Clinical potential of resistin as a novel prognostic biomarker for cellulitis

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Abstract. Cellulitis is an acute, subacute or chronic inflammation of the dermis and subdermal tissues, which is typically caused by bacteria, although other causes are possible. The present study aimed to evaluate the association between resistin levels and the recovery time of patients with cellulitis. In addition, the effect of resistin and insulin resistance on the prognosis of cellulitis was investigated. In total, 52 patients with cellulitis (male, 21; female, 31) and an age-matched group of 42 healthy individuals (male, 18; female, 24) were included in the study. The levels of serum resistin, fasting plasma glucose (FPG), homeostasis model assessment-insulin resistance (HOMA-IR), C-reactive protein (CRP) and other biochemical parameters were compared between the groups. The mean resistin levels in the cellulitis and control groups were 9.4±5.3 and 5.8±3.1 ng/ml, respectively. The levels of resistin, FPG, HOMA-IR and CRP were significantly higher in the cellulitis group compared with the control group (P<0.001). Furthermore, the mean recovery time of the patients with cellulitis was 21.2±5.6 days. Thus, increased levels of resistin (P=0.002) and HOMA-IR (P=0.005) could be used as predictive factors for the recovery time. The enhanced levels of resistin and HOMA-IR were shown to correlate with the high CRP levels in the cellulitis group. Therefore, the results indicated that increased levels of resistin may function as a prognostic marker for cellulitis.

Introduction

Cellulitis is classified as an acute, subacute or chronic inflammation of the dermis and subdermal tissues, which is generally caused by a bacterial infection. The clinical manifestations of cellulitis include erythema, swelling, local tenderness of the skin and subcutaneous tissues, in addition to fever and malaise (1). Group A *Streptococcus* and *Staphylococcus aureus* are responsible for the majority of cellulitis cases (2). The clinical severity of cellulitis ranges from a mild infection, treatable with oral antibiotics, to a severe necrotizing infection associated with a high mortality rate (3).

Resistin is an adipocytokine that is released by adipocytes, muscles cells, pancreatic islet cells, mononuclear cells, macrophages and neutrophils (4). Resistin competes with lipopolysaccharides through binding to Toll-like receptors and may function as a proinflammatory cytokine in human monocytes. In addition, resistin is a member of the cysteine-rich secretory protein family, members of which are also known as resistin-like or 'found in inflammatory zone' molecules (5). Serum resistin levels have been observed to increase during severe bacterial and viral infections (6-8). Furthermore, increased resistin levels have been associated with insulin resistance (9), and a strong correlation has been observed between C-reactive protein (CRP) and resistin (10).

Hepatocyte-derived CRP is a sensitive indicator of inflammatory and infectious processes in a variety of tissues. CRP is synthesized in the liver under the regulation of interleukin (IL)-6 (11), and serves a crucial role in inflammation and acute-phase reactions. High levels of CRP have been shown to correlate with insulin resistance in the absence of diabetes mellitus and severe inflammation (12). A CRP response is observed during the progression of cellulitis (11,13). However, using the CRP response as a biomarker for cellulitis has a number of disadvantages, including a delayed release and low specificity. Thus, numerous biomarkers, including resistin, have been studied in association with infectious diseases (8,14-16).

The aim of the present pilot study was to investigate whether levels of resistin and insulin are effective prognostic indicators for estimating the recovery time of patients with cellulitis.

Materials and methods

Study population. The current observational cross-sectional study was conducted in the Department of Infectious Diseases in the Medical Faculty at Recep Tayyip Erdogan University (Rize, Turkey). In total, 52 patients diagnosed with cellulitis

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(female, 31; male, 21) were recruited. In addition, a control group was included, consisting of 42 healthy individuals (female, 24; male, 18) with no known infectious or chronic diseases, such as diabetes, hypertension, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease or chronic renal failure. None of the subjects included in the study consumed alcohol, smoked or took drugs. The study was conducted in accordance with the Helsinki Declaration, and was approved by the local Ethics Committee of Rcep Tayyip Erdogan University (Rize, Turkey). Informed consent was obtained from all the participants.

Diagnosis of cellulitis. Cellulitis was diagnosed by an infectious disease specialist, according to the following criteria: i) Edema, rash, tenderness and hotness of the skin in the lower extremities; ii) elevated white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and CRP levels (however, normal values of these tests did not automatically exclude the diagnosis of cellulitis); iii) cultivation of the infectious agent from an aspirate or biopsy material; and iv) exclusion of the presence of deep vein thrombosis (DVT) using superficial ultrasonography (USG) and Doppler USG (1,17).

Diagnosis of DVT for differential diagnosis. DVT was defined by a radiologist as a reduction in the calibration of the femoral and popliteal veins. Furthermore, DVT was visualized as an intraluminal isoechoic thrombus, possessing a reflux with poor recanalization, which is a typical symptom of DVT (18). These examinations were performed using Doppler USG with a 10 MHz direct ultrasound probe (Xario; Toshiba Medical Systems Corporation, Tokyo, Japan).

Cellulitis recovery period. Recovery from cellulitis was determined according to previously defined guidelines (19,20). Briefly, recovery was classified as an improvement in clinical symptoms and the complete recovery from edema, rash, tenderness and hotness of the skin and soft tissues. The recovery time was estimated in accordance with the previously described guidelines.

Laboratory measurements. Biochemical parameters of the subjects were measured following a 12-h fast. Serum samples were stored at -30˚C. The levels of serum fasting plasma glucose (FPG), blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase and other biochemical parameters were determined using photometric and spectrophotometric assays using the Architect c16000 chemical analyzer (Abbott Diagnostics, Chicago, IL, USA). CRP levels were measured via the nephelometric method using an IMMAGE 800 system (Beckman Coulter, Inc., Brea, CA, USA). Hematological measurements, such as the levels of WBCs, platelets and hemoglobin, were acquired using a CELL-DYN Ruby hematology system (Abbott Diagnostics). Insulin levels were measured using a chemiluminescent microparticle immunoassay system (Architect Immunoassay Analyzer; Abbott Diagnostics).

Resistin level measurement. Serum resistin levels were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (RayBiotech, Inc., Norcross, GA, USA), according to the manufacturer's instructions. Absorbance was measured at a wavelength of 450 nm, using an ELISA reader (Multiskan™ Go, Thermo Fisher Scientific, Vantaa, Finland). Resistin levels are presented in units of ng/ml. The intra-assay and inter-assay coefficients of variation were <10 and <12%, respectively, and the sensitivity was calculated as 2 pg/ml.

Homeostasis model assessment-insulin resistance (HOMA-IR) score. The HOMA-IR score was calculated using the following formula (21): HOMA-IR = [FPG (mmol/l) x fasting serum insulin (mU/ml)]/22.5. The cut-off value of the HOMA-IR score was 2.7.

Statistical analysis. Results are presented as the mean ± standard deviation. Statistical analyses were performed using SPSS statistical software for Windows, version 13.0 (SPSS, Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was applied to all the data to determine the normal and non-normal data distributions. For each parameter, the statistical significance of the difference between the patient and control groups was analyzed using the independent-samples t-test for normally distributed parameters and the Mann-Whitney U test for non-normally distributed parameters. Subgroup analyses for gender were performed using nested analysis of variance, followed by Bonferroni analysis. The associations between variables were analyzed using Pearson's correlation analysis. Multivariate (MVA) logistic regression analyses were performed to determine the independent associations between the various subject parameters and the cellulitis recovery time. The results are expressed as odds ratios (OR) with a 95% confidence interval (CI). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Subject characteristics and laboratory measurements. The mean age of the patients in the cellulitis and control groups was 61.3±13.7 and 61.5±7.7 years, respectively. The mean recovery time for patients with cellulitis was 21.1±5.6 days (range, 12-39 days). The parameter measurements for the cellulitis group were as follows: Body mass index (BMI), 28.9±3.9 kg/m^2; resistin level, 9.4±5.3 ng/ml; FPG level, 100.6±19.3 mg/dl; insulin level, 10.9±2.2 μIU/ml; HOMA-IR, 2.6±0.7; ESR, 37.1±25.2 mm/h; CRP level, 9.3±8.3 mg/dl; and WBC count, 11.7±3.3x10^9/l. The measurements for the control group were as follows: BMI, 28.6±4.8 kg/m^2; resistin level, 5.8±3.1 ng/ml; FPG level, 89.6±8.2 mg/dl; insulin level, 8.8±0.7 μIU/ml; HOMA-IR, 2.0±0.2; ESR level, 16.5±14.4 mm/h; CRP level, 0.7±0.6 mg/dl; and WBC count, 7.3±2.5x10^9/l. The levels of resistin, FPG, insulin and CRP, the HOMA-IR, the ESR and the WBC count were significantly higher in the cellulitis group when compared with the control group ($P<0.001$). The demographic characteristics and biochemical parameters of the subjects are presented in Table I.

Correlation analysis. Pearson's correlation analyses indicated positive correlations when comparing the resistin level with the BMI ($r=0.398$, $P=0.003$), the FPG level ($r=0.345$, $P=0.002$),

Table I. Characteristics and laboratory parameters for the two groups.

Parameter	Cellulitis (n=52)	Control (n=42)	P-value
Age (years)	61.3±13.7	61.5±7.7	0.919
Gender, M/F (n)	21/31	18/24	0.403
BMI (kg/m^2)	28.9±3.9	28.6±4.8	0.645
Resistin (ng/ml)	9.4±5.3	5.8±3.1	0.001
FPG (mg/dl)	100.6±19.3	89.6±8.2	0.001
Insulin (μIU/ml)	10.9±2.2	8.8±0.7	0.001
HOMA-IR	2.6±0.7	2.0±0.2	0.001
WBC (x10^9/l)	11.7±3.3	7.3±2.5	0.001
ESR (mm/h)	37.1±25.2	16.5±14.4	0.001
CRP (mg/dl)	9.3±8.3	0.7±0.6	0.001
BUN (mg/dl)	37.6±18.3	36.4±10.8	0.718
Creatinin (mg/dl)	0.8±0.3	0.8±0.2	0.773
AST (IU/l)	26.1±15.5	23.2±9.6	0.314
ALT (IU/l)	26.5±19.3	22.1±15.6	0.280
TC (mg/dl)	223.4±52.0	189.6±32.2	0.001
TG (mg/dl)	131.4 ±47.2	120.4±57.0	0.401
HDL (mg/dl)	46.1±15.7	45.9±14.7	0.966
LDL (mg/dl)	129.8±36.4	119.0±27.5	0.149

Data are expressed as the mean ± standard deviation. M, male; F, female; BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL low-density lipoprotein.

Table II. Pearson correlation coefficients (r) between resistin levels, recovery time and measured parameters in patients with cellulitis.

	Resistin levels		Recovery time	
Parameters	R-value	P-value	R-value	P-value
Resistin	-	-	0.547	0.001
BMI	0.398	0.003	0.106	0.097
FPG	0.345	0.002	0.336	0.003
Insulin	0.541	0.001	0.500	0.001
HOMA-IR	0.622	0.001	0.575	0.001
CRP	0.438	0.001	0.531	0.001
TC	0.275	0.015	0.360	0.001

BMI, body mass index; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; CRP, C-reactive protein; TC, total cholesterol.

the insulin level (r=0.541, P<0.001), the HOMA-IR score (r=0.622, P<0.001), the CRP level (r=0.438, P<0.001) and the total cholesterol level (r=0.275, P=0.015). Furthermore, positive correlations were observed between the patient recovery time and the levels of resistin (r=0.547, P<0.001), CRP (r=0.531, P<0.001), FPG (r=0.336, P=0.003) and HOMA-IR (r=0.575, P<0.001; Table II).

Table III. Multivariate logistic regression analysis of the independent variables associated with the recovery time in patients with cellulitis.

Parameter	OR	95% CI	P-value
Resistin	0.649	0.213-0.967	0.002
CRP	0.396	0.101-0.512	0.001
ESR	0.140	0.053-0.227	0.002
WBC	1.048	0.582-1.514	0.001
HOMA-IR	0.343	0.425-2.262	0.005
BMI	0.450	0.335-0.728	0.002
Age	0.513	0.214-0.719	0.992
Gender	1.343	0.784-2.600	0.498
Hb	0.326	0.288-0.461	0.501
Platelet	0.323	0.178-0.359	0.746
Glucose	0.190	0.135-0.218	0.904
AST	0.082	0.030-0.977	0.337
ALT	0.040	0.009-0.132	0.949
BUN	0.029	0.004-0.136	0.724
Creatinine	0.650	0.150-1.99	0.131

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell; HOMA-IR, homeostasis model assessment-insulin resistance; BMI, body mass index; Hb, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; OR, odds ratio; 95% CI, 95% confidence interval.

Table IV. Subgroup analysis of the gender groups by analysis of variance.

	Cellulitis group		Control group	
Parameter	Male	Female	Male	Female
Resistin (ng/ml)	7.8±3.7[a]	10.5±5.9	5.0±2.4[b]	6.6±3.4[c]
FPG (mg/dl)	99.2±19.1	101.5±19.7	89.0±8.5[d]	90.2±8.2[e]
HOMA-IR	2.4±0.6	2.8±0.7[f]	1.9±0.2[b,g]	2.0±0.2[b,h]
CRP (mg/dl)	6.2±4.9	11.4±9.4[i]	0.7±0.9[b,j]	0.6±0.4[b,k]
WBC (x10^9/l)	12.0±3.3	11.5±3.3	8.6±3.0[l,m]	6.1±1.1[b,n,o]

[a]P=0.041, [b]P<0.001, [c]P=0.009, [d]P=0.031 and [e]P=0.039 vs. female cellulitis group; [f]P=0.011 vs. male cellulitis group; [g]P=0.028, [h]P=0.036, [i]P=0.006, [j]P=0.025, [k]P=0.017 and [l]P=0.003, vs. male cellulitis group; [m]P=0.007 vs. female cellulitis group; [n]P<0.001 vs. male cellulitis group; [o]P=0.039, vs. male control group. FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; CRP, C-reactive protein; WBC, white blood cell.

MVA analysis. MVA analyses were performed with the recovery time as the dependent variable and the resistin level, FPG level, HOMA-IR, CRP level, ESR, WBC count, age, BMI and gender as independent variables. The following parameters were observed to be independently associated with the recovery time: Resistin level (OR, 0.649; 95% CI, 0.213-0.967; P=0.002), CRP (OR, 0.396; 95% CI, 0.101-0.512; P=0.001), WBC count (OR, 1.048; 95% CI, 0.582-1.514; P<0.001), BMI (OR, 0.450; 95% CI, 0.335-0.728; P=0.002) and HOMA-IR score (OR, 0.343; 95% CI, 0.425-2.262; P=0.005). The P-values of the remaining parameters were not significant. All the results are presented in Table III.

Subgroup analyses. The study population was divided according to gender into cellulitis male (CEM), control male (COM), cellulitis female (CEF) and control female (COF) subgroups. The resistin levels in the CEF group were significantly higher when compared with the CEM (P=0.041), COM (P<0.001) and COF (P=0.009) groups. The HOMA-IR score in the CEM group was significantly higher compared with the COM (P=0.028) and COF (P=0.036) groups. In addition, HOMA-IR in the CEF group was significantly higher compared with the COM (P<0.001) and COF (P<0.001) groups (Table IV).

Discussion

In the present study, the levels of resistin, FPG, insulin and CRP, as well as the HOMA-IR score, ESR and WBC count were significantly higher in the patients with cellulitis compared with the healthy control subjects. MVA regression analysis indicated marked independent associations between the cellulitis recovery time and high levels of serum resistin, HOMA-IR, CRP and WBCs. Similarly, resistin levels were shown to positively correlate with the serum FPG, insulin, HOMA-IR and CRP levels. Thus, the results of the present study indicate that the HOMA-IR score and resistin level correlate markedly with the CRP level and the recovery time of patients with cellulitis. High levels of these parameters were observed to be concomitant with a long recovery time. Thus, resistin level may be an effective prognostic marker for estimating the recovery time of patients with cellulitis. A previous study reported an association between enhanced levels of CRP and those of resistin in patients with inflammatory diseases, and hypothesized that these increases may indicate disease activity (22). The present study also demonstrated a strong correlation between the levels of CRP and resistin. CRP is a useful marker of the severity of an infection, and resistin may function similarly as a prognostic factor.

Previous studies have reported that resistin may indicate the severity of the disease in patients with neonatal sepsis, in a similar manner to IL-6 and CRP (7,14,23,24). Furthermore, recent studies have demonstrated that resistin may serve a function in inflammation and autoimmunity (5,25). Bokarewa *et al* reported that the use of recombinant resistin resulted in a marked upregulation in the genes for tumor necrosis factor (TNF)-α and IL-6 (26). A number of studies have indicated a marked correlation between the levels of resistin and CRP in severe inflammatory diseases (22,27,28). From the results of the present study, it can be hypothesized that resistin is released by macrophages and adipose tissue during cellulitis infection, after which the levels of resistin are further increased by inflammatory processes. Furthermore, increased inflammation and the consequent elevation in resistin levels may result in the development of insulin resistance.

Notably, subgroup analyses revealed the CRP response in females with cellulitis to be higher compared with that in male patients. Furthermore, resistin and insulin resistance levels in the female cellulitis patients were increased compared with the male patients. Previous studies have reported the resistin levels of healthy female individuals to be higher compared with those in healthy males (29,30). Thus, resistin may be more useful as a prognostic factor in female patients with cellulitis. By contrast, in an alternative study, high resistin levels were reported in male and female patients with chronic obstructive lung disease (31). In addition, the results of present study indicated an increase in the levels of resistin in male patients with cellulitis. Thus, resistin may function as a prognostic factor in males with cellulitis, in addition to females. However, the limited population sample size in the present study may have affected the results. Further studies including a broader

study population are required to elucidate the difference in the resistin response between male and female patients with cellulitis.

During cellulitis infection, the skin accumulates populations of lymphoid and reticular cells with the capacity to secrete lymphocytes and cytokines. These secretions rapidly reduce the number of viable bacteria by enhancing the ability of circulating macrophages and neutrophils to infiltrate the skin (32). Furthermore, during a cellulitis infection, M1 macrophages infiltrate the adipose tissue and subsequently secrete proinflammatory cytokines and generate reactive oxygen species, which in turn recruit more macrophages and amplify the inflammatory response (33,34). Thus, resistin and cytokines may be released from the adipose tissue, causing an increase in the levels of CRP. In the present study, the levels of CRP and resistin were enhanced in the patients with cellulitis compared with the healthy subjects, which may have been in response to inflammation.

Hyperglycemia has been associated with increased levels of cytokines and counter-regulatory hormones, which may result in the development of insulin resistance. A previous study revealed an association among resistin levels, insulin resistance and obesity (34). TNF-α and IL-6 have been shown to alter the expression of peroxisome proliferator-activated receptor (PPAR)-γ in adipocytes (35,36). PPAR-γ is an anti-inflammatory nuclear protein with insulin-sensitizing functions. CRP enhances the inflammatory response, and causes systemic inflammation (37). Plasma CRP levels have been shown to correlate with circulating levels of other inflammatory biomarkers (38). Furthermore, a strong positive correlation has been observed between plasma CRP levels and insulin resistance (39). Previous studies have reported that plasma resistin levels correlate positively with insulin resistance, obesity and glucose intolerance (40,41). The proinflammatory effects of resistin were attributed to its ability to activate the nuclear factor-κB signaling pathway and subsequently enhance the production of proinflammatory cytokines, including TNF-α and IL-6, which impair insulin-signaling pathways and result in the development of insulin resistance (42,43). In addition, increased levels of proinflammatory cytokines and CRP may lead to insulin resistance. In the current study, CRP levels were higher in patients with cellulitis compared with the healthy control subjects. Thus, increased levels of CRP may also be associated with higher proinflammatory cytokine levels. A higher HOMA-IR score may mediate the effects of resistin and proinflammatory cytokines.

There were a number of limitations to the present study. As a pilot study, the sample size was small and did not represent the general population. In addition, serum samples were obtained from the patients with active cellulitis. It may have been useful to obtain samples from patients following recovery from cellulitis, in order to compare the resistin and CRP levels with the healthy levels. Thus, further investigations are required.

In conclusion, the levels of resistin and the HOMA-IR score were higher in the cellulitis group when compared with the control group. In addition, positive correlations between the resistin level and HOMA-IR with the CRP level were observed in the patients with cellulitis. Serum resistin levels may increase during cellulitis infection due to enhanced levels of proinflammatory cytokines. Consequently, insulin resistance and hyperinsulinemia may develop in patients with cellulitis. The results of the present study indicate that increased resistin levels may provide a novel prognostic factor for cellulitis.

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