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Pretreatment resistin levels are associated with erosive disease in early rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs and infliximab

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Objective: Resistin is an adipocytokine related to insulin resistance and inflammation. We investigated whether resistin is associated with disease activity and inflammation in disease-modifying anti-rheumatic drug (DMARD)-naïve rheumatoid arthritis (RA) patients, whether it has predictive value for radiological disease progression, and whether tumour necrosis factor-α (TNF-α) is involved in these effects.
Method: Ninety-nine patients with early, DMARD-naïve RA participated in the NEO-RACo study. Patients were treated for the first 4 weeks with a combination of methotrexate, sulfasalazine, hydroxychloroquine, and prednisolone (FIN-RACo treatment). Thereafter, they were randomized to receive either infliximab or placebo added to the combination for 6 months. Patients were followed for 5 years. Disease activity was evaluated using the Disease Activity Score based on 28-joint count–erythrocyte sedimentation rate, radiographs were scored with the modified Sharp–van der Heijde method, and plasma resistin concentrations were measured by immunoassay. Human THP-1 macrophages were used in the in vitro studies.
Results: A high resistin level at baseline was associated with active inflammatory disease and predicted more rapid radiological progression during 5 year follow-up. Adding infliximab to the DMARD combination delayed radiological progression and overcame the poor predictive value of resistin. Resistin increased TNF-α production in human macrophages, indicating a possible connection between resistin and TNF-α.
Conclusion: The results suggest that high resistin concentration may be a useful marker to distinguish patients with an increased risk of erosive disease in early active RA, and that adding TNF-α antagonist to the traditional DMARD combination may delay radiological progression of the disease in these patients.
The study has been registered at https://www.clinicaltrials.gov(NCT00908089).

Resistin is an adipocytokine associated with insulin resistance, inflammation, and diseases such as type 2 diabetes, cancer, sepsis, and arthritis (1, 2). Although originally found in adipose tissue in mice, macrophages are the main cellular source in humans. Within the joints of patients with rheumatoid arthritis (RA), resistin is found in synovial fluid, and in synovial membranes it is expressed by fibroblasts, macrophages, and B cells (2). Toll-like receptor-4 (TLR-4), decorin, and receptor tyrosine kinase like orphan receptor-1 (ROR1) have been reported to mediate some effects of resistin (1), but later Lee et al identified adenylyl cyclase-associated protein-1 (CAP1) as the bona fide receptor for resistin (3). Resistin binds to CAP1 in monocytes and increases cellular levels of cyclic adenosine monophosphate (cAMP), which, in turn, activates cAMP-dependent transcription factors, resulting in enhanced production of proinflammatory cytokines. In addition, resistin promotes angiogenesis and synovial inflammation and induces cartilage destruction. In patients with arthritis, resistin levels are increased compared to controls, both in serum and in synovial fluid (1, 2, 4, 5).

In the new Finnish RA Combination Therapy (NEO-RACo) trial (6), we showed excellent sustained clinical results with a treat-to-target approach in patients with early, disease-modifying anti-rheumatic drug (DMARD)-naïve RA using the intensified Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial treatment. At 2 years, Disease Activity Score based on 28-joint count (DAS28) remission was achieved in 82% of the patients, the strict American College of Rheumatology (ACR) remission in as many as 53%, and only 8% of the patients did not reach ACR 50% response (ACR50). The addition of infliximab for the first 6 months to the FIN-RACo treatment

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induced remission more rapidly, increased the percentage of patients reaching the strict ACR remission from 53% to 66% at 2 years, and retarded radiological progression. However, differences compared to the FIN-RACo plus placebo group were not statistically significant at 2 years or in the extended 5 year follow-up (6, 7).

Most of the patients achieved early remission using the intensified FIN-RACo, but some responded better to infliximab treatment. A means of predicting apparent responders would be valuable to retard disease progression in the early stages. In this post-hoc NEO-RACo study, we decided to investigate whether resistin is associated with disease activity and inflammation in DMARD-naïve RA patients, whether it has a predictive value for the disease progression, and whether tumour necrosis factor-α (TNF-α) is involved in these effects.

Method

Study design, patients, outcomes, and follow-up

This is a post-hoc study of the NEO-RACo trial, which is an investigator-initiated, multicentre, controlled study. This study recruited 99 patients with early, active RA treated with an intensified FIN-RACo treatment: methotrexate (maximum 25 mg/week), sulfasalazine (maximum 2 g/day), hydroxychloroquine (35 mg/kg/week), and prednisolone (7.5 mg/day) for 2 years, and double blindly randomized to receive either placebo or infliximab infusions at weeks 4, 6, 10, 18, and 26 (6 months). Active use of intra-articular glucocorticoid (GC) injections to all inflamed joints was part of the protocol. Between 6 and 24 months, treatment continued intensively with a combination of three conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) according to a predefined protocol; in the case of treatment failure (patient having treatment response less than ACR50 on two consecutive visits), treatment became unrestricted. After 24 months, if the patient was in remission, GCs and csDMARDs were gradually tapered off with a predefined protocol; or, in the case of non-remission, medication was modified according to the judgement of the treating rheumatologist, aiming at strict remission (7).

DAS28 with erythrocyte sedimentation rate (ESR) was calculated at baseline (8). The small joints of the hands and feet were radiographed at baseline and at 2 and 5 years, and scored by an experienced radiologist (LL), according to the modified Sharp–van der Heijde score (SHS) (9). The patient selection criteria, as well as the treatment protocol, outcomes, and follow-up, have been described previously (6, 7).

Plasma samples and enzyme-linked immunosorbent assay

Plasma samples were taken at weeks 0, 4, 10, 18, and 26, and kept at −80°C until assayed. Blood samples were available from 90 patients. Resistin concentrations were determined by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

In vitro experiments

Human THP-1 macrophages were used to study the effect of resistin on TNF-α production measured by ELISA. Immunoprecipitation of resistin was used to confirm the specificity of the resistin effect. Details of the methods can be found in the Supplementary file.

Statistics

Statistical analysis was carried out by using the t-test, bootstrap type t-test (5000 replications), or chi-squared test, as appropriate. Repeated measures were analysed using bootstrap-type generalized estimating equation (GEE) models with an unstructured correlation structure, and were adjusted for baseline rheumatoid factor (RF), DAS28, and total SHS. For the hypotheses of linearity, significance was evaluated using generalized linear models with appropriate distribution and link function. In the case of violation of the assumptions (non-normality), a bootstrap-type test was used. Results are expressed as medians with interquartile ranges or as means with standard deviation (sd) or 95% confidence intervals (CIs) obtained by bias-corrected bootstrapping, and reported as appropriate according to the distribution of the data. Receiver operating characteristics (ROC) curve analysis was used to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for resistin levels to predict progression of 3 units in the total SHS (0–60 months), as described previously (10). The optimal cut-off point for resistin was determined using Liu's method, maximizing the product of the sensitivity and specificity (11). The 95% CIs were obtained with bias-corrected bootstrapping. Results of the cell culture studies are presented as mean + sem and statistical significance was calculated by using one-way ANOVA followed by Dunnett's multiple comparisons test. Data were analysed by using STATA (StataCorp, College Station, Texas, USA) and InStat (GraphPad Software, San Diego, CA, USA).

Ethics approval

The study was conducted according to the Declaration of Helsinki and the study protocol was approved by the

national health authorities and by the ethics committee of the Hospital District of Helsinki and Uusimaa. All patients gave their informed written consent.

Results

Patient characteristics are shown in Supplementary Table SI. Resistin concentration at baseline was 18.8 ± 6.1 ng/mL (mean ± sd, n = 90), and it correlated with disease activity and inflammation measured as DAS28 and ESR: when the patients were divided into tertiles based on their plasma resistin levels at baseline, DAS28 showed positive linearity (Supplementary Table SII, Figure 1A) and association (Figure 1B) with resistin concentrations. Similarly, ESR levels increased linearly in resistin tertiles (Supplementary Table SII).

During the first 4 weeks of treatment with the intensified FIN-RACo, plasma resistin levels decreased significantly in all resistin tertiles, and when infliximab was added to the treatment, no further reduction was seen (Figure 2).

The predictive value of resistin for radiological disease progression was evaluated at 2 and 5 years. High baseline resistin levels predicted radiologically more rapidly progressing disease in the DMARD combination plus placebo group, as measured by the difference in total SHS (Figure 3A). Adding infliximab to the treatment delayed the radiological progression in the patients with high resistin and there was no difference in radiological progression between the resistin tertiles in the DMARD combination plus infliximab-treated patients (Figure 3B). ROC analysis showed an optimal cut-off value of 16 ng/mL for baseline resistin to detect progression of 3 units in the SHS in 5 years, with a sensitivity of 86% (95% CI 64–97%) and specificity of 44% (95% CI 32–58%). The positive predictive value (PPV) of a high resistin level was 35.1% and the negative predictive value (NPV) was 90.1%. When the lower limit of the highest resistin tertile level (20 ng/mL) was used as a cut-off value, specificity improved to 70% (95% CI 57–81%), while sensitivity was reduced to 43% (95% CI 22–66%), resulting in a PPV of 33.5% and an NPV of 77.7%.

The finding that a TNF-α antagonist was able to overcome the predictive value of high resistin on radiological disease progression points to the possible involvement of TNF-α in mediating the effects of resistin. In support of this hypothesis, our in vitro studies showed that resistin increased TNF-α production in human macrophages. Immunoprecipitation of resistin was used to confirm the specificity of the resistin effect, and it totally abolished resistin-induced TNF-α production (Supplementary Figure S1) by human macrophages.

Discussion

We discovered that in early DMARD-naïve RA patients, high resistin levels are associated with disease activity and inflammation, and have a predictive

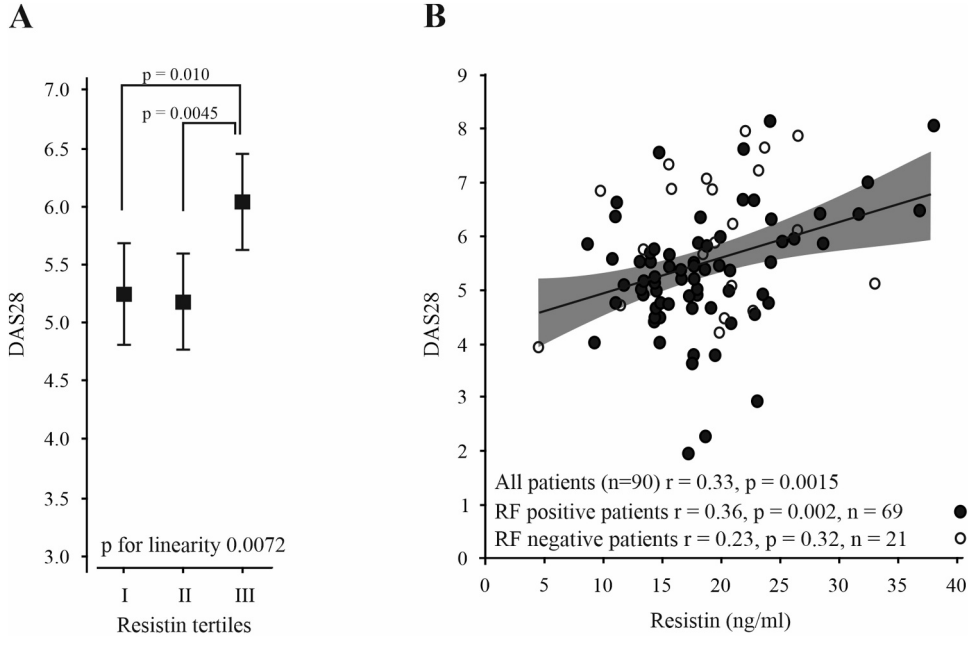

Figure 1. Resistin was associated with disease activity. The Disease Activity Score based on 28-joint count (DAS28) was used to assess disease activity. Resistin was measured in plasma by enzyme-linked immunosorbent assay. (A) Disease-modifying anti-rheumatic drug (DMARD)-naïve rheumatoid arthritis patients were divided into tertiles based on their plasma resistin levels at baseline [I, resistin < 15 ng/mL (n = 28); II, 15–20 ng/mL (n = 31); III, > 20 ng/mL (n = 31)]. Results are expressed as mean with bias-corrected bootstrapping 95% confidence interval. Statistical comparison among the groups was performed using the bootstrap-type analysis of covariance (ANCOVA), taking gender and body mass index as covariates. (B) Scatterplot showing correlation between DAS28 and resistin. RF, rheumatoid factor.

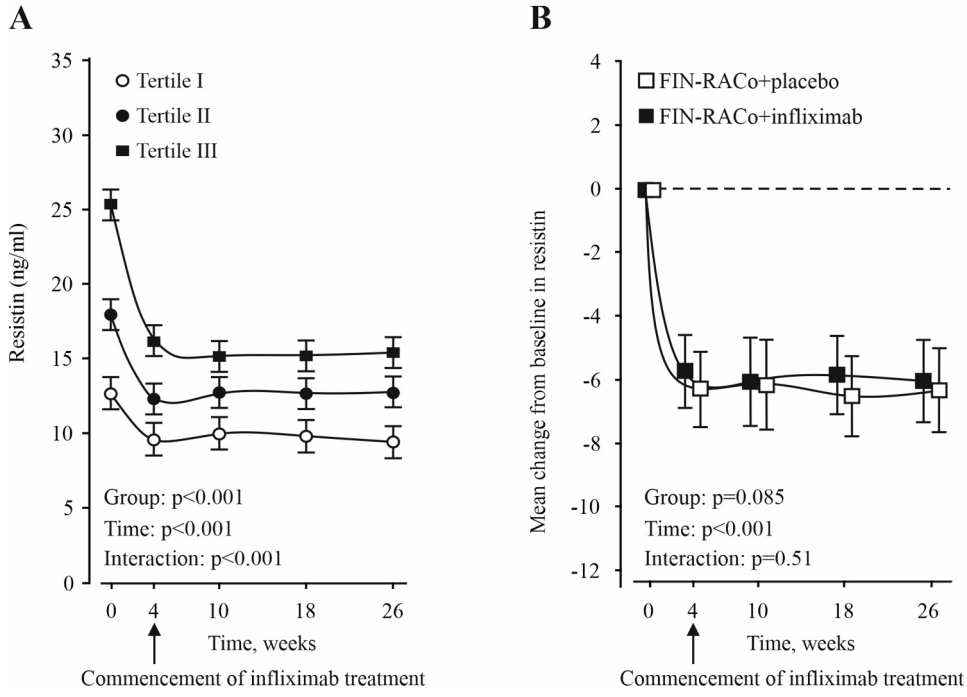

Figure 2. Resistin levels decreased during treatment with disease-modifying anti-rheumatic drug (DMARD) combination therapy, but no further reduction was seen when infliximab was added. (A) Resistin levels were analysed in tertiles based on the plasma resistin levels at baseline [I, resistin < 15 ng/mL (n = 28); II, 15–20 ng/mL (n = 31); III, > 20 ng/mL (n = 31)]. (B) Mean change in resistin levels from baseline. (A, B) Patients were treated with combination DMARD therapy, and placebo or infliximab infusions were given at weeks 4, 6, 10, 18, and 26. Results are expressed as mean with bias-corrected bootstrapping 95% confidence interval. Repeated measures were analysed using bootstrap-type generalizing estimating equation models with the unstructured correlation structure, and were adjusted for baseline rheumatoid factor, Disease Activity Score based on 28-joint count, and Sharp–van der Heijde total score. FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy.

value for radiographic disease progression. TNF-α seems to be involved in these effects, as resistin increased TNF-α production in macrophages and infliximab treatment overcame the poor predictive value of high resistin levels.

In the present study, the median duration of symptoms at baseline was 4 months. At that stage, before treatment, resistin showed a positive association with disease activity and inflammation. In support of this finding, associations with DAS28, C-reactive protein (CRP), ESR, TNF, and interleukin-6 in RA have been reported (5, 12, 13).

Resistin levels decrease in response to RA treatment, according to a paper reporting two Dutch trials: one treating patients with methotrexate, sulfasalazine, and GCs for 21 weeks, and another with adalimumab, methotrexate, and GCs if needed for 16 weeks (14). In another study, resistin levels were shown to decline shortly after infliximab infusion (13). The FIN-RACo treatment decreased resistin levels during the first 4 weeks, while no further reduction was shown with the addition of infliximab. However, the difference in resistin concentrations between baseline resistin tertiles remained during the 6 month follow-up.

In our study, patients were treated in an intensified treat-to-target manner, showing minor radiological progression in both groups during the 5 year follow-up: the mean changes in total SHS from baseline were 3.7 in the placebo group and 1.6 in the infliximab group (7). In a previous cross-sectional analysis in DMARD-treated patients, resistin was found to be associated with radiological changes in RA patients (14, 15), whereas no predictive value of baseline resistin was found in cohort studies following patients for 3–4 years (12, 16). In the present study, high resistin at baseline predicted more rapidly radiologically progressing disease in the FIN-RACo plus placebo group, showing a clinically important difference of 5 units (17) at follow-up after 2 and 5 years between the patients with the highest and the lowest resistin tertiles at baseline.

Analysis was adjusted for gender and body mass index (BMI) at baseline, but not for smoking (because of a lack of data), which is also an acknowledged predictor of radiological progression and could contribute to this finding (18, 19). Infliximab treatment is known to cause weight gain (20). Unfortunately, weight was not followed in the NEO-RACo study and we are not able to report the possible or likely effects of infliximab on weight during the 6 months of infliximab treatment. However, the results of the present study rely on the predictive value of baseline resistin levels and, as mentioned, the analysis was adjusted for baseline BMI.

RF and anti-citrullinated protein antibodies (ACPAs) are also known predictors of radiological progression

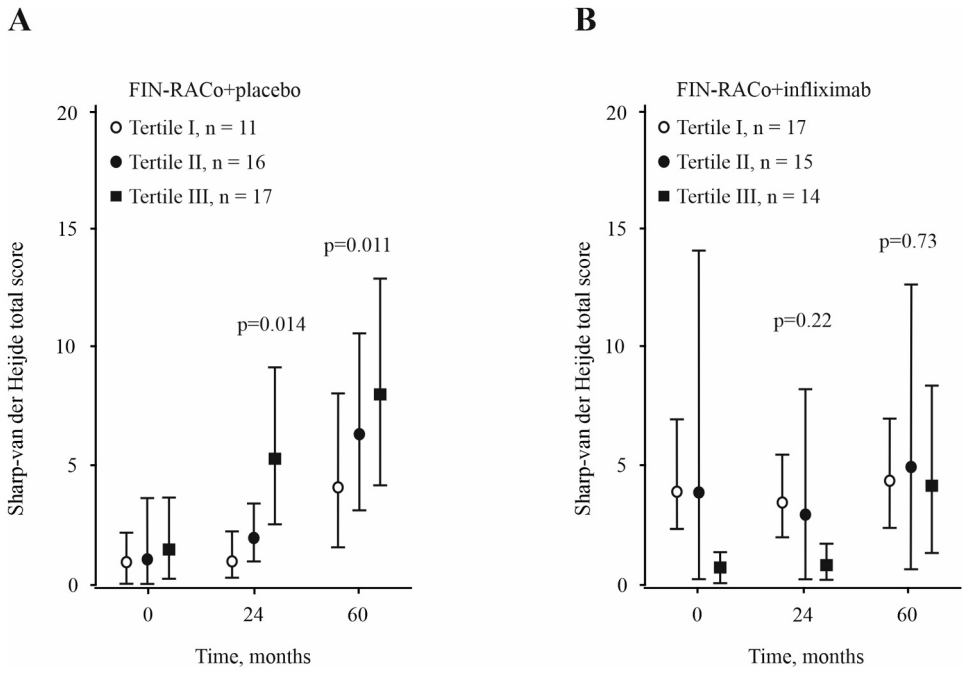

Figure 3. (A) High resistin levels at baseline predicted radiologically more rapidly progressing disease in patients treated with disease-modifying anti-rheumatic drug (DMARD) combination therapy and placebo infusions; (B) adding infliximab overcame the poor predictive value of high resistin. (A, B) Radiological disease progression was analysed in resistin tertiles based on their plasma resistin levels at baseline [I, resistin < 15 ng/mL; II, 15–20 ng/mL; III, > 20 ng/mL (n values for each group are given in the figure)]. Radiological disease progression during the 5 year follow-up was measured by the difference in Sharp–van der Heijde total score. Results are expressed as mean with bias-corrected bootstrapping 95% confidence interval. Statistical comparison among the groups was performed using the bootstrap-type analysis of covariance (ANCOVA), taking gender and body mass index as covariates. FIN-RACo, Finnish Rheumatoid Arthritis Combination Therapy.

(21). Notably, there were no significant differences between the number of RF and/or ACPA-positive patients in the resistin tertiles groups, and ACPA levels tended to be even lower in the highest resistin tertile. This supports the value of high resistin as a risk factor to predict radiological progression.

High CRP values have been suggested as predictors of radiographic progression, and a 2019 review reported PPVs of 25–55% and NPVs of 77–86% for high CRP (> 30 mg/mL) in similar clinical trials to ours (22). In the present study, the PPV of a high resistin level (optimal cut-off > 16 ng/mL) was 35.1% and the NPV was 90.1%, suggesting that resistin is superior to CRP in predicting radiographic progression in RA.

Infliximab overcame the poor predictive value of high resistin, and the in vitro data showed that resistin increases TNF-α production in macrophages. These results point to a phenotype of RA in which increased resistin levels may be linked to enhanced TNF-α production driving towards erosive disease, but further longitudinal patient studies are needed to confirm the causality of this finding.

Conclusion

High resistin levels predicted radiologically more rapidly progressing disease in patients with early, active RA, although treated with intensified csDMARD combination. When infliximab was added to the treatment, the difference in radiological progression between the resistin tertiles was abolished. Taking these results together, a high resistin concentration may distinguish patients with increased risk of erosive disease, and adding a TNF-α-antagonist can delay radiological progression of the disease in these patients.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supporting information

Additional Supporting Information may be found in the online version of this article. Supplementary file contains
Supplementary Methods for cell culture experiment

Supplementary Table SI

Supplementary Table SII

Supplementary Figure S1

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