Leptin, adiponectin, resistin, visfatin serum levels and idiopathic recurrent pericarditis: biomarkers of disease activity? A preliminary report

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Abstract

Objectives

Idiopathic recurrent acute pericarditis (IRAP) represents the most troublesome complication of acute pericarditis and is an autoimmune process. White adipose tissue produces more than 50 adipokines that participate in inflammation and autoimmunity. This study investigated whether serum leptin, resistin, visfatin and adiponectin are increased in IRAP versus healthy controls and if their levels correlate with parameters of disease activity.

Methods

Serum leptin, resistin, visfatin and adiponectin levels were assayed by enzyme-linked immunosorbent assay in 14 IRAP patients during recurrences (group 1), in 23 IRAP patients during symptom-free intervals (group 2) and in 18 healthy controls (group 3). Assessment parameters included demographic characteristics of patients and controls, clinical characteristics of patients and markers of inflammation. Comparisons between groups as well as reciprocal comparisons were evaluated.

Results

Group 1 showed serum leptin ($p<0.008$), visfatin ($p<0.002$), and adiponectin ($p<0.04$) significantly higher than group 2 and control group, whereas resistin serum levels did not significantly differ ($p=0.69$). Among IRAP patients, serum leptin significantly correlated with serum amyloid A (SAA) levels ($r_s=0.43$, $r^2= 0.27$, $p<0.02$). Other than this correlation, none of the considered adipokines significantly correlated with the other considered variables in univariate analysis

Conclusion

Leptin, adiponectin and visfatin are increased in IRAP patients versus healthy controls. Our data suggest that these adipokines might be involved in IRAP pathogenesis and that a possible increased cardiovascular risk in these patients, through an early onset atherosclerosis, should be kept in mind. SAA might be a link between IRAP and increased cardiovascular diseases.

Key words

idiopathic recurrent acute pericarditis (IRAP), leptin, visfatin, adiponectin, serum amyloid A, cardiovascular risk

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Introduction

Idiopathic recurrent acute pericarditis (IRAP) represents the most troublesome complication of acute pericarditis and is generally presumed to be an autoimmune process. This is suggested by the presence of serum anti-heart and anti-intercalated-disk antibodies and by the good response to immunosuppressive drugs administration (1). On the other hand, it has been suggested that some of these patients might have an atypical or subclinical form of an autoinflammatory disease, genetic disorders characterised by primary dysfunction of the innate immune system and caused by mutations of genes involved in the regulation and/or activation of the inflammatory response, without any apparent involvement of autoimmunity (2-7).

White adipose tissue produces more than 50 adipokines that participate in a wide variety of physiopathological processes (8-12).

Among the adipokines, leptin, resistin and visfatin are pro-inflammatory (8), whereas adiponectin has been described to have anti-inflammatory as well as pro-inflammatory properties depending on its molecular form (11). These adipokines are often associated with increased cardiovascular risks in several inflammatory and autoimmune diseases (8, 9).

The aims of our study were to evaluate serum leptin, resistin, visfatin and adiponectin levels in patients with IRAP, in comparison to healthy controls, and also to correlate their serum levels to parameters of disease activity.

Patients and methods

Patients

We collected detailed information about personal history, clinical data and response to treatment from 37 consecutive outpatients treated in our institutions for IRAP (Interdepartmental Research Centre of Systemic Autoimmune and Autoinflammatory Diseases, Rheumatology Unit, Policlinico Le Scotte, University of Siena, Siena, Italy; Internal Medicine, Ospedali Riuniti di Bergamo, Bergamo, Italy; Cardiology Department, Ospedale Maria Vittoria, Turin, Italy).

Acute pericarditis was diagnosed according to the accepted diagnostic criteria: chest pain, pericardial friction rub, electrocardiographic changes, new or worsening pericardial effusion (a clinical diagnosis of acute pericarditis was made when at least 2 of these criteria were present). Recurrence was documented by recurrent pain and ≥1 of the following signs: pericardial friction rub, electrocardiographic changes, echocardiographic evidence of pericardial effusion, and elevations in the white blood cell count, C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) (12-15).

Serum leptin, resistin, visfatin and adiponectin levels were obtained from 14 IRAP patients during IRAP recurrences (group 1), and from 23 IRAP patients during symptom-free intervals (group 2) as well as from 18 healthy controls attending our outpatient clinic (Interdepartmental Research Centre of Systemic Autoimmune and Autoinflammatory Diseases, Rheumatology Unit, Policlinico Le Scotte, University of Siena, Siena, Italy) for arthralgias and/or musculoskeletal pain (group 3). All healthy controls underwent routine clinical, laboratory, and instrumental investigations in order to rule out possible rheumatic diseases, cardiovascular disorders, infections, endocrine, and/or metabolic disorders. Nobody presented any signs of inflammation. In addition, all patients were investigated for mutations in the genes responsible for the most common hereditary autoinflammatory disorders such as the *MEFV*, *TNFRSF1A*, *NLRP3* and *MVK* genes. No mutations were found. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the Declaration of Helsinki as reflected in an *a priori* approval by the institution's human research committee.

Assessment parameters

Assessment parameters included: gender, age, age at disease onset, weight, height, body mass index (BMI), duration of the first pericarditis attack (days), average duration of recurrences (days), mean number of recurrences/year at 1st year, mean number of recur-

rences/year from the 2nd year, disease duration, time to recurrence, serum amyloid A (SAA) levels, ESR, CRP, treatments (steroids and/or colchicine and/or non-steroidal anti-inflammatory agents [NSAIDs]) and presence of concomitant pleural inflammation.

Laboratory assessments

Blood samples (6 ml) were drawn from an antecubital vein with the patient or the control in the supine position in the morning after an overnight fast. The blood was immediately centrifuged and serum was stored at -80°C until analysed.

Serum leptin levels were detected with the enzyme- immunoassay method using Leptin (human) EIA Kit (Alexis assay designes, Enzo life Sciences). Sensitivity of samples was 23.4 pg/ml. Inter- and intra-assay coefficients of variation were 3.7–15.2% and 4.4–13.4%, respectively. Serum resistin levels were detected with the enzyme-linked immunosorbent assay method using resistin (human) Elisa kit (AdipoGen Inc., Korea). Sensitivity of samples was 100 pg/ml. Inter- and intra-assay coefficients of variation were 4.2–7.2% and 2.8–5.2%, respectively. Serum visfatin levels were detected with the enzyme-linked immunosorbent assay method using Nampt (Visfatin/PBEF) (human) Elisa kit (AdipoGen Inc., Korea). Sensitivity of samples was 30 pg/ml. Inter- and intra-assay coefficients of variation were 4.7–7.2% and 2.3–9 %, respectively.

Serum adiponectin levels were determined with the enzyme-linked immunosorbent assay method using adiponectin (human) Elisa kit (AdipoGen Inc., Korea). Sensitivity of samples was 100 pg/ml. Inter- and intra-assay coefficients of variation were 2.8–5.5% and 2.9–3.8%, respectively.

Other laboratory assessment parameters included: a) ESR, b) CRP, and c) SAA. ESR was measured using the Westergren method. Values are expressed in mm/hour. An ESR <15 mm/hour was considered to be normal for males and an ESR <20 mm/hour was considered to be normal for females. Serum CRP concentrations were measured using a nephelometric immunoassay. Values are expressed in mg/dl. A CRP <0.5 mg/dl was considered to be normal.

SAA serum concentration was determined with a commercial solid phase sandwich enzyme linked-immunosorbent assay (ELISA) (Human SAA; BioSource Europe S.A., Belgium). The assay sensitivity was <4 ng/ml. The normal value of SAA was <6.4 mg/l.

Statistical analysis

All results are expressed as mean ± standard deviation (SD) or median (range). Mann-Whitney U-test, with Fisher's exact test, when appropriate, and analysis of covariance (ANCOVA) with least significant difference (LSD) correction were used to evaluate the mean differences (±SD) between groups, considering as covariates for ANCOVA the above listed demographic, clinical and laboratory-collected data. The Spearman rank correlation test was used to determine correlation coefficients between the four adipokine serum levels and the above reported entered variables. Multiple stepwise regression was performed to determine variables, including demographic variables, which could correlate independently, therefore the predictors used in the final model were those showing a significant correlation in the univariate analysis. Non-parametric tests were used, where necessary, due to the small size of our groups and to the skewness of our data. Levels of $p<0.05$ were considered statistically significant. Analyses were performed on SPSS package for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA).

Table I. Clinical and demographic characteristics of IRAP patients and healthy controls.

	Group 1 (n=14)	Group 2 (n=23)	Group 3 (n=18)	*p*-value
Demographic characteristics				
Gender (F/M)	8/6	11/12	10/8	0.8
Age (years)	39.00 ± 9.8	45.87 ± 13.4	43.82 ± 12.6	0.8
BMI	24.42 ± 2.3	23.01 ± 3.3	23.64 ± 2.8	0.31
Clinical characteristics				
Mean number of recurrences/year (1st year)	3.25 ± 2.8	3.04 ± 2.5	--	0.5
Mean number of recurrences/year (from 2nd year)	2.88 ± 2.5	4.86 ± 4.6	--	0.2
Average duration of recurrences, days	8.23 ± 3.1	6.35 ± 3.8	--	0.1
Disease duration (years)	3.25 ± 2.8	5.46 ± 4.3	--	0.1
Involvement of other serous membranes (yes/no)	8/5	14/9	--	0.8
Markers of inflammation				
SAA levels (mg/l)	775.82 ± 141.4	47.95 ± 85.4	--	0.002
CRP levels (mg/dl)	6.12 ± 1.7	0.62 ± 0.3	--	0.003
ESR levels (mm/h)	44.25 ± 34.1	6.72 ± 9.04	--	0.0001
Treatments				
Colchicine	10	12	--	0.9
NSAIDs	7	7	--	0.7
Corticosteroids	4	7	--	0.8

Group 1: IRAP patients during recurrences (active pericarditis); Group 2: IRAP patients during symptom-free intervals (quiescent pericarditis); Group 3: healthy controls.
NSAIDs: non-steroidal anti-inflammatory drugs; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SAA: serum amyloid A; BMI: body mass index.

Results

Table I summarises the clinical data of IRAP patients and the demographic characteristics of patients and controls. The 3 groups were homogeneous for gender, age at enrollment, weight, height, and BMI. Figure 1 shows that at mean of the above mentioned covariates, ANCOVA analysis showed that group 1 had serum leptin ($p<0.008$), visfatin ($p<0.002$), and adiponectin ($p<0.04$) levels significantly higher than group 2 and the control group, whereas resistin serum levels did not significantly differ ($p=0.69$). In detail, serum leptin was significantly higher in group 1 than in group 2 ($p<0.01$) and in the control group ($p<0.004$) (Fig. 1a); serum leptin did not significantly differ between group 2 and the control group ($p=0.8$); serum visfatin was significantly higher in group 1 than in the control group ($p<0.01$), but not signifi-

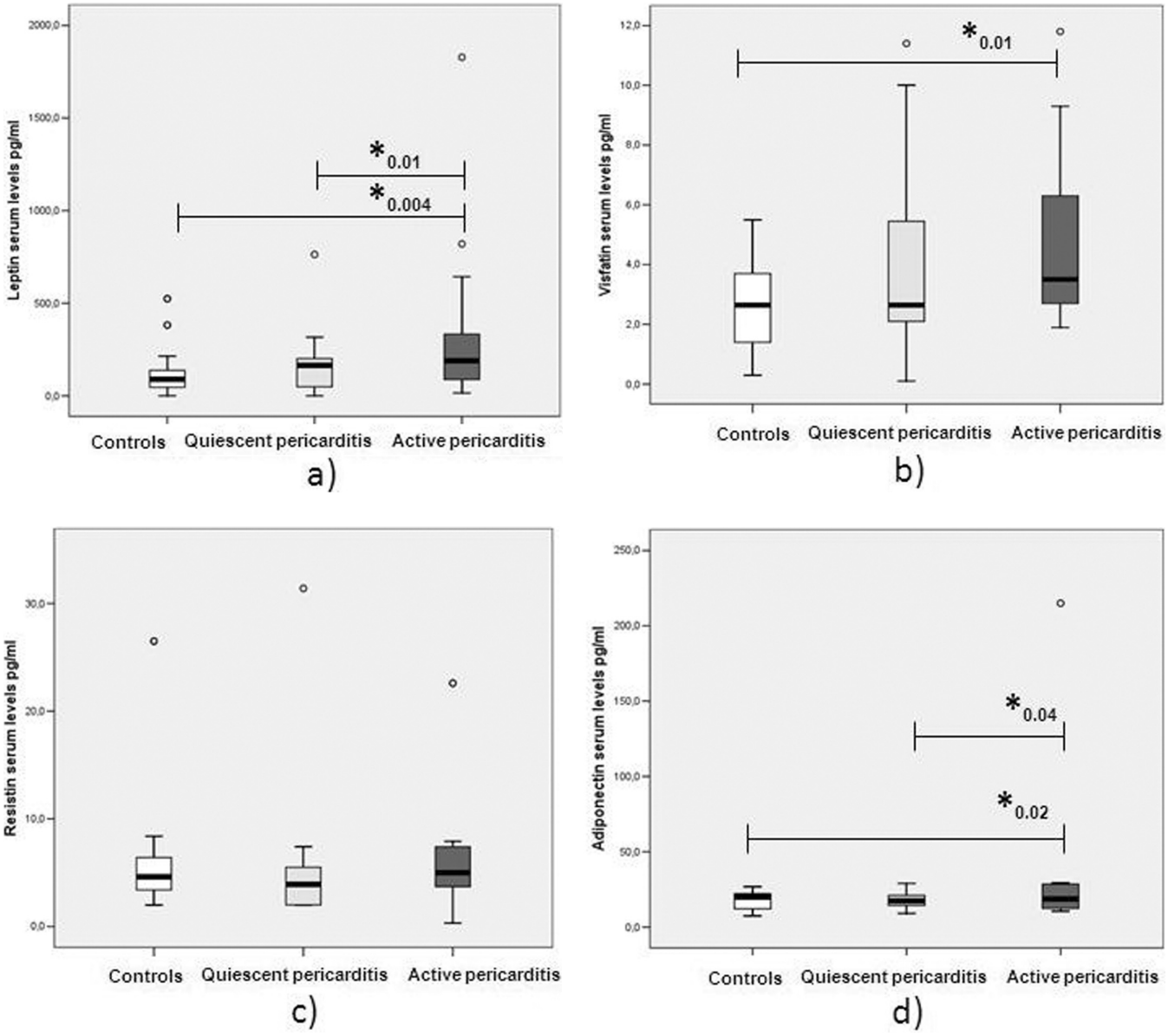

Fig. 1. Figure shows adipokines serum levels in idiopathic recurrent acute pericarditis (IRAP) patients during recurrences (active pericarditis) (n=14, grey box), IRAP patients during symptom-free intervals (quiescent pericarditis) (n=23, light grey box), and healthy controls (n=18, white box): (**a**) leptin, (**b**) visfatin, (**c**) resistin, and (**d**) adiponectin. The central line represents the distribution median, boxes span 25th to 75th percentiles, and error bars extend from 10th to 90th percentiles. Dots (°) are outlier values, higher than the 90th percentile. * represents *p*-value <0.005.
Active pericarditis: IRAP patients during IRAP recurrences (group 1); quiescent pericarditis: IRAP patients during symptom-free intervals (group 2); controls: healthy controls (group 3).

cantly higher than in group 2 (p<0.1) (Fig. 1b), whereas visfatin serum levels did not significantly differ between group 2 and the control group (p=0.1). Serum resistin was not higher in group 1 than in group 2 (p<0.32) or in the control group (p<0.53) (Fig. 1c) and did not significantly differ between group 2 and the control group (p=0.6). Serum adiponectin was significantly higher in group 1 than in group 2 (p<0.04) and in the control group (p<0.02) (Fig. 1d); serum adiponectin did not significantly differ between group 2 and the control group (p=0.9). Table II summarises leptin, visfatin, resistin and adiponectin serum levels in patients and controls. Among IRAP patients (groups 1 and 2), resistin serum levels, corrected for their specific relationships with age, weight and BMI, were shown to be respectively related to leptin (r_s=0.39, r^2=0.19, p<0.02) and to visfatin (r_s=0.41, r^2=0.29, p<0.01); leptin and visfatin did not reciprocally correlate (r_s=0.29, p=0.07). Adiponectin did not show any significant correlation with the other considered adipokines.

Among IRAP patients, serum leptin significantly correlated with SAA (r_s=0.43, r^2= 0.27, p<0.02). Other than this correlation, none of the considered adipokines showed a significant correlation with the other considered variables in univariate analysis.

Discussion

In the last few years, the modulation of immunological and inflammatory path-

Table II. The table summarises leptin, visfatin, resistin and adiponectin serum levels, reported as median and range, in patients and controls.

	Group 1 n=14	Group 2 n=23	Group 3 n=18
Leptin levels (pg/ml), median (range)	190.0 (16.0-1828)	163.50 (1.0-763)	88.75 (1-523)
Visfatin levels (pg/ml), median (range)	3.5 (1.9–-1.8)	2.65 (0.1-11.4)	2.65 (0.3-5.5)
Resistin levels (pg/ml), median (range)	5.0 (0.3-22.6)	3.90 (2.0-31.4)	4.60 (2-26.5)
Adiponectin levels (pg/ml), median (range)	18.6 (10.6-215)	17.50 (9.0-29)	19.90 (7.5-26.8)

Group 1: IRAP patients during recurrences (active pericarditis); Group 2: IRAP patients during symptom-free intervals (quiescent pericarditis); Group 3: healthy controls. Data are summarised as median and range.

ways by adipokines was extensively studied (8, 9). Recent advances in basic science have established a pivotal role for inflammation in mediating all phases of the atherosclerotic process; substantial biological data implicate inflammatory pathways in early atherogenesis, in the progression of lesions, and, finally, in the thrombotic complications of this disease (8, 9, 16).

The adipokines such as leptin and visfatin have a well-established pro-inflammatory effect and their levels have been reported to be increased in patients affected with inflammatory disorders (8, 9). Adiponectin has been described to have anti-inflammatory as well as pro-inflammatory properties depending on its molecular form (11). These subjects are more prone to an early and accelerated atherosclerosis that cannot be explained by traditional cardiovascular risk factors alone (17).

Leptin is a 16 kDa hormone synthesised by adipocytes which regulates appetite and energy expenditure at the hypothalamic level (8).

Increased serum leptin levels are a well-recognised risk factor for acute myocardial infarction, due to the exertion of many potentially atherogenic effects such as induction of endothelial dysfunction, stimulation of inflammatory reaction, oxidative stress, decrease in paraoxonase activity, platelet aggregation, migration, hypertrophy and proliferation of vascular smooth muscle cells (18). In addition, serum leptin levels significantly correlate with subclinical atherosclerosis markers (19). Adiponectin is a 244-residue adipose-specific protein which is produced in much greater quantities than leptin and is abundantly present in human plasma. The gene encoding adiponectin is located at chromosomal band 3q27, a susceptibility locus for diabetes and cardiovascular disease (20). Although adiponectin was first documented to have anti-inflammatory actions on metabolic pathways and vasculature (21, 22), it is now well-demonstrated that its pro-inflammatory effects are paradoxically more prominent than its anti-atherogenic and anti-inflammatory properties (23). Elevated adiponectin has been recently shown to be significantly correlated with a higher risk of cardiovascular disease and coronary artery disease (24). Visfatin has been identified in human atherosclerotic plaques, it is independently correlated with carotid intima-medial thickness, and its serum levels are significantly higher in patients with carotid plaques (25). Serum resistin is involved in inflammatory condition in humans and its levels in atherosclerotic patients are positively associated with other markers of inflammation (26).

Our study is the first report on leptin, resistin, visfatin and adiponectin in patients with IRAP.

Leptin and adiponectin were shown to be significantly increased during IRAP recurrences *versus* healthy controls and during IRAP recurrences *versus* IRAP symptom-free intervals; visfatin serum levels were significantly higher during IRAP recurrences than in healthy controls, but not *versus* IRAP symptom-free intervals. Serum resistin did not statistically significantly differ between IRAP patients and controls.

Whether such adipokine serum level modifications may be responsible, over time, for an increased risk of cardiovascular diseases in IRAP patients has never been studied. We also showed a significant correlation between SAA and serum leptin. Elevation in SAA has been shown to predict cardiovascular events analogously with or even better than CRP (27-29) and in this sense, it has been speculated that SAA may be one of the links – or even a proatherogenic risk factor – between inflammation and cardiovascular diseases (30, 31). SAA levels were shown to be increased during IRAP recurrences, however, its levels were slightly elevated also during symptom-free intervals. The increased SAA serum levels with normal CRP and ESR suggest that a subclinical inflammation might be present also in asymptomatic patients. In fact, it has been recently shown that SAA sensitivity in determining subclinical inflammation is much higher than other acute phase proteins such as CRP and ESR (32).

Although the precise mechanisms involved still remain to be elucidated, in IRAP, the increase of serum adipokine levels could be relevant to systemic inflammation. To date, a possible increase of cardiovascular risk in IRAP patients has never been investigated and, although further exploration is needed, it should be kept in mind. Towards this end, the evaluation, over time, of markers of subclinical atherosclerosis such as carotid artery intima-media thickness and coronary artery calcifications would be interesting.

Our study shows that leptin, adiponectin and visfatin are increased in IRAP patients *versus* healthy controls. These preliminary data suggest that these adipokines might be involved in IRAP pathogenesis and that there could be an increased cardiovascular risk in these patients.

Study limitations

The lack of correlation with additional disease activity parameters might be at least in part due to the study design. This is, in fact, a cross-sectional study: it is our aim to duplicate the results in a prospective fashion, using paired analysis for each subject, in different phases of disease activity; repeated measurements of adipokines over time might provide additional information. In addition, the numbers of participants

may be too small to substantiate more significant associations, and large-scale collaborative studies are still needed.

Authors' contributions

L. Cantarini, A. Brucato, I. Muscari, M. Galeazzi, A. Fioravanti and D. Cumetti were involved in the design of the study. M. Imazio, A. Brucato and L. Cantarini contributed to the recruitment of patients. M.G. Brizi, D. Cumetti and A. Vitale collected patient samples and clinical data. M.R. Bacarelli, I. Muscari and M. Galeazzi were involved in the processing of patient samples and production of data. G. Simonini, R. Cimaz, M. Imazio and A. Brucato contributed to the interpretation of the data. The writing of the final manuscript was by L. Cantarini, A. Fioravanti and M. Galeazzi.

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