J Med Biochem 2018; 37 (2) DOI: 10.1515/jomb-2017-0047

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 37: 148–154, 2018

Original paper
Originalni naučni rad

CHEMERIN, RESISTIN, AND ADIPONECTIN IN PATIENTS WITH CONNECTIVE TISSUE DISEASES

CHEMERIN, REZISTIN I ADIPONEKTIN U PACIJENATA SA OBOLJENJIMA KONEKTIVNIH TKIVA

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Summary

Background: The exact role of cytokines in inflammation and metabolic disorders in case of connective tissue diseases (CTDs) is under discussion.
Methods: In this study, we intended to find the relationship between the selected cytokines in inflammatory and metabolic disorders in patients with CTDs (n=55) and compared the results with those of control group subjects (n=25) matched by age and body mass. We estimated their nutritional status by the bioimpedance method. The levels of basic biochemical parameters and the levels of adiponectin, resistin, and chemerin were also estimated. Multiple regressions and area under the curve in receiver operating characteristic (AUC–ROC) curve were used to find the associations of aforementioned parameters.
Results: Patients with CTDs exhibited higher levels of chemerin than that of control group subjects. We found an inverse relationship between chemerin, RBC count, and hemoglobin levels. The concentration of adiponectin inversely correlated with the levels of platelets and concentrations of glucose and triglycerides as well as the erythrocyte sedimentation rate, whereas the concentration of resistin was positively correlated with WBC count, C-reactive protein (CRP), and the amount of used oral glucocorticosteroids. The mean ± standard deviation for the AUC–ROC curve in case of chemerin was the highest (AUC–ROC=0.714, p=0.0005) than that of both resistin and adiponectin.
Conclusions: Chemerin and resistin levels are related to the inflammatory state in patients with CTDs, whereas adiponectin levels seem to be correlated with a protective effect. Chemerin can be considered as a marker differentiating a proinflammatory state present in CTDs.

Keywords: cytokines, connective tissue diseases, inflammation, nutritional status

Kratak sadržaj

Uvod: Tačna uloga citokina kod inflamatornih i metaboličkih poremećaja kod oboljenja konektivnih tkiva (CTD) je diskutabilna.
Metode: U ovom istraživanju, ispitivan je odnos između pojedinih citokina kod pacijenata sa inflamatornim i metaboličkim poremećajima sa CTD (n= 55) i poređen sa rezultatima istih kod kontrolne grupe (n= 25) shodno godinama starosti i telesnoj težini. Ispitivan je njihov nutricioni status metodom bioimpendance. Određivani su nivoi osnovnih biohemijskih parametara, adiponektina, rezistina i chemerina. Za obradu podataka korišćena je multipla regresiona analiza sa površinom ispod krive (AUC-ROC).
Rezultati: Pacijenti sa CTD imali su više nivoe chemerina nego osobe u kontrolnoj grupi. Utvrđen je obrnut odnos između chemerina, broja eritrocita i nivoa hemoglobina. Koncentracija adiponektina bila je u obrnutoj korelaciji sa nivoima trombocita i koncentracijama glukoze i triglicerida kao i sa sedimentacijom eritrocita, dok je koncentracija rezistina bila u pozitivnoj korelaciji sa brojem leukocita, C-reaktivnim proteinom (CRP) i količinom oralno korišćenih glukokortikosteroida. Srednja vrednost ± standardna devijacija za AUC-ROC krivu u slučaju chemerina bila je veća (AUC-ROC = 0,714, p = 0,0005) nego kod rezistina i adiponektina.
Zaključak: Nivoi chemerina i rezistina bili su u korelaciji sa inflamatornim stanjem pacijenata sa CTD, dok su nivoi adiponektina bili u korelaciji sa zaštitnim efektom. Može da se smatra da je chemerin marker proinflamtornog stanja u CTD.

Ključne reči: citokini, konektivna tkivna oboljenja, inflamacija, nutriconi status

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Introduction

Of late, many studies have underlined the role of adipokines not only in metabolic disorders, but also in the inflammation and the immune responses (1, 2). Most of the studies are based on the fact that white adipose tissue is a very active organ, which synthesizes various immune and inflammatory mediators contributing toward the development of connective tissue diseases (CTDs), however, their exact role in these diseases is under discussion (3). For example, metabolic studies have shown a protective role of adiponectin in inflammatory processes; nevertheless, in CTDs the role of adiponectin is not so clear and both proinflammatory (4, 5) and anti-inflammatory properties have been described (6). Resistin, a cysteine-rich secretory adipokine, reveals proinflammatory activity in patients with CTDs such as systemic lupus erythematosus (SLE) (7) or rheumatoid arthritis (RA) (8). The secretion of resistin is induced by several cytokines (e.g., tumor necrosis factor alpha (TNF-α) or interleukin (IL-6) that are secreted during the active phase of CTDs, which increases its activity by a positive feedback mechanism (9). The association between resistin and laboratory markers of inflammation, particularly C-reactive protein (CRP), was proved in patients with CTDs (7, 10). Chemerin is not only involved in adipogenesis and glucose metabolism but is also involved in the regulation of inflammation (11). Dendritic cells, macrophages (12), and chondrocytes express chemerin and its receptor (13–15). Moreover, many proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 upregulate the expression of chemerin (14, 16). Chemerin has also been detected in skin biopsies of patients with SLE (15).

Having known that adipokine levels change in autoimmune CTDs, we considered it appropriate to study them in a group of patients with CTDs is a gender-specific population matched for age and body mass. Therefore, in this study, we estimated the relationship between adiponectin, resistin, and chemerin and the metabolic, inflammatory, and anthropometric parameters in a group of patients with CTDs and compared it with control group subjects.

Material and Methods

A total of 94 patients were selected from the Department of Rheumatology and Internal Diseases and were invited to undergo anthropometric measurements. From this group, 39 patients suffering essential diseases such as nontreated thyroidal disorders, acute liver and renal diseases (not associated with a course of the CTDs), neoplasm, acute infections, smoking, consumption of alcohol, or intake of vitamins or mineral supplements, or patients using a special diet (diabetic, nongluten, or low-caloric diet) were excluded from this analysis.

Because fat mass and lean body mass (LBM) differ between male and female participants, we decided to compare the anthropometric and biochemical parameters only in female participants, which allowed us to estimate the plasma cytokine levels reliably. The control group consisted of 25 women without CTDs and were matched for various anthropometric measures, including age and body mass. The same exclusion criteria as in the study group were applied to the control group participants. All participants enrolled in this study provided their written informed consent. This study was approved by the local Bioethics Committee of Poznan University of Medical Sciences (no. 791/15) and was performed according to the Helsinki Declaration.

Anthropometric measurements

The measurements were performed after an overnight fast. All participants were instructed not to exercise for 8 h prior to collecting their measurements and not to consume food and alcohol 12 h before the examination. The participants were measured in their innerwear for the anthropometric measurements, including basic measurements such as height, weight, waist, and hip circumferences. Weight was measured to the nearest 0.1 kg using digital scales while the subjects were minimally clothed and without shoes. Height was measured using a vertical ruler to the nearest 0.5 cm. Waist circumference was measured to the nearest 0.1 cm, at the midpoint between the inferior border of the ribcage and the superior aspect of the iliac crest using a soft measuring tape, without any pressure exerted on the body. Hip circumference was measured at the level of the greater trochanters. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2), and waist-to-hip ratio (WHR) was calculated as the proportion of waist-to-hip circumferences (17). All anthropometric components were measured twice by the study staff using a standardized protocol, and the values were averaged. Bioimpedance was performed with the patient in a supine position on a nonconductive surface with limbs at an angle of approximately 30°. The body fat (FM) content, LBM, and total body water (TBW) were assessed by the bioimpedance method using BODYSTAT 1500-a single-frequency (50 kHz) device (Bodystat Ltd, Isle of Man, United Kingdom).

Biochemical Analysis

Blood samples were collected between 7:00 am and 8:00 am following an overnight fast. Venous blood samples were collected in EDTA or heparin-containing tubes, which were immediately centrifuged. Complete blood count, CRP, erythrocyte sedimentation rate (ESR), plasma glucose, and lipid profile (total cholesterol, TC, high density lipoprotein, HDL, and triglycerides, TG), were evaluated using

enzymatic colorimetric assays (Cobas Integra 400 Plus; Roche Diagnostics, Indianapolis, IN). Low density lipoprotein (LDL) was calculated from serum TC, TG, and HDL according to the Friedewald equation (18). All the plasma levels of cytokines (chemerin, adiponectin, and resistin) were measured in strict accordance with the manufacturer's instructions, using immunoenzymatic tests as follows: Microtiter plates with fixed primary antibody (specific for the assayed molecules) were incubated with plasma (containing the antigen, namely, the measured protein) and later with secondary antibody marked with peroxidase. Finally, a reaction was performed with a substrate for chromogen and the absorbance (450 nm) was read on an MR-96 microplate reader manufactured by CLINDIAG SYSTEMS B.V.B.A. (Pollare, Belgium). The intra-assay and inter-assay coefficient of variation (CV) for adiponectin, resistin, and chemerin were respectively found to be 3.4% and 4.0%, 5.2% and 5.7%, and 4.9% and 5.8%.

Statistical analysis

The results were statistically analyzed using the STATISTICA 12.5 software with Medical Set (StatSoft Inc., USA), including analyses for comparing medians for unrelated data (Mann–Whitney *U* test), correlation between the studied variables (Pearson and Spearmantests), area under curve (AUC) calculations in receiver operating characteristic (ROC) curve (AUC–ROC), and analyses of multiple regressions. The normality of the distribution of data was checked using the Shapiro–Wilk test and homogeneity of variance was tested using Levene's test. The statistically significant level of error was established at $\alpha < 0.05$.

Results

The anthropometric and biochemical analyses revealed a similar body mass, height, FM, and TBW, and LBM among the patients with CTDs and from the control group (*Table I*). However, patients with CTDs had lower BMI, diastolic blood pressure, hemoglobin, hematocrit, and mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) and higher ESR values than that of women in the control group. About 84% of the study participants were undergoing glucocorticosteroid therapy. Chemerin level was found to be higher in patients with CTDs than that of women in the control group, whereas there was no difference between the levels of resistin and adiponectin in the analyzed groups. The correlation of selective parameters with the levels of serum cytokines revealed that adiponectin inversely correlated with the levels of platelets, glucose, triglycerides, and ESR values (*Table II*). Resistin concentration was found to be positively correlated with WBC, CRP, and the amount of used oral glucocorticosteroids (GCS). Inverse relationship between chemerin, RBC count, and hemoglobin levels was observed. The mean ± standard deviation for the AUC–ROC curve in the case of chemerin was found to be the highest (0.714±0.060) than that of resistin and adiponectin (*Table III*, *Figure 1*).

Discussion

Obesity is characterized by a low-grade chronic inflammatory state that contributes to the development of insulin resistance and glucose intolerance (19). In this study, the control group was matched according to parameters such as gender, age, and body mass so that the role of the analyzed cytokines in the development of an inflammatory state could be estimated. Moreover, the amount of fat mass and LBM were comparable, which largely contributed to eliminate the fluctuations in cytokine levels caused by the quantity of adipose tissue. Nevertheless, BMI values were found to be higher in women in the control group than that of patients with CTDs, which was the result of smaller values of height and higher values of body mass (no significant statistical differences). Patients with CTDs exhibited lower levels of hemoglobin, hematocrit, MCV, and MCHC values than that of women in the control group, which is characteristic for many CTDs. This reflects the tendency toward anemia of chronic diseases caused by inflammation-induced alterations in iron homeostasis and erythropoiesis (20). The inflammatory state in patients with CTDs was related to higher ESR; however, its level was within the recommended range, which was caused by the immunosuppressive effect of glucocorticosteroid use (21). Moreover, diastolic blood pressure was found to be lower in patients with CTDs than that of women in control group, because the patients had constant control of this parameter during the consecutive admission to the Rheumatology Department and immediate implementation of adequate hypotensive therapy. Elevated chemerin levels in patients with CTDs reflect the inflammatory state (11). This cytokine regulates the inflammatory processes and shows autocrine, paracrine, and endocrine activities (11, 22, 23). Chemerin is also a potent chemoattractant while acting as a ligand on cells expressing chemerin receptors, including cells participating in inflammation such as immature dendritic cells and macrophages (22). Thus, chemerin is considered as a potent proinflammatory peptide (23).

Table II shows the correlation of analyzed cytokines and biochemical parameters. One of the cytokine that is synthesized by the adipose tissue and described in the course of CTDs is adiponectin (4–6). This molecule acts a modulator of both B and T cells and influences inflammatory processes by inducing relevant anti-inflammatory factors such as IL-1 receptor antagonist and IL-10 (6). The protective role of adiponectin was also confirmed in this study. Adiponectin was found to inversely correlate with platelets,

Table I Anthropometric and biochemical characteristics of patients with connective tissue diseases (CTDs) and the control group.

Analysed parameters	Patients with CTDs	Control group	(n=55)
Age, years	56.0±95	57.0±3.5	NS
Height, cm	161.0±55	159.0±3.0	NS
Waist circumference, cm	78.0±8.5	74.0±9.5	NS
Hip circumference, cm	98.0±6.5	101.0±4.0	NS
Fat mass, kg	22.9±5.8	25.0±6.05	NS
Lean Body Mass, kg	38.6±4.4	40.0±3.7	NS
Bodymass, kg	63.0±8.7	66.4±7.2	NS
TBW, kg	30.40±2.05	31.90±2.05	NS
BMI, kg^2m^2	23.36±2.98	25.06±3.53	<0.002
WHR	0.818±0.053	0.776±0.074	NS
SBP, mmHg	130.0±12.5	137.0±21.5	NS
DBP, mmHg	75.0±10.0	88.0±10.5	<0.0002
WBC×10^3, l/μL	6.80±1.85	6.10±0.85	NS
RBC×10^3, l/μL	4.43±0.3	4.79±0.23	<0.003
Hb, g/L	133.0±8.0	143.0±7.0	<0.0004
Ht, %	39.30±2.85	42.0±1.40	<0.0001
MCV, fL	87.70±3.65	90.10±2.60	<0.05
MCH, pg	29.00±1.25	30.10±0.90	<0.02
MCHC, g/L	335.0±8.0	337.0±5.50	NS
PLT, ×10^3/μL	246.00±47.50	239.00±27.50	NS
ESR, mm/h	14.0±6.5	6.0±3.5	<0.00002
Glycaemia, mmol/L	4.97±0.35	5.00±0.50	NS
CRP, mg/L	1.60±3.70	2.50±0.0	NS
CH, mmol/L	5.75±0.91	5.62±0.52	NS
HDL, mmol/L	1.57±0.32	1.46±0.11	NS
TG, mmol/L	1.46±0.49	1.65±0.33	NS
LDL, mmol/L	3.40±0.71	3.49±0.36	NS
GKS*, mg/day	6.0±6.0	0.0±0.0	<0.000000
Adiponectin, μg/mL	11577±0737	11.626±0.077	NS
Resistin, μg/mL	4.503±1.263	5.462±0.783	NS
Chemerin, μg/mL	246.993±27.291	190.457±44.355	<0.002

n – number of people; p – level of statistical significance upon comparison between patients with rheumatic diseases and control group; NS – statistically insignificant difference; TBW – total body content; BMI – Body Mass Index; WHR – Waist to Hip Ratio; ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; CH – total cholesterol level; HDL – high density lipoprotein level; LDL – low density lipoprotein level; TG – triglycerides; SBP – systolic blood pressure; DBP – diastolic blood pressure: *GKS as units of methylprednisolone

Table II Indices of correlation and levels of statistical significance in cases of analyses involving relationship between resistin, adiponectin, and chemerin and selected hematological and biochemical parameters in patients with CTDs (n=55).

Analysed parameters	Adiponectin, μg/μL		Resistin, ng/mL		Chemerin, ng/mL	
	R	p	R	p	R	p
WBC×10³, l/μL	–	NS	0.33	0.015	–	NS
RBC×10⁶, l/μL	–	NS	–	NS	-0.28	0.038
Hb, g/L	–	NS	–	NS	-0.30	0.026
PLT×10³, l/μL	-0.27	0.046	–	NS	–	NS
Glycemia, mmol/L	-0.28	0.038	–	NS	–	NS
TG, mmol/L	-0.37	0.005	–	NS	–	NS
GKS*, mg/day	–	NS	0.32	0.015	–	NS
ESR, mm/h	-0.32	0.016	–	NS	–	NS
CRP, mg/mL			0.54	0.0008	–	NS

n – number of persons; R – coefficient of Pearson or Spearman (for respectively parametric or non-parametric date distributions), p-level of statistical significance, NS-statistically insignificant difference; *GKS as units of methylprednisolone

Table III Characteristics of ROC curves for index resistin, adiponectin, and chemerin for pairs of studied groups (CTDs; n=55 vs CONTR; n=25).

Parameter, unit	Cut-off value	AUC-ROC	SD (AUC-ROC)	95% CI	P
Adiponectin, μg/mL	11.611	0.578	0.069	0.444–0.713	NS
Resistin, ng/mL	4.196	0.633	0.065	0.507–0.760	<0.04
Chemerin, ng/mL	245.350	0.714	0.060	0.596–0.832	<0.0005

CTDs – patients with connective tissue diseases; CONTR – control group; n– number of persons; cut-off value – point on ROC (Receiver Operating Characteristic) curve, AUC-ROC – Area Under Curve of Receiver Operating Characteristic); SD (AUC-ROC) – standard deviation of AUC-ROC; p – level of statistical significance; NS – statistically insignificant difference

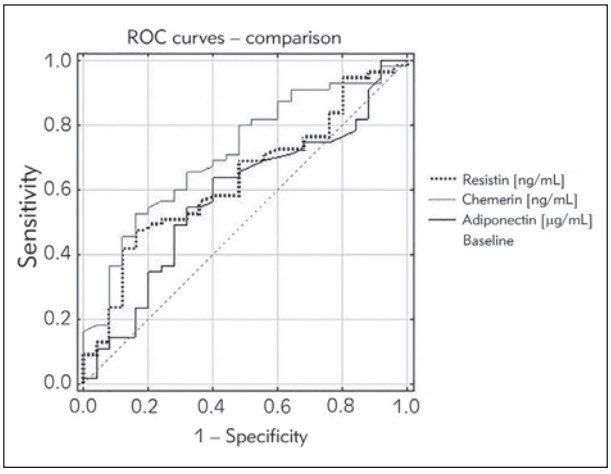

Figure 1 Receiver Operating Characteristic (ROC) curves for resistin, chemerin, and adiponectin for the differentiation between CTDs (patients with connective tissue diseases) and CONTR (control) groups.

glucose, and triglycerides levels, as well as with ESR. However, some authors showed the proinflammatory effect of this cytokine by the induction of IL-6 synthesis, metalloproteinase-1 in cyclooxygenase-2 in rheumatoid arthritis (24–26) and is claimed to be a biomarker of renal SLE flares (27).

Other cytokines secreted from the adipose tissue and by cells participating in inflammatory processes (e.g., macrophages or neutrophils) is resistin (28, 29). Many studies have described its role in inflammatory processes including CTDs such as rheumatoid arthritis (8, 9, 30) or SLE (7). In this study, resistin was found to correlate positively with the amount of oral GCS used during the treatment of active diseases and markers of inflammation such as WBC and CRP. Similar data are reported by other authors who showed positive correlation of resistin level with CRP in patients with rheumatoid arthritis (8, 10) or in patients with SLE (31). In this study, resistin also cor-

related with the dosage of glucocorticosteroids use, which is comparable with the findings in other studies (7).

Inverse relationship between chemerin, RBC count, and hemoglobin concentration was observed. Anemia of chronic diseases is one of the parameter of inflammatory state, often present in CTDs is considered to be a symptom of the underlying inflammatory disease (20). Chemerin acts as a marker of an inflammatory state expressed by macrophages (12) and endothelial cells, and is upregulated by proinflammatory cytokines such as TNF-α, IL-1β, and IL-6, which are factors that trigger inflammation in CTDs (16). The proinflammatory properties of chemerin explain the correlation of this cytokine with anemia (higher levels of chemerin correlated with the lower levels of hemoglobin). Moreover, the analysis of ROC in this study showed that chemerin is also a good parameter for differentiating the patients' group from the control group (AUC–ROC=0.714, p=0.0005).

Conclusion

Although resistin and adiponectin levels did not differ between patients with CTDs and women in control group, resistin was found to be clearly associated with general inflammation and dosage of glucocorticosteroids, whereas adiponectin displayed protective role (inversely correlated with parameters of inflammatory state). Chemerin differed significantly between groups, revealed proinflammatory activity, and was found to be correlated with inflammatory markers. Moreover, this cytokine has higher properties differentiating patients with CTDs from the control group (AUC–ROC=0.714). Thus, adipokines are involved in the regulation of inflammatory processes and autoimmunity in the light of pathogenesis of CTDs. However, further studies are required to reveal the exact roles of analyzed cytokines in the course of CTDs.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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Received: July 27, 2017

Accepted: September 5, 2017