# Anti-TNF-α therapy modulates resistin in patients with rheumatoid arthritis

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## Abstract

### Objective

*Chronic systemic inflammation plays a pivotal role in the development of atherosclerosis in rheumatoid arthritis (RA). In the present study, we investigated whether anti-TNF-α antagonist-monoclonal antibody-infliximab administration alters circulating levels of resistin, a proinflammatory adipokine. We further assessed associations of circulating resistin concentrations with CRP and ESR levels, platelet counts and metabolic syndrome and demographic characteristics in RA patients on periodical treatment with infliximab.*

### Methods

*We investigated 33 patients with RA on periodical treatment with infliximab. Serum resistin levels were determined immediately prior to and after infliximab infusion.*

### Results

*Upon infliximab administration, mean (SD) serum resistin concentrations (ng/ml) decreased from 21.9 (9.9) to 17.4 (8.9) (p=0.005). Also, a significant association between the mean ESR (r=0.405; p=0.03) and CRP (r=0.571; p=0.0005) from disease diagnosis and ESR (r=0.486; p=0.004), CRP (r=0.599; p=0.0005) and platelet count (r=0.559; p=0.0007) at the time of the study and baseline resistin levels was found.*

### Conclusions

*The present study shows that anti-TNF-α therapy results in a rapid reduction of serum resistin levels in patients with RA. It also confirms a close association between laboratory markers of inflammation, particularly CRP and resistin levels. These observations support a potential role of resistin in the inflammatory cascade in RA.*

### Key words

Rheumatoid arthritis, inflammation, resistin, anti-TNF-α antibody-infliximab.

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*Conflict of interest: Dr. M.A. Gonzalez-Gay is now on the advisory board of Centocor and has received less than $10,000; Drs. M.T. Garcia-Unzueta, C. Gonzalez-Juanatey, J.A. Miranda-Filloy, T.R. Vazquez-Rodriguez, J.M. De Matias, J. Martin, P.H. Dessein and J. Llorca have declared no competing interests.*

## Introduction

Rheumatoid arthritis (RA) is a chronic disease associated with increased cardiovascular (CV) morbidity and mortality (1). The increased risk of CV events in patients with RA is a consequence of atherosclerosis (2, 3). However, accelerated atherosclerosis in RA is not only been explained by the presence of traditional cardiovascular risk factors (4, 5). Indeed, besides genetic predisposition (6, 7), chronic systemic inflammation is now considered of pivotal importance in the development of accelerated atherosclerosis and the increased incidence of CV events in RA (7, 8).

A chronic increase of proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 causes deleterious effects including a proatherogenic lipid profile, insulin resistance and endothelial dysfunction in RA (8).

TNF-α blockers are highly effective in the treatment of RA (9, 10) and may reduce CV mortality more than traditional disease modifying rheumatic drugs (DMARDs) (11). TNF-α blockade using the chimeric anti-TNF-α monoclonal antibody-infliximab significantly improves endothelial function in RA patients (12, 13). Also, improvement of endothelial function was observed after short-term therapy with adalimumab, a fully human monoclonal antibody directed against TNF-α (14). Moreover, following infliximab infusion, RA patients with severe disease on periodical treatment with this drug, experienced a rapid improvement in insulin sensitivity (15).

Resistin is an adipocyte-derived mediator that was initially proposed to be involved in insulin resistance and type II diabetes mellitus (16). Although initial studies in mice suggested that resistin is upregulated in obesity and may contribute to the development of insulin resistance (17), further studies failed to confirm this hypothesis and demonstrated reduced resistin expression in human adipose tissues (18). Also, more recent investigations have shown that resistin plays an important role in inflammation. Although resistin can be detected at very low levels in human adipose tissue, it is found in peripheral blood mononuclear cells (PBMC) (19), and resistin gene expression in PBMC is upregulated by proinflammatory cytokines such as TNF-α (20). Interestingly, high levels of resistin have been found in synovial fluid from patients with RA (21). A positive correlation of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) with serum resistin has also been observed in RA patients (22, 23). Moreover, resistin was found to be upregulated by TNF-α and has been proposed as an important molecule in NF-κB activation and cytokine production in human PBMC (24).

In view of the above-mentioned reported findings, in the present study, we investigated whether infliximab administration alters circulating resistin concentrations. We also assessed associations of circulating resistin concentrations with CRP levels and metabolic syndrome and demographic characteristics in 33 RA patients that were on periodical treatment with the anti-TNF-α antagonist-infliximab because of severe disease refractory to therapy with DMARDs (25).

## Patients and methods

*Patients*

We investigated 33 consecutive patients that met the 1987 American College of Rheumatology criteria for RA (26) and that were recruited from Hospital Xeral-Calde, Lugo, northwestern Spain. The cohort constituted a series of patients attending hospital outpatient clinics seen over a period of 2 months (February-March 2004). Patients with diabetes were excluded. The local institutional committee approved anti-TNF-α therapy and each patient gave informed consent to participate in the study. For ethical reasons, patients included in the present study were not randomized to a placebo group. The same procedure has been found acceptable and followed in a recent study on the effect of infliximab therapy on lipid profiles in patients with RA (27). Neither this study nor previous studies on RA patients receiving periodical treatment with inflixmab (13, 15, 25) were supported by any pharmaceutical drug company.

Each of the RA patients had been switched from traditional DMARD to anti-TNF-alpha infliximab treatment

because of severe and active disease (DAS28 greater than 5.1) (28). In all patients, treatment with a DMARD had been initiated when a diagnosis of RA was made. Prior to anti-TNF-α therapy, patients were required to have been treated with at least two DMARDs including chloroquine, sulphasalazine, gold, methotrexate (at least 15 mg/week), leflunomide, and cyclosporine A (3 mg/kg/day). Infliximab therapy (initial dose of 3 mg/kg) was administered intravenously at 0, 2, 6 weeks and subsequently every 8 weeks. However, in some patients, because of disease severity, the dose was increased to 5 mg/kg and, if deemed necessary, the interval between infliximab infusions was shortened to 6 weeks.

All patients had received treatment with both non-steroidal antiinflammatory agents and low doses of prednisone (generally 5 mg bid) immediately after disease diagnosis. At the time of the study, all patients were on infliximab 3 or 5 mg/kg given at 6 or 8 weekly intervals (a range of treatment duration, 1-4.5 years), oral methotrexate 15-25 mg weekly with or without chloroquine 250 mg daily, prednisone 2.5-7.5 mg daily and a non-steroidal antiinflammatory agent (naproxen 500-1000 mg or diclofenac 50-100 mg daily). The blood pressure was below 140/90 mmHg in each patient at the time of the study. However, 7 were taking antihypertensive agents (enalapril [n=3]; losartan [n=3]; enalapril and hydrochlorothiazide [n=1]).

*Study protocol*

In each patient a disease activity score (DAS) 28 (28) was recorded by the same rheumatologist (MAG-G) prior to infliximab infusion (the same day). In all cases, the drug was given at 8 a.m. as an intravenous infusion in a saline solution over 120 minutes. None of the patients received any nutrient before and during infusion.

All measurements were made in the fasting state. Blood samples were taken at 0800 hours for determination of the ESR (Westergren), CRP (latex immuno-turbidimetry), lipids (enzymatic colorimetry), plasma glucose and serum insulin (DPC, Dipesa, Los Angeles, CA, USA) and serum resistin (human resistin was measured by ELISA kit, [Linco Research, St. Charles, MO, USA]; the assay sensitivity was 0.16 ng/ml and the intra- and interassay coefficients of variation were <5% and <7%, respectively), immediately prior to an infliximab infusion. Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the formula= (insulin ($\mu$U/ml) x glucose (mmol/l)÷22.5[7]. Also, as previously reported (25), soluble (s) circulating levels of adhesion molecules, intercellular cell adhesion molecule-1 (ICAM-1), ICAM-3, vascular cell adhesion molecule-1 (VCAM-1), E-selectin and P-selectin concentrations were measured prior to infliximab infusion.

Subsequently, final blood sampling was performed for determination of resistin concentrations immediately after infliximab was administered over 120 minutes.

*Statistical analyses*

Results were expressed as mean [95% confidence interval (CI)], geometric mean [95% CI or standard deviation] or number (n) (%). The associations between baseline characteristics and serum resistin concentrations (expressed as mean ± standard deviation [SD], and interquartile [IQ] range) were assessed by estimating the linear correlation coefficient (Pearson) for continuous variables or by the Student's paired t-test for categorical variables. Differences in resistin levels between men and women and patients with hypertension or not were assessed by Mann-Whitney U test. The changes in serum resistin concentrations upon infliximab therapy (just prior to infusion at time 0 and immediately after the end of infliximab infusion at time 120 minutes) were also evaluated using the Student's *t* test. Statistical significance was accepted at $p< 0.05$.

**Table I.** Baseline characteristics in 33 rheumatoid arthritis patients.

| | | |
|---|---|---|
| Age, years | 55 | (51-60) |
| Women, n (%) | 25 | (76) |
| Disease duration, years | 12 | (10-15) |
| Rheumatoid factor positive, n (%) | 30 | (91) |
| Disease activity | | |
| DAS28 | 4.4 | (4.0-4.7) |
| Swollen joint count, n | 5 | (3-6) |
| Tender joint count*, n | 4 | (3-5) |
| VAS patient disease activity | 41 | (35-47) |
| C-reactive protein, mg/l* | 8.3 | (5.8-12.0) |
| Erythrocyte sedimentation rate, mm/hr* | 25 | (19-31) |
| Metabolic syndrome features | | |
| Body mass index, kg/m$^2$ | 25.4 | (23.8-26.9) |
| Hypertension, n (%) | 7 | (21) |
| Systolic blood pressure, mmHg | 120 | (116-134) |
| Diastolic blood pressure, mmHg | 73 | (71-76) |
| Triglycerides, mg/dl* | 102 | (89-115) |
| HDL cholesterol, mg/dl | 64 | (59-68) |
| Glucose, mg/dl | 87 | (82-92) |
| Insulin, μU/ml* | 12.9 | (10.5-16.2) |
| HOMA-IR, μU.mmol/ml.l* | 2.75 | (2.14-3.47) |
| Total cholesterol, mg/dl | 192 | (181-203) |
| LDL cholesterol, mg/dl | 104 | (97-111) |

DAS: disease activity score; VAS: visual analog scale; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; LDL: low-density lipoprotein.
*Variables for which geometric means [95% confidence interval] are given.

## Results

*Descriptive data*

The baseline-recorded variables in the 33 RA patients on periodical treatment with infliximab are shown in Table I. Despite the use of infliximab,

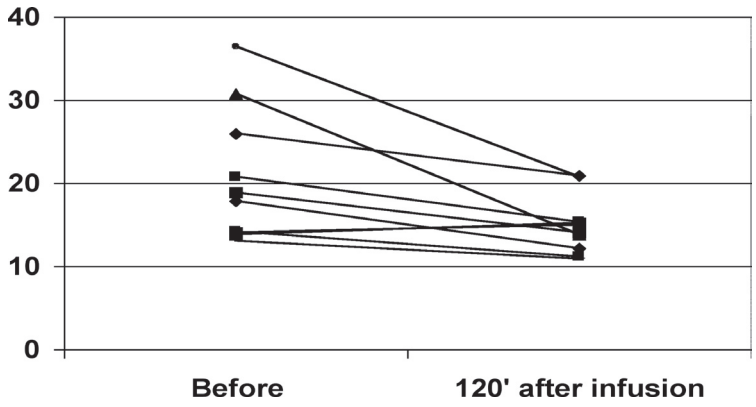


**Fig. 1**. Changes in resistin concentrations before (baseline) and 120' after infliximab therapy (10 randomly selected patients).

**Table II.** Associations between baseline patient characteristics and serum resistin levels in 33 rheumatoid arthritis patients.

| Patient characteristic | Resistin (ng/ml) | |
|---|---|---|
| | *r* | *p* |
| Age, years | | |
| At disease onset | -0.184 | 0.31 |
| At the time of the study | -0.109 | 0.55 |
| Disease duration, years | -0.004 | 0.98 |
| Disease activity | | |
| DAS28 | 0.242 | 0.17 |
| Swollen joints | 0.134 | 0.46 |
| Tender joints | 0.054 | 0.77 |
| VAS patient disease activity | 0.043 | 0.81 |
| CRP protein, mg/l at the time of the study | 0.571 | 0.0005 |
| Mean CRP from disease diagnosis | 0.599 | 0.0005 |
| ESR, mm/hr at the time of the study | 0.486 | 0.004 |
| Mean ESR from disease diagnosis | 0.405 | 0.03 |
| Platelet count/mm$^3$ at the time of the study | 0.559 | 0.0007 |
| Metabolic syndrome | | |
| BMI, kg/m$^2$ | 0.054 | 0.76 |
| Basal glucose, mg/dl | 0.190 | 0.30 |
| Basal Insulin, μU/ml | 0.075 | 0.69 |
| Basal Log HOMA-IR, μU.mmol/ml.l | -0.020 | 0.92 |
| Triglycerides, mg/dl | -0.004 | 0.98 |
| Total cholesterol, mg/dl | -0.122 | 0.50 |
| HDL cholesterol, mg/dl | -0.154 | 0.39 |
| LDL cholesterol mg/dl | -0.002 | 0.99 |
| Systolic blood pressure, mmHg | -0.128 | 0.48 |
| Diastolic blood pressure, mmHg | -0.203 | 0.26 |
| Cumulative prednisone dosage, mg | 0.015 | 0.93 |
| Time from the onset of RA to the beginning | 0.139 | 0.44 |
| of inflixmab therapy, years | | |
| sICAM-1, ng/ml | 0.021 | 0.91 |
| sICAM-3, ng/ml | 0.027 | 0.88 |
| sVICAM-1, ng/ml | 0.038 | 0.83 |
| sE-selectin | 0.240 | 0.18 |
| sP-selectin | -0.076 | 0.67 |

The data were analyzed in simple linear regression models. DAS: disease activity score; VAS: visual analog scale; BMI: body mass index; log: logarithmically transformed; HOMA-IR: homeostasis model assessment of insulin resistance; HDL: high-density lipoprotein.

prednisone and methotrexate, no patient experienced a disease remission (DAS28<2.4) (29) with the lowest recorded DAS28 being 2.57.

*Changes in serum resistin concentrations upon infliximab therapy*

A significant reduction in the serum resistin concentrations (ng/ml) was found ([21.9±9.9, median: 18.8, IQ range: 15.0–26.8] before infliximab-time 0 (baseline) and [17.4±8.9; median: 15.4: IQ range: 12.1–20.3] after infliximab infusion-time 120 minutes ($p$=0.005).

In 25 patients (73.5%), the difference between serum resistin levels at time 120 and baseline serum resistin concentrations prior to infliximab administration yielded negative values. This was the result of a reduction of serum resistin levels following infliximab infusion. Figure 1 shows changes in serum resistin concentrations before (baseline) and 120' after infliximab therapy.

High baseline resistin levels were associated with larger reductions in resistin levels upon infliximab infusion. However, no differences between patients who experienced decrease and those who showed increase in serum resistin levels after infliximab infusion were found (data not shown).

Changes in serum resistin concentrations after 120 minutes of the infliximab infusion showed a moderate correlation with changes in P-selectin ($r$=0.295; $p$=0.09). However, no correlation between changes in serum resistin concentrations and changes in other adhesion molecules after 120 minutes of the infliximab infusion was observed (data not shown).

*Associations between baseline recorded characteristics and serum resistin levels*

No significant differences in resistin concentrations (ng/ml) between men (26.6±14.4) and women (20.4±7.8) and between patients with hypertension (21.4±6.2) and patients without hypertension (22.0±10.8) were found ($p$=0.45 and $p$=0.76, respectively). No correlations between resistin levels obtained before infliximab administration and age at the time of the study or at

the onset of the disease, disease duration, tender, and swollen joints, VAS patient's disease activity, DAS28 and BMI were observed (Table II). However, significant associations between the mean ESR ($r$=0.405; $p$=0.03) and CRP ($r$=0.571; $p$=0.0005) from disease diagnosis and ESR ($r$=0.486; $p$=0.004), platelet count ($r$=0.559; $p$=0.0007) and CRP ($r$=0.599; $p$=0.0005) at the time of the study and baseline resistin levels were found (Table II). This was particularly true for CRP at the time of the study that showed a strong positive correlation with baseline levels of resistin. The other baseline-recorded characteristics were not associated with resistin concentrations (Table II).

## Discussion

In the present study, anti-TNF-α therapy resulted in a rapid reduction of serum resistin levels in RA patients with severe disease. We also confirmed a close association between laboratory markers of inflammation, particularly CRP, with serum resistin levels. These observations support the potential role of resistin in the inflammatory cascade in RA.

Although some studies did not disclose a significant difference in blood resistin levels between RA patients and controls (24, 30), others revealed higher resistin levels in RA patients than in healthy individuals (22) or patients with osteoarthritis (23).

Migita *et al*. found a positive correlation between serum resistin levels and TNF-α (22). In line with this finding, endotoxin lipopolysaccharide administration has proved to result in a dramatic and dose-responsive increase in resistin gene expression and enhanced serum resistin production that was mediated by TNF-α (31). Moreover, Bokarewa *et al*. confirmed proinflammatory properties of resistin mediated by upregulation of IL-6 and TNF-α from PBMC (24).

A strong correlation between systemic inflammation and CV disease has been observed in RA (8, 32). This contributes to the excess of CV mortality observed in RA (8). In support of this notion, Goodson *et al*. emphasized the importance of the baseline CRP concentrations as a predictor of all-cause mortality, and specifically of CV mortality, in patients with inflammatory polyarthritis in a 10-year period following the onset of the inflammatory polyarthritis (33). In keeping with these observations, we reported an association between the mean CRP levels and the development of subclinical atherosclerosis in RA patients without clinically evident CV disease or classic CV risk factors (34). Also, both the mean CRP concentrations and ESR showed a significant association with the development of CV events and CV mortality in a follow-up study of RA patients from northwestern Spain (7). CRP is known to promote atherosclerotic processes and endothelial cell activation. CRP downregulates endothelial nitric oxide synthase transcription and also decreases both basal and stimulated nitric oxide release (35).

In line with the above, in the present study we have found a strong association between serum resistin levels and laboratory markers of inflammation, particularly with CRP but not with BMI. These data are consistent with the reported findings by Migita *et al*. and Senolt *et al*. in individuals with RA with very different genetic backgrounds (22, 23).

Interestingly, in a community-based sample of 879 asymptomatic subjects who had a family history of premature coronary artery disease, serum resistin levels were positively associated with levels of inflammatory markers, including soluble TNF-α receptor-2, IL-6, and lipoprotein-associated phospholipase A2, but not with measures of insulin resistance (36). In addition, in the same study, resistin levels were significantly associated with coronary atherosclerosis.

In summary, we report, for the first time, a significant decrease in serum resistin levels following TNF-α blockade. Whether this effect may play a potential role in the reduction of CV events and CV mortality associated with anti-TNF-α therapy in patients with RA needs further investigation.

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## References

1. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, MARTIN J: Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin Arthritis Rheum* 2005; 35: 8-17.
2. DEL RINCÓN I, ESCALANTE A: Atherosclerotic cardiovascular disease in rheumatoid arthritis. *Curr Rheumatol Rep* 2003; 5: 278-86.
3. GAZI IF, BOUMPAS DT, MIKHAILIDIS DP, GANOTAKIS ES: Clustering of cardiovascular risk factors in rheumatoid arthritis: the rationale for using statins. *Clin Exp Rheumatol* 2007; 25: 102-11.
4. DEL RINCÓN I, WILLIAMS K, STERN MP, FREEMAN GL, ESCALANTE A: High incidence of cardiovascular events in rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001; 44: 2737-45.
5. DESSEIN PH, JOFFE BI, VELLER MG *et al*.: Traditional and nontraditional cardiovascular risk factors are associated with atherosclerosis in rheumatoid arthritis. *J Rheumatol* 2005; 32: 435-42.
6. GONZALEZ-JUANATEY C, TESTA A, GARCIA-CASTELO A *et al*.: HLA-DRB1 status affects endothelial function in treated patients with rheumatoid arthritis. *Am J Med* 2003; 114: 647-52.
7. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, LOPEZ-DIAZ MJ *et al*.: HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 57: 125-32.
8. SATTAR N, MCCAREY DW, CAPELL H, MCINNES IB: Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 2003; 108: 2957-63.
9. MAINI RN, BREEDVELD FC, KALDEN JR *et al*.: Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 1552-63.
10. IMPERATO AK, BINGHAM CO 3RD, ABRAMSON SB: Overview of benefit/risk of biological agents. *Clin Exp Rheumatol* 2004; 22: S108-14.
11. CARMONAL, DESCALZO MA, PEREZ-PAMPIN E *et al*.: All cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with TNF antagonists. *Ann Rheum Dis* 2007; 66: 880-5.
12. HÜRLIMANN D, FORSTER A, NOLL G *et al*.: Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. *Circulation* 2002; 106: 2184-7.
13. GONZALEZ-JUANATEY C, TESTA A, GARCIA-CASTELO A, GARCIA-PORRUA C, LLORCA J, GONZALEZ-GAY MA: Active but transient

improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti-tumor necrosis factor alpha antibody. *Arthritis Rheum* 2004; 51: 447-50.
14. GONZALEZ-JUANATEY C, LLORCA J, SANCHEZ-ANDRADE A, GARCIA-PORRUA C, MARTIN J, GONZALEZ-GAY MA: Short-term adalimumab therapy improves endothelial function in patients with rheumatoid arthritis refractory to infliximab. *Clin Exp Rheumatol* 2006; 24: 309-12.
15. GONZALEZ-GAY MA, DE MATIAS JM, GONZALEZ-JUANATEY C *et al*.: Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006; 24:83-6.
16. STEPPAN CM, BROWN EJ, WRIGHT CM *et al*.: A family of tissue-specific resistin-like molecules. *Proc Natl Acad Sci USA* 2001; 98: 502-6.
17. STEPPAN CM, BAILEY ST, BHAT S *et al*.: The hormone resistin links obesity to diabetes. *Nature* 2001; 409: 307-12.
18. LEE JH, CHAN JL, YIANNAKOURIS N, KONTOGIANNI M *et al*.: Circulating resistin levels are not associated with obesity or insulin resistance in humans and are not regulated by fasting or leptin administration: cross-sectional and interventional studies in normal, insulin-resistant, and diabetic subjects. *J Clin Endocrinol Metab* 2003; 88: 4848-56.
19. PATEL L, BUCKELS AC, KINGHORN IJ *et al*.: Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. *Biochem Biophys Res Commun* 2003; 300: 472-6.
20. KASER S, KASER A, SANDHOFER A, EBENBICHLER CF, TILG H, PATSCH JR: Resistin messenger-RNA expression is increased by proinflammatory cytokines *in vitro*. *Biochem Biophys Res Commun* 2003; 309: 286-90.
21. SCHAFFLER A, EHLING A, NEUMANN E *et al*.: Adipocytokines in synovial fluid. *JAMA* 2003; 290: 1709-10.
22. MIGITA K, MAEDA Y, MIYASHITA T *et al*.: The serum levels of resistin in rheumatoid arthritis patients. *Clin Exp Rheumatol* 2006; 24: 698-701.
23. SENOLT L, HOUSA D, VERNEROVA Z *et al*.: Resistin in rheumatoid arthritis synovial tissue, synovial fluid and serum. *Ann Rheum Dis* 2007; 66: 458-63.
24. BOKAREWA M, NAGAEV I, DAHLBERG L, SMITH U, TARKOWSKI A: Resistin, an adipokine with potent proinflammatory properties. *J Immunol* 2005; 174: 5789-95.
25. GONZALEZ-GAY MA, GARCIA-UNZUETA MT, DE MATIAS JM *et al*.: Influence of anti-TNF-alpha infliximab therapy on adhesion molecules associated with atherogenesis in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006; 24: 373-9.
26. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatology Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
27. VIS M, NURMOHAMED MT, WOLBINK G *et al*.: Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. *J Rheumatol* 2005; 32:252-5.
28. VAN GESTEL AM, STUCKI G: Evaluation of established rheumatoid arthritis. *Baillieres Best Pract Res Clin Rheumatol* 1999; 13: 629-44.
29. ALETAHA D, WARD MM, MACHOLD KP, NEIL VP, STAMM T, SMOLEN JS: Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum* 2005; 52: 2625-36.
30. OTERO M, LAGO R, GOMEZ R *et al*.: Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: 1198-201.
31. LEHRKE M, REILLY MP, MILLINGTON SC, IQBAL N, RADER DJ, LAZAR MA: An inflammatory cascade leading to hyperresistinemia in humans. *PLoS Med* 2004; 1: e45.
32. SATTAR N, MCINNES IB: Vascular comorbidity in rheumatoid arthritis: potential mechanisms and solutions. Cur*r Opin Rheumatol* 2005; 17: 286-92.
33. GOODSON NJ, SYMMONS DP, SCOTT DG, BUNN D, LUNT M, SILMAN AJ: Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year followup study of a primary care-based inception cohort. *Arthritis Rheum* 2005; 52: 2293-9.
34. GONZALEZ-GAY MA, GONZALEZ-JUANATEY C, PINEIRO A, GARCIA-PORRUA C, TESTA A, LLORCA J: High-grade C-reactive protein elevation correlates with accelerated atherogenesis in patients with rheumatoid arthritis. *J Rheumatol* 2005; 32: 1219-23.
35. VERMA S, WANG CH, LI SH, DUMONT AS, FEDAK PW, BADIWALA MV *et al*.: A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation* 2002; 106: 913-9.
36. REILLY MP, LEHRKE M, WOLFE ML, ROHATGI A, LAZAR MA, RADER DJ: Resistin is an inflammatory marker of atherosclerosis in humans. *Circulation* 2005; 111: 932-9.