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Circulating chemerin levels elevated in dilated cardiomyopathy patients with overt heart failure

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ABSTRACT

Background: Recent evidence demonstrated that the circulating concentrations of adipokine are related to the presence of heart failure secondary to ischemic heart disease and dilated cardiomyopathy (DCM). However, the plasma concentrations of chemerin in patients with DCM have yet to be investigated.
Methods: The present study enrolled 109 DCM patients with typical symptoms of heart failure and 60 healthy controls and measured plasma concentrations of chemerin, IL-6 and TNF-α using enzyme-linked immunosorbent assay. Left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) were measured using a GE ViVid E7 ultrasonography machine.
Results: Plasma chemerin, IL-6 and TNF-α concentrations were significantly higher in DCM patients compared to the control group. A correlation analysis revealed that plasma chemerin concentrations were positively correlated with the concentrations of IL-6 ($R = 0.270$, $P = 0.004$), TNF-α ($R = 0.302$, $P = 0.001$), C-reactive protein (CRP) ($R = 0.256$, $P = 0.004$), *N*-terminal pro-brain natriuretic peptide (NT-proBNP) ($R = 0.386$, $P = 0.000$), and LVEDD ($R = 0.212$, $P = 0.027$) but negatively correlated with LVEF ($R = -0.543$, $P = 0.000$). Furthermore, chemerin (OR 1.102, 95% CI 1.052 to 1.153; $p = 0.000$) was independently associated with the presence of DCM before NT-proBNP was added in the multivariable regression model.
Conclusions: The results indicate that chemerin is a novel biomarker of DCM.

1. Introduction

Dilated cardiomyopathy (DCM), the most common cardiomyopathic phenotype characterized by enlargement of one or both of the ventricles and systolic dysfunction, is a common cause of heart failure and sudden cardiac death. Although the etiology is unclear in 50% or more of patients with DCM, a close relationship between myocarditis and DCM and an important inflammatory and immune component in the pathogenesis of DCM has been established [1–6]. Accumulating evidence showed that circulating tumor necrosis factor (TNF)-α, interleukin (IL)-6 and C-reactive protein (CRP) concentrations significantly increased in DCM with or without overt heart failure, resulting in an unfavorable prognosis [7–9].

Adipose tissue is not only a site of lipid storage but also acts as an active endocrine organ that secretes multiple immune-modulatory proteins known as adipokines [10,11]. The list of adipokines continues to grow to hundreds of factors, including adiponectin, visfatin, leptin, resistin, and chemerin, among other factors. Some of these factors are pleiotropic cytokines, which participate in inflammation and immune regulation [10,11]. Indeed, TNF-α and IL-6 may also be secreted by adipose tissue. Numerous studies established that adipokines, such as adiponectin, visfatin and leptin, are involved in the pathogenesis of different cardiovascular diseases including myocardial infarction and heart failure [10–16]. Confusingly, some studies demonstrated that a high adiponectin concentration was an independent prognostic factor in chronic heart failure whereas another study found that a high adiponectin concentration indicated a favorable outcome in inflammatory DCM [17–19].

Chemerin, which is also known as tazarotene-induced gene 2 protein (TIG2) or retinoid acid receptor responder 2 (RARRES2), is a novel adipokine that plays a pivotal role in adipose differentiation, maturation and metabolism, regulation of immune response, inflammation

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and insulin resistance [20–23]. The secretion of chemerin is efficiently induced by inflammatory stimulation, including TNF-α and IL-1β [24,25], and its maturity is promoted by neutrophils, which are the first cells recruited to sites of inflammation [26]. Numerous studies established a close relationship between chemerin and chronic inflammatory disease including coronary artery disease [27,28], diabetes [29,30], rheumatoid arthritis and osteoarthritis [31,32]. Recently, we found a positive correlation between chemerin and LVEF, suggesting that chemerin is closely associated with the impaired heart function in patients with acute coronary syndrome, which is the critical phase of coronary artery disease and is another major contributor to heart failure [33].

2. Methods

2.1. Patients

One hundred nine consecutive patients diagnosed with DCM were enrolled in the present study. Twenty-five patients were classified according to the standards of the NYHA as functional class II (DCM1 group), 47 patients as class III (DCM2 group), and 37 patients as class IV (DCM3 group). Because it is difficult to find DCM patients with class I in clinic, there was no patient enrolled as class I. Inclusion criteria were (1) Left ventricular ejection fraction (LVEF) less than 50% and left ventricular end-diastolic diameter (LVEDD) more than 55 mm; (2) angiographically normal coronary arteries. The control group consisted of 60 age-matched healthy subjects. The clinical profile of patients and healthy controls is given in Table 1.

Subjects with hypertension, diabetes, coronary artery disease, congenital or valvular heart disease, myocarditis and pericarditis were excluded. Specific phenotypes of cardiomyopathy such as hypertrophic cardiomyopathy, peripartum cardiomyopathy and alcoholic cardiomyopathy were also excluded. In addition, patients with advanced liver disease, renal failure, malignant disease, septicemia or current steroid therapy, and other inflammatory disease were excluded from the study.

Written informed consent was obtained from each patient. The study was approved by the Ethics Committee of Beijing Anzhen Hospital, the People's Hospital of Guangxi Zhuang Autonomous Region and China–Japan Friendship Hospital.

2.2. Clinical data collection

Clinical data were obtained upon admission to hospital. Demographic data, height, body weight, medical history, and medication use were recorded.

2.3. Blood samples

Fasting blood samples were obtained the morning after admission. The samples were collected in sodium heparin Vacutainers (Becton-Dickinson). Blood was centrifuged for 15 min at 3000 ×*g* and the plasma was stored at −80 °C until further use.

2.4. Laboratory measurements

The concentrations of plasma chemerin (R&D Systems, USA), TNF-α and IL-6 (Westtang Bio-Tech) were measured using ELISA, following the manufacturer's instructions. The ELISA intra-assay and inter-assay CVs were <5% and <10%, respectively. All of the samples were measured in duplicate.

2.5. Doppler echocardiography

The patients underwent M-mode and 2D-echocardiography using a GE ViVid E7 ultrasonography machine (GE Healthcare) with a transthoracic 1.5–4.3 MHz probe (M5S-D). LVEDD and fractional shortening were measured. LVEF was calculated from apical four chambers position by the area–length method.

Table 1
Clinical characteristics of patients.

Characteristics	Control	DCM	DCM1	DCM2	DCM3
Age (y)	51 ± 13	54 ± 13	58 ± 11*	54 ± 12	53 ± 15
Sex (male/female)	34/26	77/32	16/9	32/15	29/8
Smoking, n (%)	13 (21.7)	24 (22.0)	3 (12)	12 (25.5)	9 (24.3)
BMI (kg/m^2)	25.4 ± 3.2	23.8 ± 3.8*	23.1 ± 3.2	23.7 ± 3.3	24.2 ± 4.7
HR (bpm)	69 ± 10	89 ± 18*	87 ± 18*	88 ± 18*	92 ± 18*
SBP (mm Hg)	121 ± 12	119 ± 14	124 ± 12	119 ± 14	117 ± 16
DBP (mm Hg)	72 ± 8	75 ± 12*	74 ± 9	75 ± 12	77 ± 14
TG (mmol/l)	1.33 (1.01)	1.09 (0.67)*	1.08 (0.42)*	1.22 (0.83)	0.99 (1.63) *
TC (mmol/l)	4.53 ± 0.95	4.20 ± 1.06	4.19 ± 1.26	4.30 ± 1.11	4.09 ± 0.84
HDL-C (mmol/l)	1.06 (0.35)	1.01 (0.46)	1.28 (0.61)	1.02 (0.38)	0.94 (0.38)*
LDL-C (mmol/l)	2.73 ± 0.81	2.70 ± 0.83	2.43 ± 0.69	2.80 ± 1.02	2.74 ± 0.59
GLU (mmol/l)	5.11 ± 0.60	4.94 ± 1.20	5.12 ± 1.50	4.78 ± 0.82	5.03 ± 1.38
Creatinine (μmol/l)	72.05 (20.37)	91.00 (28.03)*	83.01 (22.50)*	95.00 (26.00)*	92 (38)*
CKMB (ng/ml)	1.10 (1.02)	1.71 (1.55)*	1.60 (1.06)*	1.75 (2.38)*	1.80 (2.02)*
TnI (ng/ml)	0.01 (0.01)	0.03 (0.04)*	0.02 (0.05)*	0.03 (0.04)*	0.02 (0.02)*
CRP (mg/l)	0.74 (0.78)	3.67 (8.55)*	3.40 (9.38)*	3.65 (8.05)*	4.55 (12.28)*
NT-proBNP (pg/ml)	75 (133)	3127 (4642)*	2178 (3663)*	3003 (4621)*	4613 (4705)*
LVEF (%)	65.4 ± 5.7	30.9 ± 6.8*	33.8 ± 5.9*	30.8 ± 6.2*	29.2 ± 7.5*
LVEDD (mm)	47.2 ± 3.6	65.6 ± 7.7*	64.3 ± 7.4*	65.8 ± 7.4*	66.3 ± 8.2*
Medications, n (%)					
ACEI/ARB	0	39 (35.8)	10 (40)	12 (25.5)	17 (45.9)
β-blocker	0	22 (20.2)	9 (36)	7 (14.9)	6 (16.2)
Diuretics	0	50 (45.9)	12 (48)	15 (31.9)	23 (62.1)
Digitalis	0	48 (44.0)	10 (40)	15 (31.9)	23 (62.1)
Spironolactone	0	33 (30.3)	7 (28)	13 (27.7)	13 (35.1)

The data are given as the mean ± SD, median (QR) or number of patients. DCM: dilated; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimension; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.
* $P < 0.05$ vs. control.