VIA MEDICA

ORIGINAL ARTICLE

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Selected adipocytokine concentrations in patients hospitalized for exacerbated chronic heart failure

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Medical Research Journal 2022; Volume 7, Number 2, 142–150
10.5603/MRJ.a2022.0021

ISSN 2451-2591
e-ISSN 2451-4101

ABSTRACT

Introduction: The role of adipose tissue as energy storage and endocrine organ is an area of interest in the treatment of several diseases. This study aimed to to evaluate blood adiponectin (ADP), leptin, tumor necrosis factor type alpha (TNF-alpha) concentrations, and their prognostic value in patients with exacerbated chronic heart failure (CHF).

Methods and results: The following were assessed in 64 consecutive patients hospitalized for exacerbated CHF and a control group of 32 age and sex-matched individuals admitted due to life-limiting symptoms of peripheral artery disease: serum leptin, ADP, TNF-alpha concentrations, and body composition determined by bioelectrical impedance analysis. Compared to the control group, CHF patients had significantly higher blood ADP concentrations, a higher ratio of ADP to fat mass expressed as a percentage of body mass, and lower blood TNF-alpha concentrations and ratios of TNF-alpha to the visceral fat level (VFL). Compared to patients who survived, patients with CHF who died during the one-year follow-up had significantly higher values of ADP and higher ratios of ADP to body surface area. In the Cox regression model, blood ADP concentration was the only independent risk factor in respect of all-cause mortality during the one-year follow-up (HR; 95% CI: 1.16; 1.03-1.31).

Conclusions: Patients with CHF present dysregulation in the secretion of ADP and TNF-alpha. Increased blood ADP concentration was associated with an increase in one-year all-cause mortality by 16%.

Key words: chronic heart failure; adipocytokines; adiponectin; tumor necrosis factor alpha; leptin; prognosis

Med Res J 2022; 7 (2): 142–150

Introduction

An inflammatory response is recognized as an important cause of cardiovascular disease development and progression, including chronic heart failure (CHF) [1]. A patient's nutritional status, both excessive (i.e., overweight or obesity) and deficient (i.e., malnutrition or cachexia), is considered one potential source of chronic subclinical inflammatory status, which is mediated by, among other factors, adipocytokines, which are secreted by adipose tissue and regulate various body functions.

Tumor necrosis factor alpha (TNF-alpha) is the adipocytokine investigated most often in patients with CHF. It exerts pro-inflammatory and pro-fibrotic activity, and increased blood TNF-alpha concentration is recognized as a risk factor for cardiovascular disease progression [2–4]. However, this negative effect of TNF-alpha is not found in all studies [3]. Moreover, a randomized trial failed to show any benefits from anti-TNF-alpha biological treatment with etanercept in patients with CHF [3].

Leptin regulates energy intake (satiety hormone), energy balance, and metabolism [5, 6]. However, as it is also involved in pro-inflammatory and pro-fibrotic activity, it may stimulate oxidative stress, inflammation, thrombosis, arterial stiffness, angiogenesis, and atherogenesis [5–7]. Such properties of leptin signaling deficiency or leptin resistance are a potential factor involved in the pathogenesis of cardiac and vascular dysfunction and/or failure, as well as being recognized as a cause of negative electrical and structural heart remodeling [6, 7]. However, not all studies confirm this effect of leptin [6, 8–11].

Adiponectin (ADP) is the only adipocytokine that is recognized as cardioprotective [12]. It is shown to have anti-diabetic, anti-atherogenic, and anti-inflammatory properties in experimental studies [6–9], and to regulate cardiac and vascular remodeling [7, 13]. Nevertheless, in patients with CHF, the ADP level gradually increases with the severity of the disease and a higher ADP level is a factor of poor prognosis (the "adiponectin paradox"). Nevertheless, as with leptin and TNF-alpha, the outcomes of clinical studies concerning the relationship between blood ADP concentration and cardiovascular risk are ambiguous [12–17]. The adiponectin paradox, defined as an increased cardiovascular risk despite cardioprotective ADP properties, can be explained with reference to ADP resistance [16].

In the context of an increased interest in biomarkers that aid diagnosis, risk stratification, and the monitoring of the course of CHF, we compared blood concentrations of selected adipocytokines (i.e., TNF-alpha, leptin, and ADP) in patients with exacerbation of ischemic CHF caused by severe coronary artery atherosclerosis and patients with symptomatic atherosclerosis of lower limbs arteries. We also evaluated the prognostic value of TNF-alpha, leptin, and ADP in patients with ischemic CHF during a one-year observation period.

Material and methods

Patients

We enrolled in the study 64 consecutive patients who had been hospitalized in an urban university hospital for exacerbation of ischemic CHF diagnosed in accordance with the European Society of Cardiology (ESC) recommendations [18]. The severity of CHF exacerbation in these patients was class III or IV on the New York Heart Association (NYHA) classification system. The control group comprised 32 age- (within 2 years) and sex-matched patients (2:1) treated in the same clinic for life-limiting intermittent claudication (IC), without necrosis and any clinical or laboratory (e.g., N-terminal pro B-type natriuretic peptide [NT-proBNP] < 400 pg/mL) indications of CHF. The rationale for comparing CHF and IC patients was that both groups present different clinical manifestations of atherosclerosis. Patients were enrolled in the study between May 01, 2016, and February 21, 2018.

On the first day of hospitalization, a medical history was obtained from each patient enrolled in the study. A physical examination, biochemical determinations, and transthoracic echocardiography (Aplio, Toshiba, Canon, USA) were also conducted. The assessment of nutritional risk (Nutritional Risk Screening 2002 [NRS-2002] and Mini Nutritional Assessment [MNA] surveys) and status (height [cm], body weight [kg], body mass index [BMI], waist circumference [cm], and waist to height ratio [WHtR]), as well as body composition analysis using bioelectrical impedance analysis [BIA, Tanita BC 420 MA device (Tanita Corporation, Japan)], were performed twice: once on admission and once on discharge. The following BIA parameters were obtained: fat-free mass (FFM; kg); skeletal muscle mass (kg; percentage of FFM); fat mass (FM; %; kg); the visceral fat level (VFL) score; and total body water (TBW; kg).

Adipocytokines

Blood sampling for adipocytokines determination was made on the day of discharge. After coagulation, blood was centrifuged, and the plasma obtained was frozen at –80°C until the determination (not longer than 6 months). Blood leptin and ADP concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) kit from ALPCO (cat. no. 11-LEPHU-E01 and 80-ADPHU-E01, respectively). Blood TNF-alpha concentration was assessed using an ELISA kit from CUSABIO (cat. no. CSB-E04740h). All parameters were determined in accordance with the manufacturers' instructions, and the blood adipocytokine concentrations found were presented as crude values, as well as values indexed to body surface area (BSA), and BIA parameters obtained at the time of the patient's discharge (e.g., a ratio of blood ADP concentration to FM measured on discharge).

BSA was calculated using the following formula:

$$BSA\ (m^2) = 0.01666667 \times height^{0.5} \times body\ mass^{0.5}$$

Measured outcomes

During a one-year follow-up period, the following measured outcomes were obtained during routine check-ups in an ambulatory clinic and during telephone interviews with patients or their relatives: all-cause mortality, cardiovascular mortality, all-cause readmission, and readmission due to CHF exacerbation.

Bioethics Committee

The investigation was conducted in compliance with the Declaration of Helsinki for medical research, after receiving permission from the local Bioethical Committee No. 325/2016 given on April 26, 2016. Each patient signed written consent form regarding his or her participation in the study.

Statistics

Statistical analysis was conducted using the licensed version of the statistical software STATISTICA version 13.1 (data analysis software) developed by TIBCO Software Inc. (2017). The normal distribution

of the study variables was checked using the Kolmogorov-Smirnov test. The statistical significance level was set at a p-value of < 0.05. The results were presented as the mean ± standard deviation or median; interquartile range (IQR), or n, %. The statistical significance of differences between groups was verified using Student's t-test and the Mann-Whitney U-test for quantitative variables (for parametric and non-parametric tests, respectively) and the Chi^2 test for qualitative variables. A Kaplan-Meier curve was used to determine the risk of all-cause mortality or a major adverse cardiovascular event. Cut-off values for the crude and indexed (to BSA, FFM, FM, VFL) blood adipocytokine concentration composition with a predictive value for the measured outcomes were determined for maximal Youden's indices by plotting the receiver operator curves (ROC). The hazard ratio (HR) was determined for the dichotomized variables (having crude or indexed blood adipocytokine concentrations above or below established cut-offs) as the chance of an established end-point occurring in the group with a value of the respective adipocytokine (crude or indexed) or NT-proBNP higher than the established cut-off divided by the chance of the end-point occurring in the group of patients with a lower value of adipocytokine measured.

The sample size was calculated with the assumption that the blood adipocytokine concentrations would differ between the study and control groups analyzed by 20% with a 25% standard deviation in comparison to the baseline values. We also assumed in our use of Student's t-test and the Mann-Whitney U-test an alpha of 0.05 and a beta of 0.10 (with a power of analysis of at least 90%). The sample size for Kaplan-Meier survival analysis and the log rank test was estimated on the assumption of a 15% difference in mortality prevalence in the analysis of the CHF group: 80% analysis power and an alpha < 0.05. A total of 34 and 60 patients were required to complete these tests to establish group effect and survival analysis, respectively.

Results

Clinical characteristics

Compared to the control group, patients with CHF had a higher risk of all-cause death and readmission during the one-year follow-up, had higher blood creatinine and C-reactive protein (CRP) concentrations, lower blood albumin, hemoglobin, total and low-density lipoprotein cholesterol concentrations, and a lower albumin-to-CRP ratio (Tab. 1). Moreover, they had a higher FFM on discharge (Tab. 1). All patients were treated according to the current ESC recommendations [18], i.e. with angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, statins, and acetylsalicylic acid. All study participants had sinus rhythm of the heart.

Blood adipocytokine concentration

Compared to the control group, CHF patients had a significantly higher crude blood ADP concentration and the ratio of ADP to FM expressed as a percentage of body mass (FM%), as well as a lower blood TNF-alpha concentration and ratios of TNF-alpha to VFL (Tab. 2). Neither the crude nor the indexed (for BSA, FM%, VFL) values of the adipocytokines differed between CHF patients classified in relation to the severity of symptoms on admission (III *vs.* IV NYHA class) (Tab. 3), and LVEF determined in transthoracic echocardiography ($< 50\%$ *vs.* $\geq 50\%$; Tab. 4).

Prognosis

Compared to patients who survived, patients with CHF who died during the one-year follow-up had significantly higher values of ADP and ratios of ADP to BSA (Tab. 5).

In the Kaplan-Meier analysis, elevated blood ADP concentration, both crude and indexed to FM% or VFL, was related to higher all-cause mortality (log rank test; Fig. 1). One-year all-cause mortality among CHF patients was also related to higher blood NT-proBNP concentration (log rank test in Kaplan Meier analysis; ≥ 2010 pg/mL *vs.* < 2010 pg/mL; $p < 0.01$, Fig. 1). We observed that the shapes of the Kaplan-Meier curves obtained for NT-proBNP, crude ADP, and indexed ADP were similar. However, LVEF failed to reach statistical significance in respect of our patients' survival (log rank test in Kaplan-Meier analysis; LVEF $\geq 15\%$ *vs.* $< 15\%$; $p = 0.19$). In univariate analysis, the established cut-off values for the ratio of ADP to VFL achieved statistical significance for the HR in relation to one-year all-cause mortality risk (Fig. 1). In our Cox regression model, blood ADP concentration was the only independent risk factor for all-cause mortality during the one-year follow-up, which increased significantly the risk of one-year mortality by 16% (Tab. 6).

Discussion

In this study, CHF patients, compared to the control group, had similar FM, greater signs of abdominal distribution of adipose tissue (WHtR), higher CRP, and a lower albumin-to-CRP ratio (Tab. 1). CHF patients also presented significantly higher ADP, only slightly, but not significantly higher, blood leptin, and lower TNF-alpha concentrations (Tab. 2). As a result of the differences mentioned in nutritional and inflammatory status, and

Table 1. Clinical and biochemical characteristics of patients with CHF and in the control group

Parameter	CHF patients (n = 65)	Control group (n = 32)	P-value
Age (years)	72.08 ± 9.12	70.13 ± 7.58	0.299
Male gender n (%)	43 (66.2)	20 (62.5)	0.726
All-cause death during one-year follow-up; n (%)	11 (16.9)	1 (3.1)	0.052
Patients readmitted during one-year follow-up; n (%)	47 (72.3)	15 (46.9)	0.014
Diabetes mellitus; n (%)	34 (52.3)	12 (37.5)	0.173
Smoking habit: present/past (n, %)	7 (10.8/ 41 (63.1)	7 (21.9)/ 24 (75.0)	0.241
CCI (score)	5.8 ± 1.99	3.56 ± 1.24	< 0.001
NT-proBNP [pg/mL]	2551; 1560.0–5872.0	88.8; 37.5–122.5	< 0.001
Albumin [g/dL]	3.78 ± 0.41	4.28 ± 0.35	< 0.001
Hemoglobin [g/dL]	13.07 ± 1.74	14.24 ± 1.26	< 0.001
TLC [G/L]	1.59 ± 0.70	2.18 ± 0.66	< 0.001
Creatinine [mg/dL]	1.30 ± 0.46	0.89 ± 0.22	< 0.001
LDL cholesterol [mg/dL]	69; 55.0–93.0	89.0; 71.0–122.0	0.0015
Triglycerides [mg/dL]	74; 62.0–127.0	115.0; 84.0–185.0	0.100
Blood glucose [mg/dL]	117.98 ± 34.9	111.29 ± 29.1	0.384
CRP [mg/L]	6.9; 4.2–16.5	1.4; 0.8–4.8	0.044
Albumin-to-CRP ratio	0.55; 0.21–1.30	3.07; 0.93–5.76	< 0.001
Body mass on discharge [kg]	84.34 ± 22.97	77.36 ± 14.67	0.121
BMI on discharge [kg/m^2]	29.66 ± 7.42	27.38 ± 4.07	0.114
WHtR on discharge	0.64; 0.56–0.71	0.59; 0.56–0.63	0.036
FM on discharge expressed as percentage of body mass (%)	27.4; 18.8–34.30	30.00; 26.30–37.10	0.114
VFL level on discharge	14.00; 10.00–18.00	12.50; 10.00–16.00	0.300
FFM on discharge [kg]	58.90; 51.00–71.50	53.30; 43.15–60.55	0.025

Data are presented as mean ± SD or median; IQR (interquartile range); or as n (%). BMI — body mass index; CCI — Charlson Comorbidity Index (age-adjusted); CHF — chronic heart failure; CRP — C-reactive protein; FFM — fat-free mass; FM — fat mass; LDL — low-density lipoprotein; NT-proBNP — N-terminal pro B-type natriuretic peptide; TLC — total lymphocyte count; VFL — visceral fat level; WHtR — waist-to-height ratio

Table 2. Blood adipocytokine concentrations as measured in CHF patients and in the control group

Parameter	CHF patients (n = 65)	Control group (n = 32)	P-value
ADP [mcg/mL]	7.96; 5.60–12.64	5.08; 3.74–6.62	0.030
LEP [ng/mL]	24.26; 8.00–66.47	28.72; 10.17–41.54	0.296
TNF-alpha [pg/mL]	34.24; 20.80–58.56	39.15; 24.32–101.71	0.004
ADP-to-FM (%) ratio	0.26; 0.15–0.74	0.16; 0.12–0.21	0.020
ADP-to-VFL ratio	0.54; 0.28–1.17	0.39; 0.23–0.66	0.189
LEP-to-FM (%) ratio	0.89; 0.37–1.94	0.77; 0.44–1.25	0.194
LEP-to-VFL ratio	1.56; 0.64–3.88	1.83; 0.88–3.02	0.950
TNF-alpha-to-FM (%) ratio	1.36 – 0.75–2.25	1.49; 0.61–3.13	0.264
TNF-alpha-to-VFL ratio	2.58; 1.43–4.22	3.58; 1.50–10.21	0.005

Data are presented as median; IQR (interquartile range). ADP — adiponectin; CHF — chronic heart failure; FM — fat mass; LEP — leptin; TNF-alpha — tumor necrosis factor alpha; VFL — visceral fat level

Table 3. Blood adipocytokine concentrations measured in CHF patients divided in relation to LVEF preservation (LVEF ≥ 50%)

Parameter	LVEF ≥ 50% (n = 28)	LVEF < 50% (n= 37)	P-value
ADP [mcg/mL]	7.12; 3.78–11.91	9.36; 5.77–13.46	0.183
LEP [ng/mL]	33.05; 8.21–90.23	18.30; 5.87–66.47	0.427
TNF-alpha [pg/mL]	29.27; 19.09–42.13	40.53; 23.15–62.62	0.567
ADP-to-FM (%) ratio	0.24; 0.14–0.63	0.33; 0.16–0.77	0.419
ADP-to-VFL ratio	0.46; 0.23–0.97	0.58; 0.29–1.35	0.657
LEP-to-FM (%) ratio	0.97; 0.37–2.01	0.70; 0.28–1.92	0.368
LEP-to-VFL ratio	1.59; 0.59–5.30	1.32; 0.64–3.40	0.216
TNF-alpha-to-FM (%) ratio	1.32; 0.74–2.03	1.39; 0.77–2.30	0.373
TNF-alpha-to-VFL ratio	2.55; 1.43–4.03	2.67; 1.38–4.77	0.301

Data are presented as median; IQR (interquartile range). ADP — adiponectin; CHF — chronic heart failure; FM — fat mass; LEP — leptin; LVEF — left ventricular ejection fraction; TNF-alpha — tumor necrosis factor alpha; VFL — visceral fat level

Table 4. Blood adipocytokine concentrations measured in CHF patients divided in relation to severity of symptoms on admission according to NYHA classification

Parameter	Klasa III wg NYHA (n = 30)	Klasa IV wg NYHA (n = 35)	P-value
ADP [mcg/mL]	9.10; 5.92–13.64	7.90; 4.49–12.21	0.454
LEP [ng/mL]	24.58; 9.77–53.17	20.05; 5.87–87.61	0.899
TNF-alpha [pg/mL]	36.43; 22.19–47.25	30.40; 19.20–62.62	0.842
ADP-to-FM (%) ratio	0.30; 0.18–0.64	0.25; 0.14–0.77	0.784
ADP-to-VFL ratio	0.53; 0.34–1.14	0.58; 0.25–1.21	0.604
LEP-to-FM (%) ratio	1.00; 0.44–1.86	0.59; 0.41–1.53	0.996
LEP-to-VFL ratio	1.58; 0.65–3.40	1.52; 0.59–5.93	0.571
TNF-alpha-to-FM (%) ratio	1.58; 0.95–2.02	1.33; 0.74–2.35	0.306
TNF-alpha-to-VFL ratio	2.62; 1.58–3.81	2.55; 1.38–5.52	0.402

Data are presented as median; IQR (interquartile range). ADP — adiponectin; CHF — chronic heart failure; FM — fat mass; LEP — leptin; NYHA — New York Heart Association; TNF-alpha — tumor necrosis factor alpha; VFL — visceral fat level

Table 5. Comparison of crude and indexed blood adipocytokine concentrations in CHF patients who died and those who survived during the one-year follow-up

Parameter	Died (n = 11)	Survived (n = 54)	P-value
ADP [mcg/mL]	9.86; 6.34–18.65	6.53; 4.04–10.10	0.02
LEP [ng/mL]	11.73; 4.16–38.11	27.26; 9.24–53.17	0.30
TNF-alpha [pg/mL]	35.90; 25.17–57.82	36.05; 21.65–64.43	0.66
ADP indexed to BSA	6.29; 3.12–10.24	3.68; 2.31–5.83	0.01
ADP-to-FM (%) ratio	0.57; 0.19–1.08	0.20; 0.14–0.38	0.07
ADP-to-VFL ratio	0.91; 0.57–1.89	0.42; 0.25–0.82	0.08
LEP indexed to BSA	3.76; 2.31–17.18	12.66; 4.45–35.66	0.36
LEP-to-FM (%) ratio	0.50; 0.31–1.17	0.89; 0.44–1.70	0.38
LEP-to-VFL ratio	0.88; 0.65–2.76	1.65; 0.69–3.59	0.41
TNF-alpha indexed to BSA	20.05; 13.88–33.65	17.19; 10.19–30.02	0.52
TNF-alpha-to-FM (%) ratio	1.35; 0.92–2.93	1.47; 0.74–2.49	0.40
TNF-alpha-to-VFL ratio	2.79; 1.89–4.67	2.62; 1.45–5.52	0.33

Data are presented as mean ± SD or median; IQR (interquartile range). ADP — adiponectin; BSA — body surface area; CHF — chronic heart failure; FFM — fat-free mass; FM — fat mass; LEP — leptin; TNF-alpha — tumor necrosis factor alpha; VFL — visceral fat level

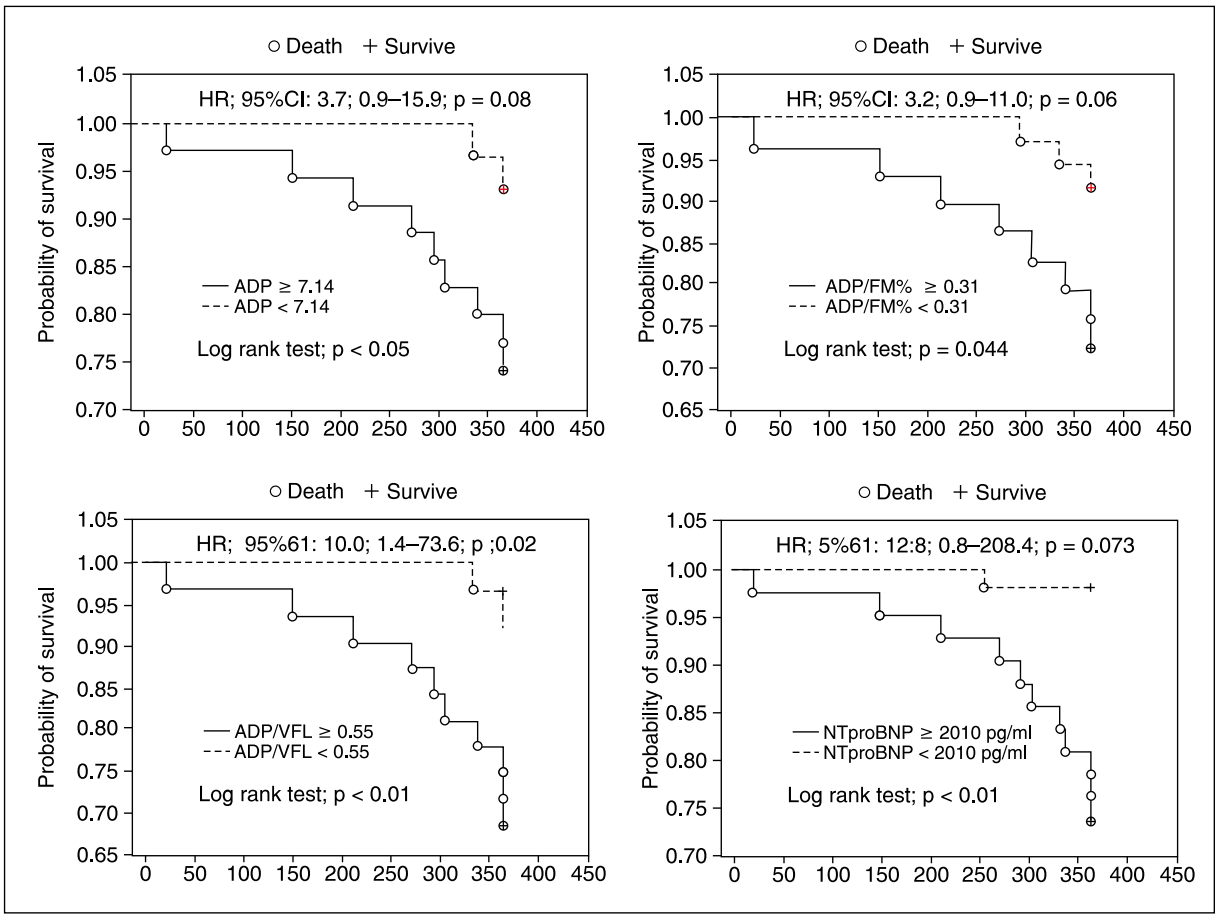

Figure 1. The Kaplan-Meier curve showing crude and indexed blood ADP concentrations in comparison to NT-proBNP with respect to survival probability of patients with CHF. ADP — adiponectin; FM% — percentage fat mass in whole body weight; HR — hazard ratio; NTproBNP — N-terminal pro B-type natriuretic peptide; VFL — visceral fat level

Table 6. Cox regression model of one-year all-cause mortality among the CHF patients studied

Parameter	Beta; 95% CI	Standard error	P-value	HR; 95% CI
ADP [mcg/mL	0.15; 0.03–0.27	0.06	0.01	1.16; 1.03–1.31
Age (years)	–0.03; –0.13–0.07	0.05	0.53	0.97; 0.88–1.07
Male gender	0.47; –0.86–1.81	0.68	0.49	1.61; 0.42–6.11
LVEF (%)	0.01; –0.05–0.06	0.03	0.86	1.01; 0.95–1.06
CCI (score)	0.04; –0.36–0.44	0.20	0.85	1.04; 0.70–1.55
NT-proBNP [pg/mL]	0.00;	0.00	0.11	1.00; 1.00–1.00

ADP — adiponectin; CCI — Charlson Comorbidity Index (age-adjusted); CHF — chronic heart failure; CI — confidence interval; HR — hazard ratio; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro B-type natriuretic peptide

adiposity distribution between the study groups (Tab. 1), we compared the two groups not only in terms of crude but also indexed values of the adipocytokines measured (Tab. 2). The analysis showed that CHF patients presented hypersecretion of ADP and undersecretion of TNF-alpha per unit of the whole (FM%) and visceral adipose tissue (VFL) (Tab. 2). Those dysregulations in the endocrine function of adipose tissue were associated with significantly higher blood ADP concentrations in CHF patients who died, compared to those who survived the observation period (Tab. 5), and with a ten-fold increase in the HR of one-year mortality for ADP/VFL ratio ≥ 0.55 (Fig. 1). The poor prognosis related to higher ADP blood concentration was also confirmed in both the Kaplan-Meier (statistically significant log rank tests, Fig. 1) and Cox regression model analyses (Tab. 4).

It was surprising that despite the small patient sample, elevated blood ADP concentration in CHF patients was the only independent factor predicting patient death during the one-year follow-up. In contrast to ADP, such well-known prognostic CHF markers as LVEF and blood NT-proBNP concentration did not reach statistical significance as independent prognostic factors (Tab. 6). The obtained results corroborate data presented in recent publications showing that increased blood ADP concentration is a factor in the poor prognosis in CHF patients [12–17]. The association of poor prognosis in CHF patients with higher blood ADP concentration, which should, theoretically, exert cardioprotective action, is known as the "ADP paradox", and is recognized as the result of ADP resistance [16]. On the other hand, our results are inconsistent with those of a study by Mayer et al. [19], who showed that the associations between higher blood ADP concentration and patient mortality and risk of CHF disappeared after data adjustment for blood NT-proBNP concentration.

In our study, we did not find any relationships between crude and indexed blood adipocytokine concentrations and severity of CHF exacerbation according to the NYHA classification (Tab. 3) and/or the presence of preserved (≥ 50%) or non-preserved (< 50%) LVEF (Tab. 4). In the available articles, data concerning those relationships with regard to ADP, leptin, and TNF-alpha are ambiguous [4, 5, 12–17]. Despite potential cardioprotective effects of ADP, Mado et al. [12] summarize in their review that the adiponectin level gradually increases with the severity of CHF. Horbal et al. [16] showed positive and negative NT-proBNP relationships with ADP and leptin, respectively. In comparison, Nakamura et al. [20] demonstrated in a mice model that higher ADP enhanced mesenchymal stem-cell-driven therapy of heart failure. With regard to TNF-alpha, our results are contrary to the data showing associations between elevated blood TNF-alpha concentration and a worsening of heart failure symptoms [4]. Our results are also not consistent with clinical trials on the use of anti-TNF-alpha therapy in the treatment of CHF patients. However, it should be underlined that such therapy failed to improve CHF patients' prognosis [3].

In our study, we not only presented blood adipocytokine concentrations as crude values but also as values indexed to BSA and parameters of body composition (i.e., FM and VFL). To the best of our knowledge, this was the first use of this kind of analysis. We assumed that adipocytokine indexation would make it possible to estimate production of the respective adipocytokines per unit of adipose tissue. In this way, we found dysregulation in adipocytokine secretion through adipocytes in CHF patients, which mainly concerned ADP overexpression and decreased expression of TNF-alpha (Tab. 2). Hypersecretion of ADP, expressed as elevated ratios of ADP to FM (%) and ADP to VFL, influenced the one-year mortality of CHF patients according to the Kaplan-Meier analysis (Fig. 1). It is possible that abnormalities in ADP and TNF-alfa blood concentrations in CHF patients may be an effect of resistance to the action of those cytokines [16].

In our study, CHF patients compared to the control group had significantly higher blood LDL cholesterol and CRP concentrations (Tab. 1). It seems to be important whether these differences affected blood adipocytokine concentrations as a potential confounding factor. Excess of adipose tissue, which is the source of adiponectin and leptin, causes chronic low-grade inflammation expressed, for example, by an elevated high sensitivity CRP blood level [21]. However, the opposite relationship, i.e. influence of the inflammatory process on adipocytokines secretion, was not reported. Similarly, a chronic inflammatory state, expressed by elevated TNF-alpha and CRP, may induce production of oxidized-LDL with intensified proatherogenic action. However, the relationships between urinary adiponectin and severity of metabolic abnormalities, including plasma lipids, were not confirmed, admittedly, in peri- and postmenopausal women only [22]. In CHF patients we did not also find significant correlations between blood adipocytokines, LDL, and CRP concentrations, both in whole study population and the study groups (CHF patients and controls separately). However, it is known that a combination of elevated levels of both LDL cholesterol and CRP is the risk factor for endothelial dysfunction, progression of ischemic heart failure [2–5, 12, 17, 21–29], and unfavorable outcomes, including mortality and readmission, especially in men [30] and in CHF patients with preserved LVEF [25, 31]. On the other hand, lower, rather than higher, blood LDL cholesterol concentration was related to a poor prognosis in CHF patients and other advanced diseases requiring hospitalization, which is known as the "cholesterol paradox" [32].

Study strengths and limitations

The first strength of our study lies in the multifactorial analysis of the endocrine function of adipose tissue in relation to parameters of body composition (indexation), which has not previously been done. The second advantage is that parameters of body composition were compared to the control group on the day of discharge. This was because of the loss of, on average, 5 kg of water in CHF patients during hospitalization, which, in turn, affects especially the results concerning FFM, which is strongly related to overhydration. Such analysis made it possible to compare "dry (not-overhydrated) weight" of CHF patients with the usual weight of patients

who acted as the control group. The third strength is the one-year follow-up period, which is of sufficient length to observe changes in patients' outcomes in relation to their adipocytokine status.

The main limitation of our study is the small sample size. However, the number of patients was determined as sufficient to achieve the statistical power of assumed differences and is comparable to that in other published works [4]. On the other hand, multifactorial analysis has a limited value when performed in a small sample, which was probably the reason why age, low LVEF, and NT-proBNP did not reach statistical significance (Tab. 6). Therefore, the data presented in Table 6 ought to be interpreted carefully. However, it should be underlined that the number of patients included in the study resulted from established inclusion criteria that excluded individuals with comorbidities that might potentially affect the endocrine function of adipose tissue. The second limitation might be related to the choice of the control group. Nonetheless, in our opinion, comparing the results to those from a healthy control group would have been less valuable than a comparison with the group of cardiovascular patients who were chosen. The third limitation is the lack detailed data on severity of coronary artery disease (i.e. one-, two-, three vessels disease, left main stem disease).

Conclusions

Patients with CHF present hypersecretion of ADP, which was associated with an increase in one-year all-cause mortality by 16%. Further studies are needed to estimate the cause of ADP hypersecretion and outcomes of interventions on the reduction of a chronic inflammatory status related to dysregulation in the endocrine function of the adipose tissue in CHF patients.

Conflict of interest: *None.*

Acknowledgment: *This study was supported by a grant from Nicolaus Copernicus University in Toruń for scientific research conducted by the Department of Vascular and Internal Diseases, and a grant from Nicolaus Copernicus University in Toruń (MN-SDZ-4/WNoZ/2017 to A.W.) for the development of young scientists.*

References

1. Wawrzeńczyk A, Anaszewicz M, Wawrzeńczyk A, et al. Clinical significance of nutritional status in patients with chronic heart failure-a systematic review. Heart Fail Rev. 2019; 24(5): 671–700, doi: 10.1007/s10741-019-09793-2, indexed in Pubmed: 31016426.
2. Mocan M, Mocan Hognogi LD, Anton FP, et al. Biomarkers of inflammation in left ventricular diastolic dysfunction. Dis Markers. 2019; 2019: 7583690, doi: 10.1155/2019/7583690, indexed in Pubmed: 31275453.
3. Hanna A, Frangogiannis NG. Inflammatory cytokines and chemokines as therapeutic targets in heart failure. Cardiovasc Drugs Ther. 2020; 34(6): 849–863, doi: 10.1007/s10557-020-07071-0, indexed in Pubmed: 32902739.
4. El Missiri AM, Alzurfi AS, Keddeas VW. The relationship between tumor necrosis factor alpha and left ventricular diastolic function. J Cardiovasc Echogr. 2020; 30(2): 62–67, doi: 10.4103/jcecho.jcecho_1_20, indexed in Pubmed: 33282642.
5. Rostoff P, Siniarski A, Haberka M, et al. Relationship among the leptin-to-adiponectin ratio, systemic inflammation, and anisocytosis in well-controlled type 2 diabetic patients with atherosclerotic cardiovascular disease. Kardiol Pol. 2020; 78(5): 420–428, doi: 10.33963/KP.15257, indexed in Pubmed: 32210218.
6. Poetsch MS, Strano A, Guan K. Role of Leptin in Cardiovascular Diseases. Front Endocrinol (Lausanne). 2020; 11: 354, doi: 10.3389/fendo.2020.00354, indexed in Pubmed: 32655492.
7. Sawaguchi T, Nakajima T, Haruyama A, et al. Association of serum leptin and adiponectin concentrations with echocardiographic parameters and pathophysiological states in patients with cardiovascular disease receiving cardiovascular surgery. PLoS One. 2019; 14(11): e0225008, doi: 10.1371/journal.pone.0225008, indexed in Pubmed: 31703113.
8. Dadarlat-Pop A, Pop D, Procopciuc L, et al. Leptin, galectin-3 and angiotensin II type 1 receptor polymorphism in overweight and obese patients with heart failure - role and functional interplay. Int J Gen Med. 2021; 14: 1727–1737, doi: 10.2147/IJGM.S301285, indexed in Pubmed: 33994803.
9. Kita S, Shimomura I. Stimulation of exosome biogenesis by adiponectin, a circulating factor secreted from adipocytes. J Biochem. 2021; 169(2): 173–179, doi: 10.1093/jb/mvaa105, indexed in Pubmed: 32979268.
10. Shimada YJ. Is leptin protective against heart failure with preserved ejection fraction? A complex interrelationship among leptin, obesity, and left ventricular hypertrophy. Hypertens Res. 2019; 42(2): 141–142, doi: 10.1038/s41440-018-0135-0, indexed in Pubmed: 30420723.
11. Ahiante BO, Smith W, Lammertyn L, et al. Leptin and the vasculature in young adults: The African-PREDICT study. Eur J Clin Invest. 2019; 49(1): e13039, doi: 10.1111/eci.13039, indexed in Pubmed: 30347447.
12. Mado H, Szczurek W, Gąsior M, et al. Adiponectin in heart failure. Future Cardiol. 2021; 17(4): 757–764, doi: 10.2217/fca-2020-0095, indexed in Pubmed: 32915067.
13. Lakshmanan S, Jankowich M, Wu WC, et al. Association of plasma adiponectin with pulmonary hypertension, mortality and heart failure in African Americans: Jackson Heart Study. Pulm Circ. 2020; 10(4): 2045894020961242, doi: 10.1177/2045894020961242, indexed in Pubmed: 33240486.
14. Jauhiainen R, Jauhiainen M, Vangipurapu J, et al. Novel biomarkers associated with incident heart failure in 10 106 Finnish men. ESC Heart Fail. 2021; 8(1): 605–614, doi: 10.1002/ehf2.13132, indexed in Pubmed: 33660951.
15. Luo D, Chen P, Yang Z, et al. High plasma adiponectin is associated with increased pulmonary blood flow and reduced right ventricular function in patients with pulmonary hypertension. BMC Pulm Med. 2020; 20(1): 204, doi: 10.1186/s12890-020-01233-4, indexed in Pubmed: 32731857.
16. Horbal SR, Hall ME, Dinh PC, et al. Associations of adiponectin and leptin with brain natriuretic peptide in African Americans: the Jackson Heart Study. Cardiovasc Endocrinol Metab. 2020; 9(2): 49–55, doi: 10.1097/XCE.0000000000000198, indexed in Pubmed: 32537565.
17. Monzo L, Kotrc M, Benes J, et al. Clinical and humoral determinants of congestion in heart failure: potential role of adiponectin. Kidney Blood Press Res. 2019; 44(5): 1271–1284, doi: 10.1159/000502975, indexed in Pubmed: 31553971.
18. Ponikowski P, Voors AA, Anker SD, et al. Authors/Task Force Members, Document Reviewers. 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 J Heart Fail. 2016; 18(8): 891–975, doi: 10.1002/ejhf.592, indexed in Pubmed: 27207191.
19. Mayer O, Seidlerová J, Bruthans J, et al. Is there really an association of high circulating adiponectin concentration and mortality or morbidity risk in stable coronary artery disease? Horm Metab Res. 2020; 52(12): 861–868, doi: 10.1055/a-1212-8759, indexed in Pubmed: 32746485.

20. Nakamura Y, Kita S, Tanaka Y, et al. Adiponectin stimulates exosome release to enhance mesenchymal stem-cell-driven therapy of heart failure in mice. Mol Ther. 2020; 28(10): 2203–2219, doi: 10.1016/j.ymthe.2020.06.026, indexed in Pubmed: 32652045.
21. Sagris M, Theofilis P, Antonopoulos AS, et al. Inflammation in Coronary Microvascular Dysfunction. Int J Mol Sci. 2021; 22(24), doi: 10.3390/ijms222413471, indexed in Pubmed: 34948272.
22. Vichinsartvichai P, Teeramara R, Jirasawas T, et al. Comparison of urinary adiponectin in the presence of metabolic syndrome in peri- and postmenopausal women. BMC Womens Health. 2022; 22(1): 70, doi: 10.1186/s12905-022-01655-8, indexed in Pubmed: 35287667.
23. Henning RJ. Obesity and obesity-induced inflammatory disease contribute to atherosclerosis: a review of the pathophysiology and treatment of obesity. Am J Cardiovasc Dis. 2021; 11(4): 504–529, indexed in Pubmed: 34548951.
24. Hanna A, Frangogiannis NG. Inflammatory cytokines and chemokines as therapeutic targets in heart failure. Cardiovasc Drugs Ther. 2020; 34(6): 849–863, doi: 10.1007/s10557-020-07071-0, indexed in Pubmed: 32902739.
25. Albar Z, Albakri M, Hajjari J, et al. Inflammatory markers and risk of heart failure with reduced to preserved ejection fraction. Am J Cardiol. 2022; 167: 68–75, doi: 10.1016/j.amjcard.2021.11.045, indexed in Pubmed: 34986991.
26. Chaikijurajai T, Tang WH. Reappraisal of inflammatory biomarkers in heart failure. Curr Heart Fail Rep. 2020; 17(1): 9–19, doi: 10.1007/s11897-019-00450-1, indexed in Pubmed: 31916187.
27. Roytman AP, Sedova NA, Ivanova EA, et al. The importance of laboratory parameters of the lipid transport system and adipose tissue hormones in assessing the course of chronic. Klin Lab Diagn. 2022; 67(2): 85–90, doi: 10.51620/0869-2084-2022-67-2-85-90, indexed in Pubmed: 35192753.
28. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. J Am Coll Cardiol. 2019; 74(10): 1376–1414, doi: 10.1016/j.jacc.2019.03.009, indexed in Pubmed: 30894319.
29. Chamberlain AM, Cohen SS, Weston SA, et al. Relation of cardiovascular events and deaths to low-density lipoprotein cholesterol level among statin-treated patients with atherosclerotic cardiovascular disease. Am J Cardiol. 2019; 123(11): 1739–1744, doi: 10.1016/j.amjcard.2019.02.043, indexed in Pubmed: 30948001.
30. Saleh ZT, Alraoush AT, Aqel AA, et al. Sex differences in the association between inflammation and event-free survival in patients with heart failure. J Cardiovasc Nurs. 2021 [Epub ahead of print], doi: 10.1097/JCN.0000000000000831, indexed in Pubmed: 34238839.
31. Reina-Couto M, Pereira-Terra P, Quelhas-Santos J, et al. Inflammation in human heart failure: major mediators and therapeutic targets. Front Physiol. 2021; 12: 746494, doi: 10.3389/fphys.2021.746494, indexed in Pubmed: 34707513.
32. Budzyński J, Tojek K, Wustrau B, et al. The "cholesterol paradox" among inpatients - retrospective analysis of medical documentation. Arch Med Sci Atheroscler Dis. 2018; 3: e46–e57, doi: 10.5114/amsad.2018.74736, indexed in Pubmed: 30775589.