa; niewydolność serca*

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Introduction

Non-ischaemic dilated cardiomyopathy (NIDCM) is a primary disease of the myocardium, which is characterised by dilatation and impaired function of left or both ventricles, leading to chronic heart failure (HF). Although the integrated therapeutic approach has improved the long-term prognosis of NIDCM during the last decade, in some cases the course is severe with rapid progression to end-stage heart failure and death [1]. Elevated natriuretic peptide levels are commonly known as laboratory markers for the diagnosis and assessment of HF severity in NIDCM. However, identification of a subgroup of patients with poor prognosis due to progressive HF or sudden cardiac death remains a challenge. Chronic HF is known as the status of many neurohormonal disturbances, and proinflammatory activation that promotes the catabolic processes with cachexia in the end stage of disease. Enhanced lipolysis and release of free fatty acids from adipose tissue is observed. The results of some recent studies have demonstrated the unexpected finding that obese patients have better prognosis. This phenomenon called the "obesity paradox" is not precisely explained but may be associated with the endocrine function of adipose tissue [2, 3]. It may be possible that adipokines, like leptin and adiponectin, could be involved in pathophysiology of HF [4]. Hyperleptinaemia is associated with HF in the absence of obesity and may have protective effects in HF [5]. On the other hand, higher leptin levels are associated with progression of HF [6].

Adiponectin levels are reduced in obesity, diabetes mellitus, and hypertension but paradoxically are elevated in HF. Higher concentrations of adiponectin are connected with worse prognosis in chronic HF [7]. A limited number of studies have evaluated the associations between leptin and adiponectin concentrations with prognosis in subjects with NIDCM. Concerning biomarkers in prognostic stratification could be useful to identify the patients of unfavourable prognosis, who should be monitored more intensively. The objective of the study was to evaluate relationships between body mass index (BMI), leptin and adiponectin concentrations, and prognosis of HF due to NIDCM.

Material and methods

We recruited 128 patients with NIDCM, diagnosed according to the WHO criteria, hospitalised in our centre (2nd Department of Cardiology) in 2008–2010 for assessment including generally invasive procedure. Patients were clinically stable and their therapy was not changed for at least one month before enrolment. Heart transplantation was considered as a therapeutic option in patients who met standard criteria for this procedure. Exclusion criteria were: valvular heart disease, connective tissue disease, inflammatory or infectious disorders, and diseases which, by themselves, could reduce survival. All patients received optimal conventional HF therapy according to current guidelines. Follow-up visits were conducted on an outpatient basis according to clinical status not less than every six months, for three years. None of the patients was lost to follow-up. The study protocol was approved by the Bioethics Committee of the Medical University of Silesia. Written informed consent was obtained from all enrolled patients.

Clinical assessment

The NYHA classification was used to assess functional capacity. BMI was calculated according to the following formula: weight in kilograms divided by the square of the height in metres. Physical examination, ECG, and echocardiography (VIVID 7, GE) were performed. Left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were obtained from the apical four- and two-chamber views by the modified Simpson's method. Left ventricular ejection fraction (LVEF) was calculated as follows: (EDV–ESV) x 100 / EDV to determine ventricular systolic function.

Biochemical methods

Blood samples for laboratory assessments were obtained from the patients on the day of clinical assessment at the start of the study. 10 mL of blood was drawn from the antecubital vein of all patients. 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 and adiponectin were measured using ELISA method (Human Leptin Quantikine kit, Human Total Adiponectin Quantikine kit, R&D System, Abingdon Science Park, United Kingdom). Calibration of the assay was performed according to the manufacturer's recommendations. Blood haemoglobin, sodium, creatinine, and lipid parameter concentrations were determined using routine techniques on Roche Cobas Integra 800. NT-proBNP was measured by chemiluminescence method on Roche Cobas 6000e501 (Roche Diagnostics GmbH, Mannheim, Germany). The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using a Cockcroft-Gault Equation.

Endpoints of study

Death, urgent heart transplantation or combined endpoint death, or urgent heart transplantation

Statistical analysis

The entire study group was divided, for the purpose of the analysis, depending on the outcome: A — patients

who survived without endpoints, B — patients who were transplanted, C — patients who died, and D — patients who achieved combined endpoint. Normality of the distribution of the continuous data in the whole group of patients and in subgroups was analysed by Shapiro-Wilk test. Categorical data were presented as numbers and percentages, and continuous data were expressed as the median and interquartile range (25–75%). The significance of baseline differences between groups were determined using the Chi^2 test with Yates correction or the unpaired "U" Mann-Whitney test, as appropriate. Spearman correlation coefficient was counted for particular parameters. Cumulative survival curves were constructed as time to the endpoint by Kaplan-Meier methods, and the differences between normal, overweight, and obese patients, and leptin and adiponectin concentrations below and above the median value were tested for significance by the log-rank test. In multivariable Cox proportional hazard analyses, the association between serum leptin, adiponectin, BMI, and endpoints was examined. Those parameters were treated as continuous variables and were included in the basic model 1. Furthermore, model 1 was adjusted to variables that were known as prognostic markers of HF or were significantly different in subgroups depending on prognosis — model 2. The results were considered statistically significant if $p < 0.05$. Statistical analysis was performed with Statistica 10.0 software (Statsoft Inc., Tulsa, USA).

Results

Baseline patient's clinical characteristics and medical treatment

A total of 128 patients (21 females, 107 males) with NIDCM were enrolled into the study. The median age of patients was 46.26 (37.25–54.80) years, and the duration of disease was 4.74 (1.60–6.94) years. They presented severe left ventricle systolic dysfunctions with ejection fraction 24.0 % (18.00–28.50). Most of the patients (64.84%) were in NYHA functional class I and II at the time of enrolment into the study. From the entire group 38 (29.7%) patients were of normal weight, 58 (45.3%) were overweight (25–29.9 kg/m^2), and 32 (25.0%) were obese (≥ 30 kg/m^2) — defined on the basis of WHO definitions. In three-year follow-up 14 (10.9%) patients underwent heart transplantation, and 15 (11.7%) patients died. The baseline clinical characteristics of patients divided according to the outcomes are presented in Table I.

Except for the BMI, echocardiography parameters, and NYHA functional class, other demographic and

Table I. *Demographic, clinical, and selected echocardiography data in the whole group and subgroups separated according to prognosis*

Tabela I. *Dane demograficzne, kliniczne i wybrane echokardiograficzne w całej grupie chorych i podgrupach w zależności od rokowania*

	A -survivors n = 99	B -OHT n = 14	C -Death n = 15	D -OHT or Death n = 29
sex (female) n (%)	16 (16.16)	1 (7.14)	4 (26.67)	5 (17.2)
Age (years)	49.23 37.62–54.69	47.88 37.43–49.83	49.55 35.24–56.47	45.75 35.55–55.94
BMI [kg/m^2]	27.76 (25.78–31.22)	25.31 (23.96–29.05)	26.23 (23.77–30.19)	25.82 (23.81–29.70)
NYHA class I–II/III–IV (%)	72/27 (72.72/27.28)	4/10*** (28.57/71.43)	7/8 (46.67/53.33)	11/18** (37.93/62.07)
Duration of illness (years)	3.21 (1.35–6.92)	5.05 (2.13–8.84)	4.16 (2.41–6.35)	4.64 (2.41–7.82)
ICD n (%)	35 (35.35)	7 (50.0)	3 (20.00)	10 (34.48)
AH n (%)	23 (23.23)	2 (14.29)	6 (40)	8 (31.03)
DM t.2 n (%)	10 (10.10)	1 (7,14)	1 (6.67)	2 (6.90)
AF n (%)	26 (26.26)	4 (28.57)	4(26.67)	8 (27.59)
LVEF (%)	25.0 (20.0–30.0)	15.0*** (15.0–20.0)	20,0 (15.0–28.0)	19.0*** (15.0–21.0)
LVEDV [mL]	188.0 (153.0–247.00)	216.0 (164.0–254.0)	247.0* (200.0–340.0)	232.0* (180.0–275.0)
LVEDD [mm]	67.00 (61.0–74.0)	72.5 (68.0–79.0)	69.00 (65.0–80.0)	71.00* (66.0–79.0)

Statistical significance: *$p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ when compared to A group; OHT — orthotopic heart transplantation, BMI — body mass index, NYHA class — New York Heart Association functional class, ICD — implantable cardioverter-defibrillator, AH — arterial hypertension, DM t.2 — diabetes mellitus t.2, AF — atrial fibrillation, LVEF — left ventricle ejection fraction, LVEDV — left ventricle end-diastolic volume, LVEDD — left ventricle end-diastolic diameter

Table II. *Pharmacological treatment in the whole group and subgroups separated according to prognosis*
Tabela II. *Leczenie farmakologiczne w całej grupie chorych i podgrupach w zależności od rokowania*

	A survivors (n = 99)	B OHT (n = 14)	C Death (n = 15)	D OHT or Death (N = 29)
BB n (%)	94 (94.9)	13 (92.9)	14 (93.3)	27 (93.1)
ACE-I n (%)	93 (93.9)	12 (85.7)	14 (93.3)	26 (89.7)
ARB n (%)	35 (35.4)	4 (28.6)	5 (33.3)	9 (31.0)
MRA n (%)	86 (86.9)	14 (100)**	15 (100) ***	29 (100)***
AM n (%)	9 (9.10)	2 (14.3)	4 (26.7)	6 (20.7)
LD n (%)	52 (52.5)	9 (64.3)	11 (73.3)	20 (69.0)
TD n (%)	19 (19.2)	3 (21.4)	4 (26.7)	7 (24.1)
OAK n (%)	46 (46.5)	6 (42.9)	7 (46.7)	13 (44.8)
DIG n (%)	47 (47.5)	10 (71.4)	14 (93.3) **	24 (82.8)*

Statistical significance: *p < 0.05; **p < 0.01; ***p < 0.001 when compared to A group; OHT — orthotopic heart transplantation, BB — β-blocker, ACE-I — angiotensin-converting enzyme inhibitors, ARB — angiotensin receptor blockers, MRA — mineralocorticoid receptor antagonists, AM — amiodarone, LD — loop diuretics, TD — thiazide diuretic, OAK — oral anticoagulation, DIG — digitalis

Table III. *Level of serum biomarkers in the whole group and subgroups separated according to prognosis*
Tabela III. *Stężenie biomarkerów w surowicy w całej grupie chorych i podgrupach w zależności od rokowania*

	A survivors (n = 99)	B OHT (n = 14)	C Death (n = 15)	D OHT or Death (n = 29)
NT-proBNP [pg/mL]	795.0 (340.0–1610)	2584 *** (1589–4548)	2066 ** (1085–3000)	2230*** (1328–3000)
eGFR [ml/min]	120.0 (99.23–145.2)	105.5 (77.08–135.8)	100.5* (86.87–116.3)	101.2** (85-87–120.0)
sodium [mmol/L]	137.0 (135.0–139.0)	136.0 (130.0–137.0)	136.0 (131.0–141.0)	136.0 (131.0–139.0)
Leptin [ng/mL]	5.62 (3.42–12.77)	3.29 ^ ^ (2.45–5.16)	14.67 ** (5.72–27.10)	5.72 (3.34–15.59)
Adiponectin [μg/mL]	2.05 (1.45–3.71)	5.23 ** (2.62–9.98)	2.42 (2.21–3.65)	3.40* (2.26–6.23)
Haemoglobin [g/dL]	146.0 (134.0–155.0)	133.0 ** (129.0–140.0)	132.0 * (124.0–154.0)	133.0** (126.0–141.0)
cholesterol [mg/dL]	185.0 (160.0–217.0)	169.0 (138.0–193.0)	160.0 (123.0–213.0)	168.50* (127.0–193.5)
HDL [mg/dL]	42.70 (36.60–54.70)	33.00** 27.00–40.00)	34.0 (22.80–57.10	33.50** (26.35–49.10)
Triglycerides [mg/dL]	129.5 (102.0–198.0)	97.00* (76.00–140.0)	86.00** (78.00–143.0)	91.5*** (77.50–141.50)

OHT — orthotopic heart transplantation, NT-proBNP — N-terminal pro-B-type natriuretic peptide, eGFR — estimated glomerular filtration rate, Statistic significance: *p<0.05; **p < 0.01; ***p < 0.001 when compared to A group, ^ ^p<0.01 group C *vs.* B

clinical parameters did not differ significantly between studied groups (Table I). Patients from groups B, C, and D significantly often received MRA, and from groups C and D — digoxin (Table II).

Adipokines and laboratory parameters assessment and their correlations in all NIDCM groups

Leptin concentration was significantly elevated in group C, and adiponectin concentrations were higher in groups B and D than in group A. Patients of groups B, C, and D had significantly higher NT-proBNP concentrations when compared to group A. In addition, lower concentrations of haemoglobin and triglycerides were found in these groups. HDL cholesterol levels were significantly lower in groups B and D than in group A, and total cholesterol concentration was lower in group D when compared with group A. eGFR was lower in groups C and D compared to group A (Table III). The

Table IV. *Correlations between adipokines, BMI, and laboratory and echocardiographic parameters in all dilated cardiomyopathy patients*

Tabela IV. *Korelacje pomiędzy adipokinami, BMI oraz parametrami laboratoryjnymi i echokardiograficznymi w całej grupie chorych z kardiomiopaią rozstrzeniową*

	Adiponectin		Leptin		BMI	
	R	p	R	p	R	p
Leptin	–0.264	0.003	x	x	0.322	0.000
BMI	–0.182	0.040	0.322	0.000	x	x
age	–0.031	0.727	–0.005	0.952	0.165	0.063
NTproBNP	0.065	0.467	–0.134	0.134	–0.221	0.012
eGFR	–0.073	0.424	0.082	0.371	0.364	0.000
Sodium	–0.015	0.873	0.112	0.217	0.159	0.079
Haemoglobin	–0.048	0.594	–0.058	0.513	0.085	0.341
Total cholesterol	–0.105	0.240	0.115	0.199	0.125	0.164
HDL	–0.080	0.374	0.028	0.757	–0.049	0.587
Triglycerides	–0.206	0.020	0.178	0.047	0.522	0.000
NYHA	0.175	0.049	–0.132	0.138	–0.043	0.634
LVEF	–0.087	0.330	0.113	0.204	0.045	0.614
EDD	0.003	0.977	0.161	0.070	0.055	0.541
EDV	–0.090	0.310	0.165	0.063	0.038	0.669

BMI — body mass index, NT-proBNP — N-terminal pro-B-type natriuretic peptide, eGFR — estimated glomerular filtration rate, NYHA class — New York Heart Association functional class, LVEF — left ventricle ejection fraction, LVEDD — left ventricle end-diastolic diameter, LVEDV — left ventricle end-diastolic volume

associations among adipokines, BMI, and laboratory and echo parameters are shown in Table IV.

Follow-up and predictors of unfavourable outcomes

Kaplan-Maier curves estimated endpoint-free survival rate depending on BMI and on median of leptin and adiponectin concentrations were shown in Figures 1–3. Normal-weight patients showed lower endpoint-free survival rate than overweight or obese patients (with clinical significance for combined endpoint $p = 0.013$). Patients with leptin concentration below median or with adiponectin concentration above median were more often transplanted in three years of follow-up ($p = 0.029$, $p = 0.022$, respectively). The cumulative probability of death was greater in patients with concentration of leptin above median ($p = 0.024$)

In the multivariable Cox proportional hazards analyses, increasing leptin concentration and lower BMI were predictors of death. Additional adjustment to NYHA class, LVEF, and serum NT-proBNP, haemoglobin, total cholesterol, HDL, and triglycerides concentrations (model 2) did not attenuate the association between leptin and death ($p < 0.001$). Adiponectin was associated with higher risk of heart transplantation in model 1 ($p = 0.005$) and model 2 ($p = 0.005$). Both an inverse association of BMI and positive association of leptin and adiponectin with combined endpoint were discovered. Further adjustment in model 2 abolished association between combined endpoint and BMI, and modestly attenuate with adiponectin ($p = 0.033$) and leptin concentration ($p = 0.021$) (Table V).

Discussion

Numerous investigators have demonstrated that lower BMI is associated with worse survival in patients with HF [8]. Consistent with the previous studies, we have confirmed the negative effect of BMI on mortality or combined endpoint. However, this effect was completely abolished if we introduced to analysis the widely accepted clinical markers of poor prognosis: haemoglobin and lipid status. The obtained results may be affected because of the fact that BMI reflects the combined mass of adipose and non-adipose tissue. Therefore, despite the stable condition of patients, in some cases BMI can be overestimated due to congestion. In the present study we demonstrated that serum leptin and adiponectin levels in stable condition are more useful factors in predicting adverse outcome in NIDCM patients than BMI. We would emphasise that, as well as accepted prognostic marker NT-proBNP, haemoglobin and lipids assays also appeared as informative risk factors. In particular, haemoglobin concentration was lower in patients with poor prognosis.

Table V. *Multivariable Cox proportional hazard analyses of endpoints. Model 1 and Model 2*
Tabela V. *Analiza wystąpienia punktów końcowych, wieloczynnikowy model proporcjonalnego hazardu Coxa. Model 1 i Model 2*

	OHT		Death		OHT or death	
Model 1						
Variable	**Hazard ratio (95%CI)**	**p**	**Hazard ratio (95%CI)**	**p**	**Hazard ratio (95%CI)**	**p**
BMI [1 kg/m^2]	0.90 (0.78–1.03)	0.111	0.87 (0.77–0.98)	0.027	0.89 (0.81–0.97)	0.007
Adiponectin [1 μg/mL]	1.08 (1.02–1.13)	0.005	0.97 (0.82–1.15)	0.747	1.06 (1.01–1.11)	0.022
Leptin [1 ng/mL]	0.99 (0.92–1.05)	0.693	1.04 (1.02–1.07)	0.001	1.03 (1.01–1.05)	0.014
Model 2						
BMI [1 kg/m^2]	0.99 (0.84–1.16)	0.908	1.01 (0.88–1.16)	0.909	1.00 (0.90–1.10)	0.987
Adiponectin [1 μg/mL]	1.10 (1.03–1.18)	0.004	0.99 (0.85–1.15)	0.864	1.06 (1.00–1.11)	0.035
Leptin [1 ng/mL]	0.99 (0.93–1.05)	0.708	1.05 (1.02–1.09)	0.001	1.03 (1.00–1.05)	0.021
NYHA class [I class]	2.82 (1.14–6.99)	0.025	1.41 (0.51–3.86)	0.508	1.84 (1.00–3.38)	0.049
LVEF [1%]	0.85 (0.75–0.97)	0.015	1.00 (0.92–1.08)	0.960	0.95 (0.90–1.01)	0.105
NT-proBNP [100 pg/mL]	1.06 (1.01–1.10)	0.015	1.02 (0.98–1.07)	0.375	1.03 (1.00–1.06)	0.043
Haemoglobin [1 g/d/]	0.95 (0.90–1.00)	0.067	0.98 (0.94–1.01)	0.209	0.96 (0.93–0.99)	0.021
Cholesterol [1 mg/dL]	1.02 (1.00–1.03)	0.012	1.01 (0.99–1.02)	0.317	1.01 (1.00–1.02)	0.041
HDL [1 mg/dL]	0.96 (0.92–1.01)	0.135	0.97 (0.94–1.01)	0.132	0.98 (0.95–1.00)	0.071
Triglycerides [1 mg/dL]	0.99 (0.98–1.01)	0.494	0.98s (0.97–1.00)	0.017	0.99 (0.98–1.00)	0.040

OHT — orthotopic heart transplantation, BMI — body mass index, NYHA class — New York Heart Association functional class, LVEF — left ventricle ejection fraction, NT-proBNP — N-terminal pro-B-type natriuretic peptide

Leptin is mainly secreted by adipocytes, and serum concentrations directly correlate with adipose tissue mass. It is also secreted by vascular smooth muscle cells and cardiomyocytes. This adipokine affects the glucose and lipid metabolism, and high levels of serum leptin contribute to such cardiovascular risk factors as dyslipidaemia and insulin resistance. The impact of leptin on the cardiovascular system also includes activation of sympathetic nervous system and initiation of haemodynamic effects involving increased heart rate and blood pressure. Hyperleptinaemia is involved in the pathogenesis of obesity-related hypertension and diabetes mellitus. Different studies have linked higher leptin concentrations with the presence of coronary artery disease [9], ischaemic cerebral stroke [10] and heart dysfunction [4]. However, investigators from the Multi-Ethnic Study of Atherosclerosis have revealed that serum leptin concentrations were not associated with incident cardiovascular events [11].

Growing evidence suggests that leptin can regulate metabolism and function of the heart, and may contribute to HF. Leptin receptors are highly expressed in the heart, and this adipokine may exert effects through central and direct mechanisms [12].

In a study conducted by Bobbert et al. [6] hyperleptinaemia was associated with HF progression in patients with NIDCM. In contrast, Wannamethee et al. demonstrated inverse association of leptin with mortality in HF patients [13]. Results obtained in the Framingham Heart Study have showed that a nonlinear, U-shaped relation between leptin and mortality was observed, with greater risk of all-cause (but not cardiovascular) death evident at both low and high leptin levels [14]. Our results are consistent with those previous reports.

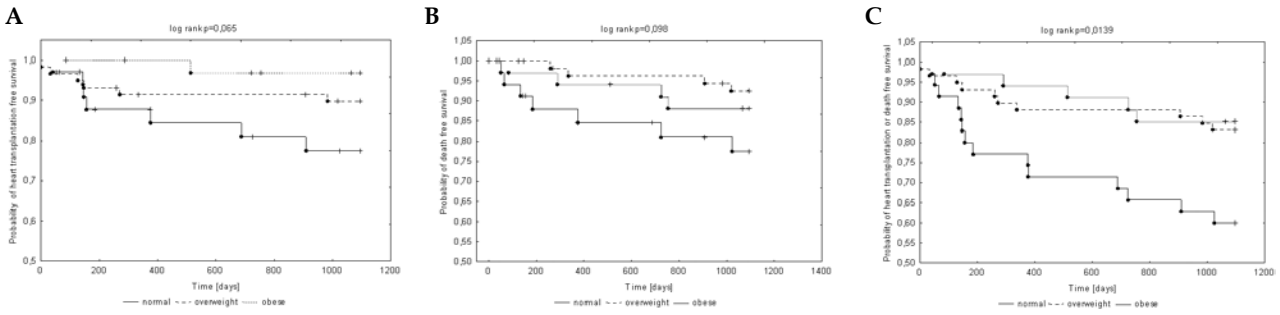

Figure 1. *Kaplan-Meier curve and log rank analysis. Event-free survival plot for body mass index and endpoints*

Rycina 1. *Krzywe przeżycia Kaplana-Meiera i analiza log rank. Czas przeżycia wolny od punktów końcowych w zależności od BMI*

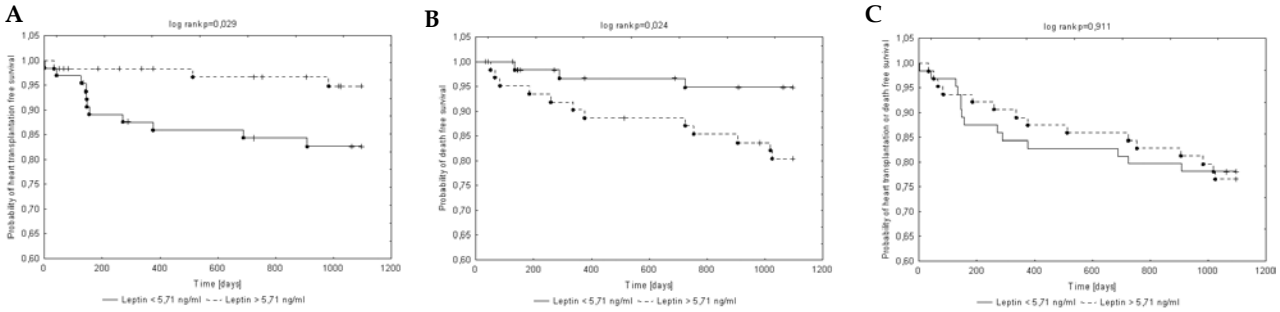

Figure 2. *Kaplan-Meier curve and log rank analysis. Event-free survival plot for leptin concentrations and endpoints*

Rycina 2. *Krzywe przeżycia Kaplana-Meiera i analiza log rank. Czas przeżycia wolny od punktów końcowych w zależności od stężenia leptyny.*

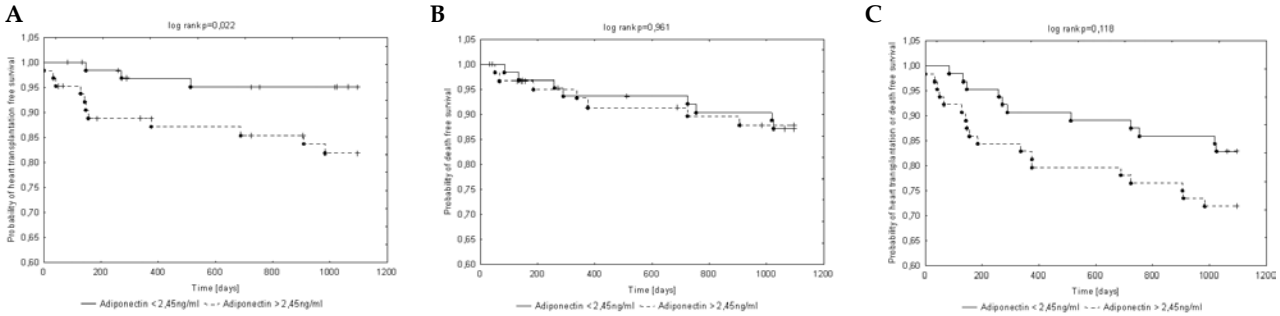

Figure 3. *Kaplan-Meier curve and log rank analysis. Event-free survival plot for adiponectin concentrations and endpoints*

Rycina 3. *Krzywe przeżycia Kaplana-Meiera i analiza log rank. Czas przeżycia wolny od punktów końcowych w zależności od stężenia adiponektyny.*

We demonstrated that higher leptin concentration was a predictor of death even after adjustment for the established factors, but low leptin concentration was a strong predictor of progression of disease leading to heart transplantation. These unexpected findings suggest that leptin may have diverse-deleterious and counterbalance roles in HF. Higher leptin levels are likely to reflect the mass of adipose tissue, but lower levels may be associated with loss of protective effects of this adipokine in HF. Wannamethee et al. suggest that leptin neutralises the detrimental influence of tumour necrosis factor α in HF [13]. Other investigators have shown that leptin exerts beneficial effects on myocardial fatty acid and glucose metabolism and normalises diastolic dysfunction [12]. It is obvious that adipokine attenuates cardiac apoptosis and protects against heart lipotoxicity. In experimental studies locally produced leptin via multiple cell signalling mechanisms induces hypertrophy [15,16], but there are a few reports that documented its antihypertrophic effect [5].

Adiponectin is an adipocyte-derived peptide whose plasma concentrations are reduced in obesity [17]. Similarly to leptin, cells other than adipocytes can produce adiponectin. This adipokine has antiatherogenic, anti-inflammatory, and antidiabetic properties. Decreased levels are observed in insulin resistance, diabetes

mellitus type 2, proinflammatory states, and lipodystrophies. Although adiponectin is considered to have a beneficial effect on cardiovascular disease, the results concerning serum adiponectin concentration as a risk factor of heart disease and cardiovascular mortality are inconclusive [18, 19]. Its higher levels are paradoxically associated with worse prognosis among patients with HF. Bogomolovas et al. revealed that serum adiponectin is increased in end-stage dilated cardiomyopathy [20]. It was confirmed by George et al. that adiponectin was a predictor of total mortality, hospitalisations, or a composite of these endpoints over a two-year prospective follow-up in congestive HF patients [7]. Increased adiponectin was associated with higher mortality in ischaemic but not in non-ischaemic HF Japanese patients [21]. In our observation higher concentration of adiponectin was related to urgent heart transplantation and to combined endpoint in NIDCM patients, which is partly consistent with the results obtained by Yin et al. [22]. However, we demonstrated that higher concentration of adiponectin was not a predictive marker for death, and in this aspect our results are concordant with the findings of Tamura et al. [21].

The results of existing studies concerning the role of adiponectin in HF are contradictory. An auto/paracrine adiponectin regulation within the heart in patients with dilated cardiomyopathy was described. The experimental study suggests cardioprotective effects of adiponectin against the development of systolic dysfunction. The reduction of left ventricular hypertrophy and interstitial fibrosis [23] and attenuation myocyte damage in viral myocarditis [24] were observed. However, cardiomyocytes adiponectin downregulation was independent of adiponectin serum levels in dilated cardiomyopathy [25].

The associations of adipokines and prognosis are not clearly understood, and our study does not explain the nature of those relationships. Some authors described the positive correlations between adiponectin, severity of HF, and NT-proBNP [7, 21], whereas Melenovsky et al. found an inverse relationship between plasma BNP and concentrations of leptin in HF patients [26]. We observed no correlation with leptin or adiponectin concentration. In accordance with previous studies we found inverse correlation between BMI and NTproBNP in all groups. The mechanisms remain unclear, but it appears that direct activation of lipolysis in adipocytes by natriuretic peptides may be responsible for the loss of adipose tissue and may explain the obesity paradox [27,28]. Since leptin and adiponectin are related with body mass, we speculate that those adipokines could be a link between obesity paradox and natriuretic peptides [29]. In our study triglycerides correlated positively with BMI and leptin and negatively with adiponectin. Higher concentrations of triglycerides appeared to protect patients from death or combined endpoint. According to previous observations, higher circulating lipoproteins in obese patients may bind and detoxify lipopolysaccharides increased in patients with heart failure. Therefore, they play a role as an inhibitor of disadvantageous inflammation process [30]

Limitations of the study: First, although the sample size was representative for NIDCM, the study was limited by the number of endpoints. Secondly, lack of data about BMI before study enrolment did not allow the exclusion that some patients might have had an increased catabolic state. Thirdly, we knew only the BMI (without ratio of fat to muscle mass). Finally, we did not measure levels of receptor for adipokines or inflammatory markers.

However, it is worth noting that our study is a first in the Polish population, and the benefit of the work is that we assessed a group of patients with homogenous non-ischaemic aetiology of dilated cardiomyopathy. Our NIDCM patients were younger (47 ± 10 years) than patients in other studies with mixed or ischaemic aetiology, and the percentage of comorbidities like arterial hypertension and diabetes mellitus was lower; therefore, the three-year mortality rate was relatively low at 11.7% and transplant-free survival was 89.1% [8, 13].

Conclusions

The results of this study have shown that leptin and adiponectin could be better risk markers for prognosis in patients with NIDCM than BMI.

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