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# DOES THE COURSE OF DISEASE INFLUENCE THE DEVELOPMENT OF FATIGUE IN RHEUMATOID ARTHRITIS PATIENTS?

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*Patients with rheumatoid arthritis (RA) typically have many permanently inflamed joints. The inflammation inside the body can lead to general physical weakness, exhaustion, and drowsiness. This feeling of extreme tiredness is also called "fatigue". Some people find this to be the worst symptom of the disease. However, the clinical significance of fatigue and its pathogenesis have not been recognised. This study aimed to determine the development of fatigue depending on activity and aggressiveness of RA. To achieve the goal, patients were interviewed and indicators of disease activity and aggressiveness were determined: rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), immunoglobulins IgA RF, IgM RF, IgG RF and anti-carbamylated protein antibodies (anti-CarP). Based on the results of the survey, RA patients were divided into two groups — with and without fatigue. In the group of RA patients with fatigue, statistically more often an increase in IgA RF, IgM RF, and IgG RF levels was observed in those with elevated RF level, higher IgM RF and IgG RF levels were associated with increase in IgA RF level, and increase in the IgG RF and anti-CarP levels with elevation in the IgM RF level. A higher IgG RF level contributed to a higher anti-CarP level increase. Significant differences in the levels of clinical and laboratory inflammatory markers were not observed between the RA patients with and without fatigue. The obtained data suggest that the aggressive course of RA, more than inflammation, may contribute to the development of fatigue in RA patients.*

**Key words:** *immunology, tiredness, disease activity, aggressiveness.*

## INTRODUCTION

Fatigue is very common in many rheumatic diseases, including rheumatoid arthritis (RA), and is reported by patients as one of the most important outcomes of the disease (Hewlett *et al*., 2005). Fatigue that is present in RA is experienced differently, as viewed by patients, from 'normal' tiredness to overwhelming, uncontrollable, and, often, untreatable (Katz, 2017). Although fatigue is not clearly defined, fatigue affects at least three-quarters of RA patients (Wolfe *et al*., 1996; Pollard *et al*., 2006). Using a fatigue Visual Analogue Scale, 50% of RA patients have fatigue, which is at least five out of 10 (Hewlett *et al*., 2005) and 40% have severe fatigue (Andersson *et al*., 2013).

The importance of fatigue in RA is underlined by the finding that more severe fatigue is predictive for decreased mental and physical health-related quality of life, loss of work ability and depression (Breedveld *et al*., 2005; Lacaille *et al*., 2007; Wolfe *et al*., 2009). Both a Patient Perspective Workshop at OMERACT (Outcome Measures in Rheumatology) in 2007 and a EULAR/ACR task force in 2008 recommended that "each trial should report on fatigue" (Kirwan *et al*., 2007; Aletaha *et al*., 2008).

The cause of fatigue in RA is thought to be multifactorial. A conceptual model suggests that fatigue is the result of interactions between several factors: behavioural factors (feelings, thoughts, behaviours) and disease-process related factors, cognitive and personal factors (personal life issues) (Hewlett *et al*., 2011). Scientific data supporting this model are mostly derived from cross-sectional studies and are conflicting. Fatigue tends to correlate with disease activity, but often the association is weak (Bergman *et al*., 2009; Van Hoogmoed *et al*., 2010; Nikolaus *et al*., 2013; Madsen *et al*., 2016). More strong correlation is with pain and physical impairments (Pollard *et al*., 2006; Nikolaus *et al*., 2013). When RA flare develops, usually pain and fatigue increase (Barlett *et al*., 2012). Reports on fatigue in cases of RA are not always consistent between studies. In one study, high fatigue was associated with female gender, disease activity, joint dysfunction, treatment and multimorbidity (especially obesity and depression). However, severe fatigue in another study was associated with RA patients' self-rated poor health, pain and anxiety/depression, but not physical function (Demmelmaier *et al*., 2018).

Fatigue is often present even if RA activity is low. This can be due to common chronic pain in RA, which can lead to poor sleep, depressed mood, and fatigue (Katz, 2017; Bingham *et al*., 2019; Junghaenel *et al*., 2019; Primdahl *et al*., 2019; Silva *et al*, 2019). Also, 10% of RA patients report depression in early RA (Holdren *et al*., 2019). Residual fatigue persists for many RA patients with a sustained state of low disease activity (Strand *et al*., 2015). Approximately 15% of RA patients were not in fatigue remission when the disease activity score (DAS) was in the remission stage (DAS of < 2.6) (Druce *et al*., 2016). The presence of sicca symptoms, greater severity of morning stiffness, and presence of psychological distress at baseline were associated with baseline fatigue and persistent fatigue at five years, and association between baseline fatigue or persistent fatigue and the DAS28 (erythrocyte sedimentation reaction (ESR)) (Rodríguez-Muguruza *et al*., 2020).

Previous studies have shown that a combined increase in immunoglobulin IgM rheumatoid factor (RF) and IgA RF, with or without IgG RF, is the most common RF pattern found in RA patients. Several studies have shown that RA patients with an increase in IgA RF develop a more severe disease, with bone erosions or extra-articular manifestations, or both, than patients without IgA RF (Jonsson *et al*., 1998).

Anti-carbamylated proteins antibodies (anti-CarP) have been identified as a newer biomarker in RA, with a prevalence of 16–45% and a significant association with erosive damage and radiographic progression (Shi *et al*., 2013; Shi *et al*., 2014; van Delft *et al*., 2017; Truchetet *et al*., 2017).

From previous studies, it remains unclear whether RA patients suffer from higher levels of fatigue, and whether excessive fatigue is related to the disease. In addition, the role of inflammation and autoantibodies produced in RA in relation to fatigue is unclear. Therefore, we identified a need to carry out a study in RA patients, assessing the degree of inflammation by means of clinical and laboratory indices. We used a validated fatigue questionnaire (Minnock *et al*., 2017) to determine if RA patients' fatigue could be predicted by clinical and laboratory disease-related variables, particularly inflammation and aggressiveness.

## MATERIALS AND METHODS

**Patients groups.** This prospective cohort study included patients from Rīga East Clinical University Hospital in the period from February to May 2020. Patient inclusion criteria were: primary or remotely diagnosed with RA, and age over 18 years. All patients met the RA classification criteria of the American College of Rheumatology and the European League Against Rheumatism in 2010 (Aletaha *et al*., 2010). The exclusion criteria were: other rheumatic or inflammatory diseases, and age below 18. Respondents with RA were divided into two groups according to whether they had any kind of subjective fatigue, based on the answers of a written questionnaire.

Thirty Caucasian RA patients were included in the study: 23 female (76.7%) and 7 male (23.3%). The average age of the respondents was 59.5 ± 11.2 (ranging from 39 to 79). From all responders, 20 patients reported fatigue, 16 of them were female (80%) and 4 were male (20%), with the average age 59.2 ± 10.7 (ranging from 39 to 75). Ten RA patients without subjective symptoms of fatigue were included in the control group — seven female (70%) and three male (30%), with average age 60.2 ± 12.0 (ranging from 45 to 79). In the RA group of patients with fatigue, the mean pain score on the visual analogue scale (VAS) in cm was 4.72 ± 2.16, morning stiffness (in hours) median was IQR 1.75 (0.5–3.0) and the integrated parameter DAS28 (CRP) was 3.58 ± 1.15. However, in the RA group of patients without fatigue, the mean pain score on the visual analogue scale (in cm) was 4.52 ± 2.16, morning stiffness (in hours) was median IQR 1.00 (0.39–2.13) and the integrated parameter DAS28 (CRP) as 3.58 ± 1.15.

The Ethics Committee of Rīga Stradiņš University approved the study protocol and all individuals participating in this study provided informed consent before their inclusion.

**Sample collection and preparation.** All clinical laboratory indicators were determined in a respective clinic's local laboratory. Ethylene Diaminetetraacetic acid (EDTA) anti-coagulated peripheral blood samples were collected from RA patients with and without fatigue. Plasma was separated from peripheral blood by centrifugation. The following parameters were estimated in both groups: RF, anti-cyclic citrullinated peptide antibodies (anti-CCP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulins IgA RF, IgG RF, IgM RF and anti-carbamylated proteins antibodies (anti-CarP). CRP level higher than 8 mg/l, and ESR level greater than 30 mm/h were noted to signify active disease. The Disease Activity Score 28

(DAS28) was calculated using the CRP result. The following DAS28 reference intervals were taken into account: < 2.6 remission, > 2.6–3.2 low disease activity, > 3.2–5.1 moderate disease activity and > 5.1 high RA activity (Jensen Hansen *et al*., 2017). Remission was observed in 13.3% of RA patients, low disease activity in 30.0% patients, moderately high in 43.3% and high disease activity in 13.3% of RA patients. The laboratory results of RF and anti-CCP were obtained to analyse the aggressiveness of RA. A RF level ≤ 14 IU/ml and anti-CCP antibody level ≤ 17 U/ml were evaluated as increased, taking into account local laboratory reference intervals.

**Detection of IgA RF, IgG RF, and IgM RF.** IgA RF, IgG RF and IgM RF levels were determined using a solid phase enzyme immunoassay (ELISA) with highly purified Fc fragment of human immunoglobulin IgG (IBL International GMBH, Germany). The reaction was carried out according to the manufacturer's protocol.

In short, 100 µl of diluted plasma samples were added to the corresponding wells as well as calibrators, positive and negative controls. The microtitre plate was incubated for 30 minutes at 20–32°C and washed three times with 300 µl washing buffer. 100 µl of conjugate was added into each well, incubated for 30 minutes at 20–32°C and washed three times with 300 µl washing buffer. After that, 100 µl of TMB substrate was added to the wells, incubated for 30 minutes at 20–32°C with the subsequent addition of 100 µl of stop solution followed by incubation for at least five minutes. The microtitre plate was agitated carefully for 5 seconds and the optical density was measured spectrophotometrically at a wavelength of 450 nm within the next 30 minutes.

**Detection of anti-CarP**. Anti-CarP antibodies were detected using a Novateinbio ELISA kit (Novatein Biosciences, USA) following the manufacturers protocol. 50 µl of diluted standards, a sample diluent serving as a zero standard and samples were added to the corresponding microtitre plate wells. Subsequently, 100 µl of conjugate was added to each well and mixed well. The plate was covered and incubated for 1 hour at 37 °C. Then the microtitre plate was washed five times by filling each well with the diluted wash solution. 50 µl chromogen solution A and 50 µl chromogen solution B was added to each well, the plate was covered and incubated for 15 minutes at 37 °C. Then 50 µl of stop solution was added to each well and mixed. The optical density was measured spectrophotometrically at a wavelength of 450 nm immediately after.

**Statistical analysis.** The Spearman rank correlation test was used to measure the strength and direction of association between variables in RA patients groups with and without fatigue. The value of the Spearman's correlation coefficient ($r_s$) ranged from –1 to 1, with –1 being a very strong negative correlation and 1 being a very strong positive correlation. Statistical significance was set at $p < 0.05$.

All analyses and graphing were performed using Prism 8.01 for MacOS software (Graph Pad, San Diego, CA, USA).

## RESULTS

**RA patients without fatigue.** In the RA patient group without fatigue, the duration of morning stiffness, DAS28 and CRP levels increased with increasing pain intensity (r = 0.7, 0.7, and 0.7, respectively), and with increasing duration of morning stiffness, the level of DAS28 increased (r = 0.9; Fig. 1). In contrast, increase in pain intensity was correlated with a decrease of IgA RF (r = 0.5) and IgG RF (r = 0.6) level. Increased morning stiffness, duration of pain and DAS28 level were not significantly related to the level of other parameters (Fig. 1).

Among the RA group patients without fatigue, in those with increased RF level the IgM RF (r = 0.6) and anti-CCP (r = 0.6) level was significantly increased, but the level of other parameters (ESR, CRP, IgA RF, IgG RF and anti-CarP) did not change significantly (Figs. 1, 2).

In contrast, an increase in the anti-CCP level in the RA patient group without fatigue was correlated with increase in IgA RF (r = 0.8) and IgM RF (r = 0.6) levels, but the levels of other parameters (ESR, CRP, IgG RF and anti-CarP) did not change significantly (Fig. 1).

In cases when increased levels of ESR was detected no significant changes in the levels of IgA RF, IgM RF, IgG RF, and anti-CarP were observed. However, and increase of CRP was correlated with decrease of IgA RF (r = 0.8) and IgG RF (r = 0.6) levels (Fig. 1).

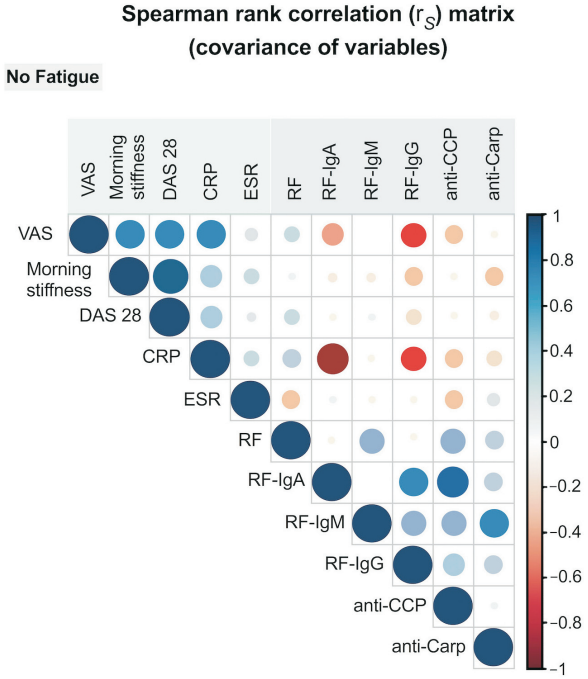


*Fig. 1.* Association strength between different variables measured: VAS (mean pain score on the visual analogue scale), morning stiffness, DAS28 (disease activity score 28(, RF (rheumatoid factor), anti-CCP (anti-cyclic citrullinated peptide antibodies), ESR (erythrocyte sedimentation rate), CRP (C reactive protein), Ig (immunoglobulin)A RF, IgM RF, IgG RF and CarP antibodies level) in RA patients without fatigue. Colour-filled circles in matrix graph represent Spearman's rank correlation coefficients (rs) where size and color of the circles reflect the value of rs, and more intense colour and bigger size corresponds to higher value of the coefficient (see the scale on the right side).

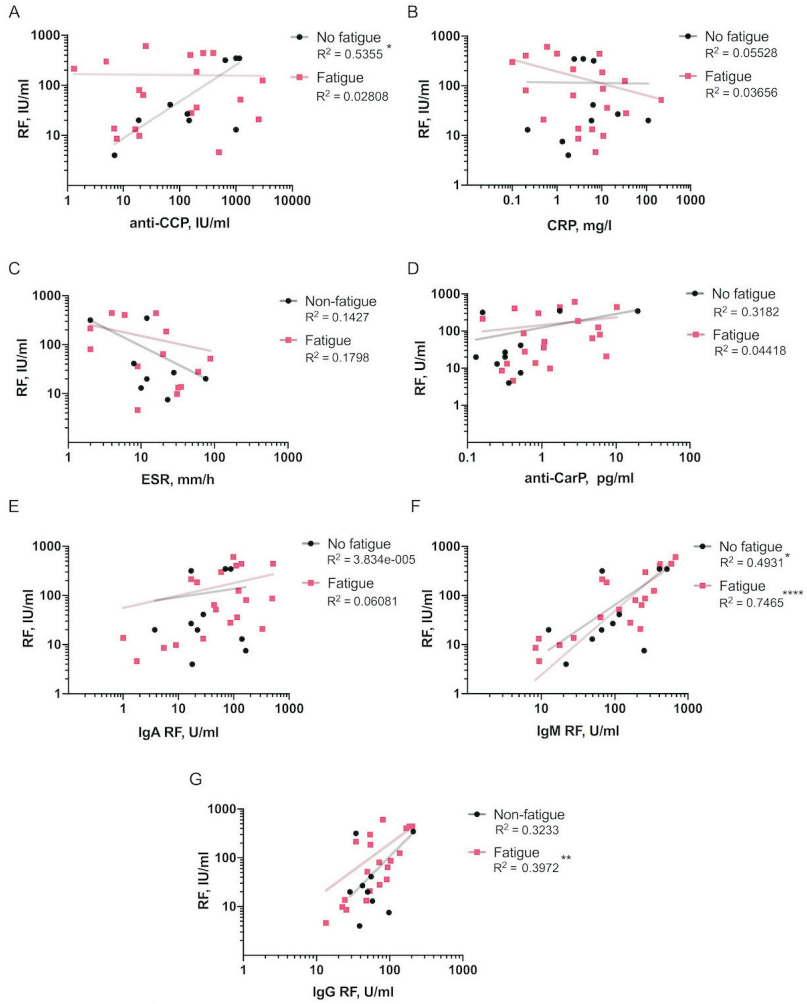


*Fig. 2.* Associations of RF and Anti-CCP (A), CRP (B), ESR (C), anti-CarP (D), IgA RF (E), IgM RF (F), IgG RF (G) levels in RA patients with weakness and RA patients without fatigue.

In the group of RA patients without fatigue, increase in IgA RF level was significantly correlated also IgG RF level increased significantly (r = 0.7), but by increase in IgM RF level the level of IgG RF (r = 0.6; Fig. 4) and anti-CarP (r = 0.7) level increased significantly (Figs. 1, 5).

The increase in IgG RF level did not affect the anti-CarP level significantly (Figs. 1, 5).

**RA patients with fatigue.** In the RA group of patients with fatigue, the level of DAS28 increased with increasing pain intensity (r = 0.8) and duration of morning stiffness (r = 0.7; Fig. 3). Increased morning stiffness was correlated with pain intensity (r = 0.5) but was not significantly correlated with other parameters (Fig. 3).

In the group of RA patients with fatigue, RF level was positively correlated with ESR (r = 0.5) and the IgA RF, IgM RF, and IgG RF levels (r = 0.5, r = 0.9, and r = 0.7, respectively). There was no significant relationship between RF level and the levels of anti-CCP, CRP, and anti-CarP (Figs. 2, 3).

An increase in anti-CCP in RA patients with fatigue was related to a tendency of increased CRP (r = 0.4) and IgG RF (r = 0.4), and significant increase of IgA RF (r = 0.5), anti-CarP (r = 0.5) levels, but the levels of ESR and IgM RF did not change significantly (Fig. 3).

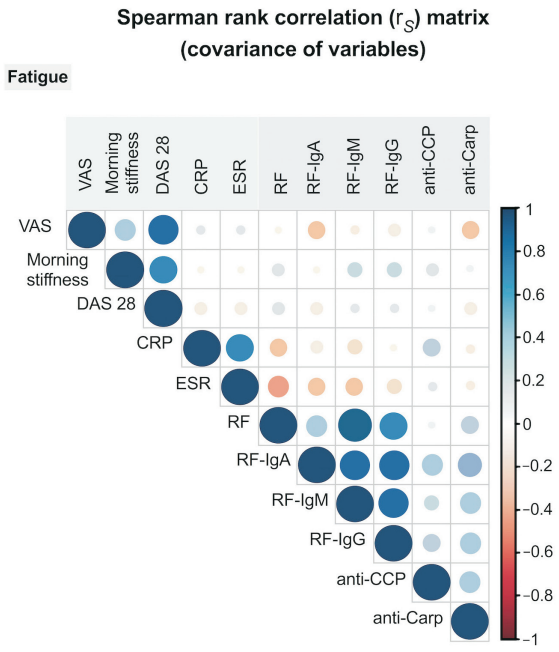


*Fig. 3.* Association strength between different variables measured (VAS, morning stiffness, DAS28, RF, anti-CCP, ESR, CRP, IgA RF, IgM RF, IgG RF and CarP antibodies level) in RA patients with fatigue. Colour-filled circles in matrix graph represent Spearman's rank correlation coefficients (rs) where size and color of the circles reflect the value of rs, and more intense colour and bigger size corresponds to higher value of the coefficient (see the scale on the right side)..

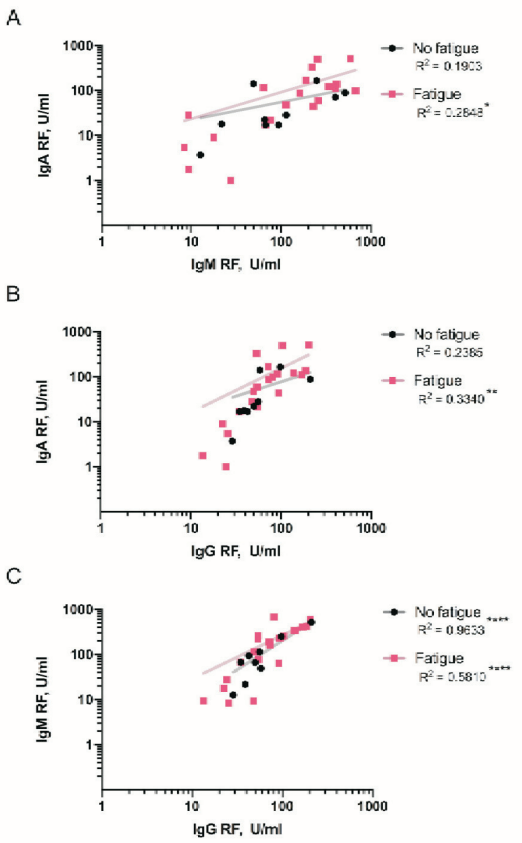


*Fig. 4.* Associations of IgA RF, IgM RF and IgG RF levels (A, B, C) in RA patients with weakness and RA patients without fatigue.

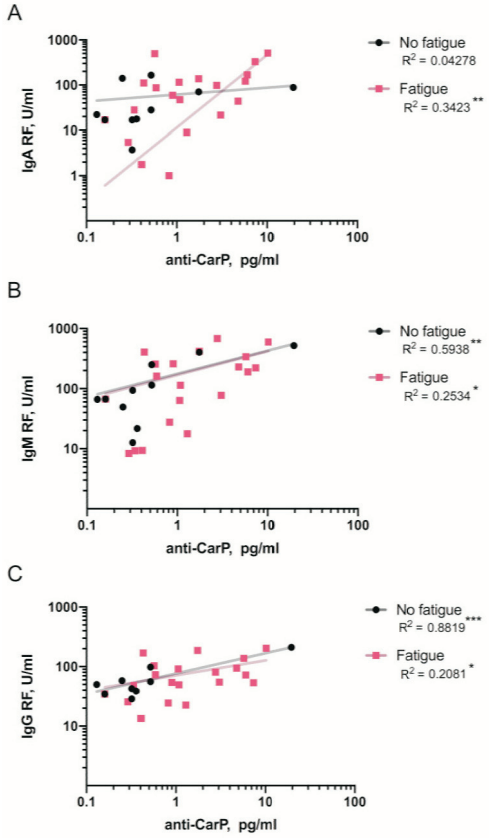


*Fig. 5.* Associations of anti-CarP level and IgA RF (A), IgM RF (B), IgG RF (C) levels in RA patients with weakness and RA patients without fatigue.

The level of ESR was positively correlated with the level of CRP (r = 0.7), while no significant relationship with levels of IgA RF, IgM RF, IgG RF, and anti-CarP was observed (Fig. 3).

In RA patients with fatigue, an increase of CRP level did not result in significant changes of IgA RF, IgM RF, IgG RF, and anti-CarP levels (Fig. 3).

In the group of RA patients with fatigue, IgA RF level, IgM RF, IgG RF levels were significantly correlated with anti-CarP levels (r = 0.8, r = 0.8, and r = 0.6, respectively; Figs. 4, 5). In the cases when IgM RF level increased, also IgG RF (r = 0.8; Fig. 4) and anti-CarP (r = 0.5; Fig. 5) levels increased significantly (Fig. 3).

In RA patients with fatigue, an increase in IgG RF level was significantly correlated with increased anti-CarP level (r = 0.5; Figs. 3, 5).

## DISCUSSION

Fatigue in RA is highly prevalent and affects at least three-quarters of patients (Pollard *et al*., 2006). Fatigue in RA is multifactorial. There are many different causes of fatigue in RA patients (Hewlett *et al*., 2005; Pollard *et al*., 2006; Nikolaus *et al*., 2013; Walsh *et al*., 2014; Katz, 2017; Zielinski *et al*., 2019), which are difficult to interpret in clinical practice. Previous research has shown that active RA with inflammation (Madsen *et al*., 2016) and pain cause fatigue directly by altered cytokines and also disruption of sleep due to pain (Nikolaus *et al*., 2013; Walsh *et al*., 2014; Zielinski *et al*., 2019). Also, persistent pain alters sleep through changes in mood affecting sleep patterns (Pollard *et al*., 2006; Andersson *et al*., 2013; Katz, 2017; Szady *et al*., 2017; Silva *et al*., 2019; Zielinski *et al*., 2019). Decreased physical activity and stress caused by chronic life-changing RA can also negatively affect energy (Demmelmaier *et al*., 2018).

Several studies have shown that RA patients with elevated immunoglobulin IgA RF and anti-CarP levels have a significantly more aggressive clinical course of RA with erosive lesions and radiographic progression (Jonsson *et al*., 1998; Shi *et al*., 2013; Shi *et al*., 2014; van Delft *et al*., 2017; Truchetet *et al*., 2017) and extra-articular manifestations (Jonsson *et al*., 1998). Although the fatigue in RA patients is being studied, there are quite a few studies about different RF subtypes and the role of anti-CarP in its development. The goal of our study was to evaluate the role of activity and aggressiveness indices of RA in the severity of fatigue development in patients who suffer from this disease.

Based on the results of the survey, the RA patients included in the study were divided into two groups — with and without fatigue. Changes in arthritis clinical parameters (pain severity, duration of morning stiffness), activity (CRP, ESR, DAS28(CRP)) and aggressiveness parameters' (RF, anti-

CCP, immunoglobulins IgA RF, IgM RF, IgG RF, and anti-CarP) levels were compared in both groups.

Comparing RA patients with and without fatigue, we found that in RA patients an increased RF level was significantly correlated with IgA RF, IgM RF, and IgG RF levels. Several studies have shown that RA patients with an increase in RA levels, especially in IgA RF, develop a more severe disease than patients without IgA RF (Jonsson *et al*., 1998). This suggests that the aggressive course of the disease with erosion and the development of extracellular damage may contribute to the development of fatigue in RA patients. Opposite results, using a multivariate approach, were found by Riemsma with colleagues (Riemsma *et al*., 1998), who showed that pain explained 37% of the variance in fatigue, while ESR, RF, and haemoglobin do not contribute to fatigue.

We find that an increase in anti-CCP in RA patients without fatigue resulted in an increase in IgA RF (r = 0.8) and IgM RF (r = 0.6) levels, while increase in anti-CCP in RA patients with fatigue resulted in an increase in IgA RF (r = 0.5) and anti-CarP (r = 0.5) levels. This suggests that high anti-CCP also tends to influence the development of fatigue, leading to a more aggressive course of the disease in RA patients with fatigue. Earlier, Cappelli *et al*. (2015) found that lower levels of anti-CCP contribute to the development of fatigue in RA patients.

Like other authors, we did not find a significant effect of inflammation on the development of fatigue in RA patients. Similarly, also Van Hoogmoed *et al.* (2010), and Repping-Wuts *et al.* (2007) reported that pain, disability, depression, and low self-efficacy were associated with greater fatigue, but inflammatory indices were not correlated with fatigue severity. The fatigue in RA patients may be only partially related to disease activity, which may have accounted for poor agreement with respect to a fatigue domain within a flare questionnaire in RA (Pope, 2020). We found no significant difference in pain intensity and morning stiffness duration between the two study groups. This may be due to the fact that patients were not observed in dynamics.

In RA patients with fatigue, IgM RF and IgG RF levels increased with an increase of IgA RF level increases, and IgG RF and anti-CarP levels increased with increase of IgM RF level, while a higher IgG RF level contributed to increase of anti-CarP level. No such patter was observed in RA patients without fatigue. As noted above, the various RF subtypes as well as anti-CarP, contribute to the development of aggressive erosive arthritis and extracellular damage. The finding leads to the idea that disease aggressiveness has a role in the development of fatigue in RA patients. The obtained data suggest that the aggressive course of RA, more than inflammation, may contribute to the development of fatigue in RA patients.

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## VAI SLIMĪBAS GAITA IETEKMĒ REIMATOĪDĀ ARTRĪTA PACIENTU NOGURUMA ATTĪSTĪBU?

Reimatoīdā artrīta (RA) pacientiem daudzas locītavas bieži ir pastāvīgi iekaisušas. Ilgstošs iekaisums organismā var izraisīt vispārēju fizisku nespēku, spēku izsīkumu un miegainību. Šo ārkārtēja nespēka sajūtu sauc par "nogurumu". Daļa pacientu uzskata, ka tas ir vissliktākais slimības simptoms. Tomēr noguruma klīniskā nozīme un patoģenēze nav pilnībā skaidra. Šī pētījuma mērķis bija noteikt noguruma attīstību atkarībā no RA aktivitātes un agresivitātes. Mērķa sasniegšanai pacienti tika aptaujāti un tika noteikti laboratoriski slimības aktivitātes un agresivitātes rādītāji: reimatoīdais faktors (RF), antivielas pret ciklisko citrulinēto peptīdu (anti-CCP), eritrocītu grimšanas ātrums (EGĀ), C reaktīvais olbaltums (CRO), imūnglobulīni IgA RF, IgM RF, IgG RF un anti-karbamilēto olbaltumvielu antivielas (anti-CarP). Pamatojoties uz aptaujas rezultātiem, RA pacienti tika sadalīti divās grupās — ar nogurumu un bez tā. RA pacientu ar nogurumu grupā statistiski biežāk IgA RF, IgM RF un IgG RF līmeņa paaugstināšanās tika novērota pacientiem ar paaugstinātu RF līmeni, augstāks IgM RF un IgG RF līmenis bija saistīts ar IgA RF līmeņa paaugstināšanos, savukārt palielināts IgG RF un anti-CarP līmenis — ar IgM RF līmeņa paaugstināšanos. Augstāks IgG RF līmenis arī veicināja anti-CarP līmeņa paaugstināšanos. Būtiskas klīnisko un laboratorisko iekaisuma marķieru līmeņa atšķirības starp RA pacientiem ar noguruma un bez tā netika novērotas. Iegūtie dati liecina, ka RA agresīvā gaita vairāk nekā iekaisums var veicināt RA pacientu noguruma attīstību.