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Short communication

Plasma leptin, but not resistin, TNF-α and adiponectin, is associated with echocardiographic parameters of cardiac remodeling in patients with coronary artery disease

Anca Daniela Farcaş[a], Adriana Rusu[b,*], Mirela Anca Stoia[a], Luminiţa Animarie Vida-Simiti[a]

[a] Internal Medicine Department, "Iuliu Haţieganu" University of Medicine and Pharmacy, 8 Victor Babes Street, 400012 Cluj-Napoca, Romania
[b] Department of Diabetes and Nutrition, "Iuliu Haţieganu" University of Medicine and Pharmacy, 4-6 Clinicilor Street, 400006 Cluj-Napoca, Romania

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ABSTRACT

The aim of this research was to assess the relationship between plasma adiponectin, leptin, resistin, tumor necrosis factor alpha (TNF-α) levels and echocardiographic parameters of ventricular remodeling in patients with coronary artery disease, without acute myocardial infarction. The study population consisted of 49 patients with echocardiographic measurements performed. After adjustment for age, gender, body mass index, systolic and diastolic blood pressure, and glycaemia, adiponectin was statistically significant associated with interventricular septum thickness (β = −0.304), left ventricular posterior wall thickness (β = −0.402), left ventricular end diastolic diameter (LVEDD; β = 0.385) and left ventricular relative wall thickness (β = −0.448, $p < .05$ for all). The associations were no longer significant when only patients without diabetes were included in the analysis. Leptin was associated with LVEDD (β = −0.354) and left ventricular relative wall thickness (β = 0.385, $p < .05$ for all). No associations between resistin, TNF-α and echocardiographic left ventricular parameters assessed were found in these patients. In conclusion, in patients with coronary artery disease and without acute myocardial infarction leptin may represent a potential mechanism of adverse cardiac remodeling. Resistin and TNF-α might not be involved in ventricular remodeling in these patients.

1. Introduction

Myocardial remodeling, defined by structural, shape, and functional changes of the myocardium, represents the main mechanism of development and progression of heart failure [1]. In coronary artery disease, ventricular remodeling appears initially as an adaptive response of myocardium to the cardiac ischemic injury [1]. Reduced contractility of the ischemic regions and increased contractility of the non-ischemic ones are accompanied by inflammatory changes and decreased resistance in the ischemic myocardium while cardiomyocytes grow in length and become hypertrophic in the non-ischemic myocardium [1]. In the long term these changes are followed by ventricular wall thinning, loss of contractility and finally ventricular dysfunction [2]. The activation of neurohormonal pathways, lipid metabolism, nitric oxide cGMP pathway, oxidative stress pathway, and immune changes are several pathogenetic mechanisms involved in myocardial remodeling [1].

Proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) have been shown to play an important role in myocardial remodeling following myocardial infarction [3,4] and together with adipokines have been associated with an increased risk of ventricular dysfunction [4–6]. However, little is known about their involvement in myocardial remodeling in patients with coronary artery disease without previous myocardial infarction.

The aim of the research presented here was to assess the relationship between plasma adiponectin, leptin, resistin, TNF-α levels and echocardiographic parameters of ventricular remodeling in patients with coronary artery disease, without acute myocardial infarction.

2. Material and methods

2.1. Study design and participants

This was a non-interventional prospective study performed in the Cardiology Department of the Emergency County Clinical Hospital Cluj-Napoca, Romania [7]. Fifty-nine consecutive adult patients with coronary artery disease admitted in this department were enrolled and

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; DBP, diastolic blood pressure; IVS, interventricular septum; LV, left ventricle; LVEDD, left ventricular end diastolic diameter; LVPW, left ventricular posterior wall; LVRWT, left ventricular relative wall thickness; SBP, systolic blood pressure; TNF-α, tumour necrosis factor alpha

* Corresponding author.
E-mail addresses: ancafarcas@yahoo.com (A.D. Farcaş), adriana.rusu@umfcluj.ro (A. Rusu), mirelastoia@yahoo.com (M.A. Stoia), lvscardio@yahoo.com (L.A. Vida-Simiti).

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followed for 2 years with the aim of assessing the impact of different parameters on the incidence of new ischemic cardiovascular events. Exclusion criteria included any infectious disease, medical history of neoplasia, acute coronary syndrome at admittance or during the hospitalization, medical history of stroke, hepatic or renal failure, and severe heart failure. Here we present the analysis of data collected at baseline for patients with echocardiographic parameters available.

The study was approved by the Institutional Ethics Committee and was conducted according to the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent before any study procedure.

2.2. Study assessments

Fasting plasma glucose, total and HDL-cholesterol, triglycerides, creatinine, adiponectin, leptin, TNF-α and resistin were collected at baseline, in fasting conditions, in the institutional laboratory. Biochemical measurements were performed on the day of collection using routine enzymatic methods (Konelab 30, Thermo Fisher Scientific Inc, Finland). Samples for the assessment of resistin, adiponectin, leptin and TNF-α were centrifuged in the same day and stored at −80 °C until assessment by commercially available ELISA sandwich test, using Quantikine® reagents (R&D Systems, USA).

Height, weight, and blood pressure were measured according to local procedures. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Cardiac ultrasound measurements were performed immediately after medical examination and blood sample collection using Siemens Acuson X300 with a 2–5 MHz probe. According to European Society of Cardiology recommendations [8], the measurement of left ventricular posterior wall (LVPW) thickness, interventricular septum (IVS) thickness, and left ventricular end diastolic diameter (LVEDD) was performed in M mode using the parasternal long-axis view. Left ventricular mass was calculated by modified Devereux formula [9] and was expressed as g/m^2. Left ventricular relative wall thickness was calculated as (2 × LVPW)/LVEDD [8].

2.3. Statistical analysis

Data is presented as proportions for qualitative variables and as mean and standard deviation or median (quartile 1; quartile 3) for continuous variables. Leptin and TNF-α values were logarithmically transformed to fit the normal distribution. The association between echocardiography measured parameters and the assessed cytokines was assessed by linear regression analysis. A two-sided p value ≤.05 was considered statistically significant. Statistical analyses were performed with IBM® SPSS® Statistics version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Of the 59 patients with coronary artery disease enrolled fulfilling the inclusion criteria and without exclusion criteria, we included in the analysis presented here 49 patients with echocardiographic measurements available at baseline. The mean age of the sample analyzed was 65.8 years (ranging between 27 years and 84 years) and 51.0% of patients were women. Mean values for adiponectin and resistin were 1922.4 ng/ml and 13.1 ng/ml, respectively; median leptin and TNF-α values were 2118.0 pg/ml and 19.0 ng/ml, respectively. Left ventricular mass ranged between 130.3 and 473.3, with a mean value of 235.8. IVS thickness ranged between 5 mm and 15.0 mm (mean 11.2 mm), LVPW thickness ranged between 8.0 mm and 14.0 mm (mean 10.6 mm) and LVEDD ranged between 38.0 mm and 74.0 mm (mean 53.0 mm; Table 1).

In an unadjusted linear regression analysis adiponectin levels were negatively associated with the IVS thickness (β = −0.340, p = .017), LVPW thickness (β = −0.429, p = .002) and left ventricular relative wall thickness (β = −0.468, p = −.001) and positively associated with LVEDD (β = 0.381, p = .007). LgLeptin (logarithm leptin) was associated with LVPW thickness (β = −0.317, p = .026) and left ventricular relative wall thickness (β = 0.360, p = .011). No association between resistin and lgTNF-α and the echocardiographic measured left ventricular parameters was observed in this model. After adjustment for age, gender, BMI, glycaemia, systolic and diastolic blood pressure, adiponectin remained statistically significant associated with IVS thickness, LVPW thickness, LVEDD and left ventricular relative wall thickness and lgLeptin with LVEDD and left ventricular relative wall thickness (p < .05 for all). No association between left ventricular mass, LVPW thickness and IVS thickness, lgLeptin, resistin and lgTNF-α levels was found in this adjusted model (Table 2).

We further analyzed the data in patients without diabetes (Supplementary Table). The observed associations remained statistically significant for LgLeptin and no association was observed in this sub-set of patients for TNF-α and resistin. For adiponectin the associations were no longer statistically significant in this sub-group.

Table 1
Characteristics of patients enrolled.

Parameter	Study population N = 49
Women, n (%)	25 (51.0%)
Age, years	65.8 ± 12.3
Weight, kg	83.4 ± 17.1
BMI, kg/m^2	29.3 ± 7.8
Medical history, n (%)	
CHD	49 (100%)
HBP	23 (46.9%)
HF NYHA II,III	44 (89.8%)
Atrial fibrillation	10 (20.4%)
PAD	38 (77.6%)
Diabetes	13 (26.5%)
Concomitant therapy, n (%)	
Statins	31 (63.3%)
β-blockers	26 (53.1%)
Diuretics	14 (28.6%)
ACEI	20 (40.8%)
Antiplatelet	25 (51.0%)
Anticoagulants	18 (36.7%)
Pentoxifylline	10 (20.4%)
Fasting plasma glucose, mg/dl	124.5 ± 55.6
Total cholesterol, mg/dl	195.2 ± 76.0
HDL-cholesterol, mg/dl	54.0 ± 14.7
LDL-cholesterol, mg/dl	120.1 ± 69.9
Triglycerides, mg/dl	146.4 ± 87.2
Creatinine, mg/dl*	1.1 (1.0; 1.5)
SBP, mmHg	129.0 ± 17.3
DBP, mmHg	75.4 ± 9.6
Adiponectin, ng/ml	1922.4 ± 1431.8
Leptin, pg/ml*	2118.0 (482.0; 5338.0)
Resistin, ng/ml	13.1 ± 6.2
TNF-α, ng/ml*	19.0 (1.1; 37.0)
LV mass, g/m^2	235.8 ± 84.7
IVS thickness, mm	11.2 ± 2.1
LVPW thickness, mm	10.6 ± 1.5
LVEDD, mm	53.0 ± 9.8
LVRTW	0.4 ± 0.1

BMI = body mass index; CHD = coronary heart disease; HBP = high blood pressure; HF = heart failure; PAD = peripheral arterial disease; ACEI = angiotensin-converting-enzyme inhibitor; FPG = fasting plasma glucose; SBP = systolic blood pressure; DBP = diastolic blood pressure; TNF-α = tumor necrosis factor alpha; LV = left ventricle; IVS = interventricular septum; LVPW = left ventricular posterior wall; LVEDD = left ventricular end diastolic diameter; LVRWT = left ventricular relative wall thickness.

* Data are presented as median (Quartile 1; Quartile 3). All other data in the table are presented as mean ± SD.