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ORIGINAL ARTICLE

The Relationship Between Serum Angiogenic Factor Levels and Disease Activity in Rheumatoid Arthritis

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ABSTRACT

Objectives: This study aims to evaluate the relationship between serum angiogenic factor levels and disease activity in patients with rheumatoid arthritis (RA) using both clinical and dynamic wrist magnetic resonance imaging (MRI) data.

Patients and methods: Simultaneous serum angiogenesis markers [vascular endothelial growth factor (VEGF), angiopoietin-1 (ANG1), ANG2, and tyrosine-protein kinase receptor for angiopoietin (Tie-2)] were studied in 40 patients with RA (13 males, 27 females; mean age 51.1±10.8 years; range, 23 to 69 years) and 20 healthy controls (11 males, 9 females; mean age 47.3±12.8 years; range, 29 to 69 years) and dynamic contrast-enhanced wrist MRI was performed in 40 RA patients and seven controls. Rate of early in 55th second (REE) and Relative enhancement (REt) values were calculated from the signal time curve values obtained from the analysis of images. In clinical assessment, duration of morning stiffness, patient pain assessment [visual analog scale (VAS)], physician and patient global assessments (VAS) were recorded. The number of tender joints and swollen joints were determined. Disease activity score 28 and Ritchie scores were calculated. Health assessment questionnaire was used for functional evaluation. Anti-cyclic citrullinated peptide, rheumatoid factor, erythrocyte sedimentation rate and high sensitive C-reactive protein analyses were performed.

Results: Serum VEGF, REE and REt values were significantly higher in RA patients than healthy controls (p=0.002, p=0.00, p=0.00, respectively). There was no significant correlation between serum angiogenesis markers and clinical parameters or REE and REt (p>0.05). VEGF value correlated positively with disease duration (p=0.024).

Conclusion: Serum VEGF was higher in RA patients. While its level was associated with disease duration, no significant correlation was found with disease activity. As a diagnostic test, dynamic contrast-enhanced MRI was a valuable method for showing disease activity.

Keywords: Disease activity, dynamic contrast-enhanced magnetic resonance imaging, rheumatoid arthritis, vascular endothelial growth factor.

Rheumatoid arthritis (RA) affects mainly the synovial tissue, resulting in hypertrophic synovial membrane (pannus) invasion-associated joint and cartilage damage of the joint cartilage.[1-3] Neovascularization is necessary for the continuation of oxygen and nutrient support of the growing pannus, the transport of inflammatory cells in the inflamed synovium and the continuation of the chronic inflammatory condition.[1,3-7] Therefore, synovial angiogenesis plays a key role in the formation and continuation of rheumatoid pannus. Synovial angiogenesis is achieved by the balance between various cytokines, inhibitors and activator factors. Vascular endothelial growth factor (VEGF) has a central role in angiogenesis. VEGF and members of the angiopoietin family and tyrosine-

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protein kinase receptor for angiopoietin (Tie-2) are the main pro-angiogenic factors.[5]

The effects of VEGF include proliferation and migration of endothelial cells and increase in the vascular permeability. Angiopoietin-1 (ANG1) works synergistically with VEGF to support stabilization and maturation of newly formed vessels. It is believed that angiopoietin-2 (ANG2) is a natural antagonist of ANG1, which sensitizes endothelial cells against the effects of VEGF. In RA, ANG1 level is higher than ANG2 and Tie-2 pathway induced by ANG1 is dominant in neovascularization.[8] There are studies in the literature showing the elevation of VEGF, ANG1, ANG2 and Tie-2 in synovial tissue in RA patients.[2,8-10] However, the number of studies evaluating these parameters simultaneously with serum and clinical and radiological findings is very few.

Studies have been carried out to demonstrate that magnetic resonance imaging (MRI) is more sensitive than direct imaging and clinical examination in the early detection and subsequent follow-up of synovitis, bone marrow edema, and bone erosions in RA.[11,12] Dynamic contrast-enhanced MRI is an important method for demonstrating disease activity. This is based on the acquisition of images in sequence with rapid shots taken every few seconds during and after the infusion of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA). In contrast images, time-dependent changes in the signal intensity of the synovial membrane are recorded and then these images allow analysis of the time-line of the synovial spread. Contrast ratio is correlated with synovial volume, erosion, vascularity, capillary permeability and metabolic activity, and with bone marrow edema and erosion, indicating that rapid contrasting tissue is associated with erosive disease.[13-16] In this study, we aimed to evaluate the relationship between serum angiogenic factor levels and disease activity in patients with RA using both clinical and dynamic wrist MRI data.

PATIENTS AND METHODS

This study was conducted at Manisa Celal Bayar University Faculty of Medicine between January 2009 and June 2011. The minimum sample size required for the research was calculated using power analysis and the minimum sample size for each group was determined as 20, with a power of 70%, alpha=0.05 and effect size=0.80. The study group (group 1) included 40 patients (13 males, 27 females; mean age 51.1±10.8 years; range, 23 to 69 years), twice as much as the control group, diagnosed with RA according to the 1987 ACR diagnostic criteria, while the control group (group 2) included 20 healthy volunteers (11 males, 9 females; mean age 47.3±12.8 years; range, 29 to 69 years). Groups 1 and 2 were advised to avoid intensive activity for the wrists within 24 hours before the examination.[16] The volunteers in group 2 were recruited from healthy hospital workers similar to the patient group in terms of age and sex. Patients with known additional inflammatory disease or malignant disease story were excluded. The demographic and clinical evaluations of the patients were performed by the same physiatrist. Age, sex, duration of illness (months), duration of morning stiffness (minutes), and medications were questioned. The patients participating in the study were anti-tumor necrosis factor (anti-TNF) naive patients. The patients were divided into three categories according to the treatment they received: those who did not use drugs, those using one disease-modifying antirheumatic drug (DMARD), or those using two or more DMARDs. The study protocol was approved by the Manisa Celal Bayar University Faculty of Medicine Ethics Committee. A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Visual analog scale (VAS) was used in the evaluation as follows: pain assessment (0: no pain, 10: unbearable pain), assessment of the general condition of the patient (0: very good, 10: severely poor), and the physician's assessment of the patient (0: very good, 10: severely poor). Disease activity was assessed by disease activity score 28 (DAS28) and Ritchie score. The 28 joints used in DAS28 calculation were individually examined for swelling and sensitivity.[17] A DAS28 was calculated by entering the data into the software in a computer program, including the number of swollen joints, number of sensitive joints, sedimentation, and the patient's global assessment (VAS). DAS28 value higher than 5.1

was assessed as high disease activity, between 3.2-5.1 as moderate disease activity, between 2.6-3.2 as mild disease activity, and between 0-2.6 as remission. The joints assessed on the Ritchie score was rated between 0 and 3 on the sensitivity scale after finger pressure was applied on the joints.[18] The functional status of the patients was questioned by the health assessment questionnaire (HAQ) index including a total of 20 questions about dressing, self-care, getting up, eating, walking, hygiene, reaching, gripping and difficulty in normal daily activities in the last one week.[19]

The erythrocyte sedimentation rate (ESR) of both groups was assessed by Westergren method, high sensitive C-reactive protein (HsCRP) by nephelometric method, immunoglobulin M rheumatoid factor (RF) by nephelometric method and anti-cyclic citrullinated peptide (anti-CCP) by enzyme-linked immunosorbent assay (ELISA) method.

Blood samples were centrifuged for serum VEGF, ANG1, ANG2, and Tie-2 concentrations and serum samples were stored at -20 °C and assayed by R&D Systems ELISA kits (Minneapolis, MN, USA).

A dynamic contrast-enhanced MRI of hand-wrists was performed in 40 RA patients and seven healthy volunteers. Dynamic contrast-enhanced MRI was performed in more severely affected hand-wrists of patients with active RA and patients with symmetric hand-wrist involvement, while dominant hand-wrist imaging was performed in control patients.

Imaging of the subjects was performed by General Electric Signa HDx 1.5 Tesla brand MR device (Milwaukee, Wisconsin, USA) with superconductive equipment and a limb spiral. The imaging area was adjusted to cover from the carpal bones of the wrist to the proximal interphalangeal joints (PIF) joints. After wrist positioning, images were obtained in pre-contrast coronal T1A fast spin-echo sequences (TR: 360 ms, time to echo (TE): min full, Matrix: 352×256, number of acquisitions (NEx): 2, field of view (FOV): 16 cm, Thickness: 2.5/0.3 mm and short T1 inversion recovery time to repeat (Tr): 3,825 ms, TE: 35 ms, inversion time (TI): 145. Matrix: 288×192, NEx: 2, Thickness: 2.5/0.3 mm).

Three-dimensional dynamic time resolved imaging of contrast kinetics (TRICKS) sequence (Flip angle: 30, TE: min full, Matrix: 256×192 NEX: 1, FOV: 17, Thickness: 2.6 mm, 16 sections) was used for dynamic contrast-enhanced MRI after intravenous (IV) contrast (Gd-DTPA) infusion. In this sequence, sectional images were obtained by taking 16 coronal images at each phase and repeating each phase at intervals of about 9.7 seconds. The oil-printed TRICKS sequence used in dynamic images was repeated once before and 47 times after the contrast. In all cases, 0.1 mmol/kg Gd-DTPA (MultiHance) was administered at a rate of 2 mL/second

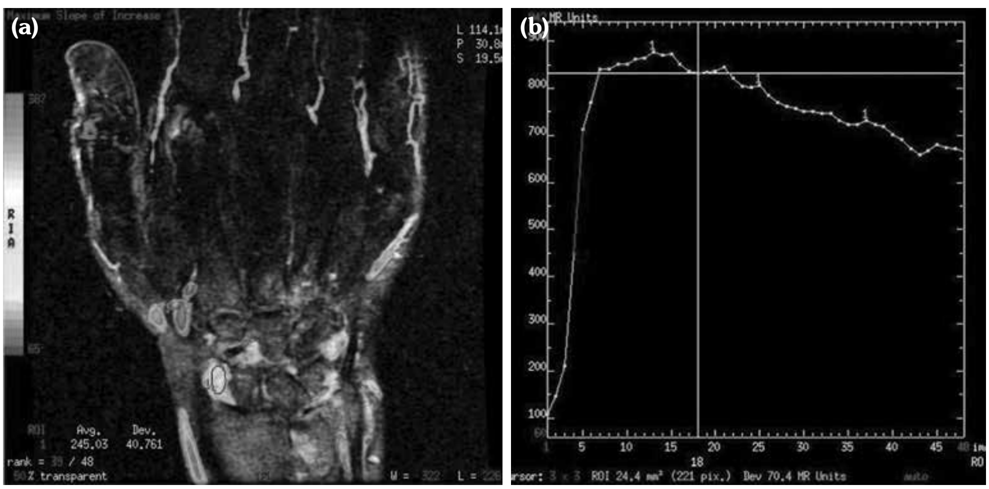

Figure 1. (a) Color map of wrist dynamic contrast-enhanced magnetic resonance imaging and **(b)** 48-phase signal time curve.

with 25 mL saline in an autologous injector as IV contrast medium. The examination took 15 minutes in total.

Dynamic contrast-enhanced MR base images were examined using the Advantage Workstation 4.4 software (Milwaukee, Wisconsin, USA). Dynamic contrast-enhanced MRI studies were evaluated by a single blinded radiologist. In each case, a maximum synovial involvement area on the wrist was selected for analysis (Figure 1). Signal time curves were obtained by placing a circular region of interest that would cover two-thirds of the selected region.

The phase to be measured for early contrast enhancement was selected as the phase after 55 seconds (S55). When the time signal curves are colored according to the maximum slope of increase, 55^{th} second was chosen as it was determined to be the time interval where contrasting increases the fastest in these phase of cases.

Early and relative contrast ratios were calculated from the obtained curve. Rate of early enhancement (REE) was calculated according to REE55= (S55-S0)/(S0×55)×100% for 55^{th} second. According to the same formula, the relative enhancement in t seconds (REt) was calculated according to the formula REt= (St-S0)/S0×100% for time t. In these formulas, S0 and St represent the signal intensity of the image before the contrast injection and after t seconds, respectively (the MR signal in phase reaching the signal time curve maximum).

Statistical analysis

The SPSS version 16.0 Windows software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis of the obtained data. Whether the variables show normal distribution or not was analyzed by the Shapiro-Wilk test. Since the variables did not show normal distribution, non-parametric tests, which were more suitable than statistical tests, were used. Mann-Whitney U test was used in comparison of patients with healthy volunteers as well as in binary group comparisons. Kruskal-Wallis H test was used to compare more than two groups. Spearman correlation analysis was used to determine the relationship between numerical variables. P value <0.05 was considered statistically significant for all tests.

RESULTS

No statistically significant difference was found regarding age, sex and body mass index between the two groups (p=0.096, p=0.246 and p=0.950, respectively). When laboratory data were compared, ESR, HsCRP values, RF and anti-CCP titrations were higher in group 1 than group 2 (p<0.001) (Table 1).

The average disease duration of group 1 was 28.8±24.7 months. The mean DAS28 score of group 1 was 5.0±1.3, the mean HAQ score was 0.7±0.5, and the mean Ritchie score was 11.5±5.9. Thirty-four patients (85%) were on medication, 22 were receiving monotherapy, and 12 were receiving combination therapy.

Table 1. Comparison of age, sex, body mass index, and laboratory findings between rheumatoid arthritis patients (group 1) and controls (group 2)

	Group 1 (n=40)			Group 2 (n=20)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			51.1±10.8			47.3±12.8	0.096
Sex							0.246
Female	27	67.5			9	45	
Male	13	32.5			11	55	
Body mass index (kg/m²)			26.4±3.8			26.2±3.0	0.950
Erythrocyte sedimentation rate (mm/h)			31.2±18.0			12.8±7.8	<0.001
High sensitive C-reactive protein (mg/L)			7.6±6.7			2.2±0.5	<0.001
Anti-cyclic citrullinated peptide (U/mL)			249.8±208.8			20.0±0.0	<0.001
Rheumatoid factor (IU/mL)			136.2±203.9			9.0±0.0	<0.001

SD: Standard deviation; Mann-Whitney U test was used.

Table 2. Comparison of dynamic contrast-enhanced magnetic resonance imaging findings and angiogenesis factors between rheumatoid arthritis patients (group 1) and controls (group 2)

	Group 1	Group 2	
	Mean±SD	Mean±SD	*p*
Rate of early enhancement	7.6±4.4	0.8±0.5	0.000
Relative enhancement in t seconds	687.3±275.1	170.6±97.3	0.000
Vascular endothelial growth factor (pg/mL)	523.7±319.1	286.7±222.2	0.002
Angiopoietin 1 (pg/mL)	61282.1±18984.7	58700.4±20636.2	0.466
Angiopoietin 2 (pg/mL)	4055.2±1301.9	3948.0±1488.6	0.644
Tyrosine-protein kinase receptor for angiopoietin (ng/mL)	31.3±9.6	33.0±17.0	0.826

SD: Standard deviation; Mann-Whitney U test was used.

Dynamic contrast-enhanced MRI REE and REt values and VEGF levels of group 1 were significantly higher than group 2 (Table 2). ANG1 and ANG2 were higher in patients with RA. However, this difference was not statistically significant (p>0.05).

Rate of early enhancement value was significantly correlated with all clinical parameters

Table 3. Correlation of patients with angiogenesis markers and magnetic resonance imaging and clinical findings

	Dynamic MRI REE	Dynamic MRI REt	VGEF	ANG 1	ANG 2	Tie-2
Duration of morning stiffness						
r	0.428	0.208	-0.041	-0.178	-0.218	0.013
p	0.006	0.98	0.800	0.271	0.176	0.936
Number of swollen joints						
r	0.591	0.364	0.045	0.021	0.030	0.117
p	0.000	0.021	0.781	0.896	0.855	0.474
Number of sensitive joints						
r	0.464	0.329	-0.021	-0.022	-0.020	0.055
p	0.003	0.038	0.895	0.891	0.904	0.736
Pain assessment of the patient						
r	0.422	0.297	0.084	-0.060	-0.083	0.119
p	0.007	0.063	0.607	0.711	0.609	0.463
General assessment of patient condition						
r	0.423	0.275	-0.043	-0.068	-0.050	-0.105
p	0.007	0.085	0.791	0.678	0.758	0.520
General assessment by the physician						
r	0.384	0.221	0.111	0.067	0.035	-0.011
p	0.015	0.171	0.497	0.683	0.832	0.945
DAS28 score						
r	0.514	0.315	0.084	-0.060	-0.083	0.119
p	0.001	0.047	0.607	0.711	0.609	0.463
Ritchie score						
r	0.575	0.449	-0.041	-0.178	-0.218	0.013
p	0.000	0.004	0.800	0.271	0.176	0.936
HAQ score						
r	0.439	0.455	0.045	0.021	0.030	0.117
p	0.005	0.003	0.781	0.896	0.855	0.474

MRI: Magnetic resonance imaging; REE: Rate of early enhancement, REt: Relative enhancement in t seconds; VEGF: Vascular endothelial growth factor; ANG: Angiopoietin; Tie-2: Tyrosine-protein kinase receptor for angiopoietin; DAS28: Disease activity score 28; HAQ: Health assessment questionnaire; R: Spearman correlation coefficient.

Table 4. Comparison of clinical and angiogenesis factors according to treatment type of rheumatoid arthritis patients (n=40)

	Without drug (n=6)		Monotherapy (n=22)		Combination therapy (n=12)		
	Mean±SD	Min-Max	Mean±SD	Min-Max	Mean±SD	Min-Max	*p*
Duration of morning stiffness	60.0±62.3	10-180	33.0±46.7	0-120	10.0±18.6	0-60	0.026
Number of swollen joints	8.7±5.1	1-15	2.9±3.2	0-10	3.9±3.7	0-10	0.038
Number of sensitive joints	14.5±7.9	1-21	10.8±8.3	1-27	13.1±8.9	0-26	0.529
General assessment of patient condition	5.8±1.2	4-7	3.6±1.8	1-7	4.3±2.1	1-7	0.041
General assessment by the physician	5.7±1.0	4-7	3.5±1.8	1-6	4.2±2.1	1-7	0.033
Pain assessment of the patient	5.7±1.2	4-7	3.7±1.9	1-7.5	4.5±1.9	1-7	0.072
DAS28 score	6.1±1.3	4.06-7.48	4.7±1.2	2.72-7.24	5.0±1.5	2.64-6.89	0.102
Ritchie score	17.0±7.1	5-26	10.2±5.2	3-23	10.9±5.5	2-17	0.067
HAQ score	0.9±0.5	0.25-1.62	0.6±0.57	0-2	0.6±0.4	0-1.37	0.429
VEGF (pg/mL)	387.3±319.7	162.52-926.21	586.9±354.5	120.39-1460	476.0±232.6	93.36-892.31	0.341
ANG1 (pg/mL)	55032.0±15531.2	40372.25-80179.12	66097.4±21212.0	24398.63-115656.58	55579.0±14354.4	36412.78-81210.54	0.119
ANG2 (pg/mL)	3696.3±1255.4	2453.56-5723.26	4384.5±1388.08	1584.82-7094.11	3630.9±1063.6	2169.10-5519.82	0.181
Tie-2 (ng/mL)	32.8±7.5	24.10-41.12	32.8±11.6	15.70-58.03	27.9±5.3	18-35.41G	0.427

SD: Standard deviation; Min: Minimum; Max: Maximum; DAS28: Disease activity score 28; HAQ: Health assessment questionnaire; VEGF: Vascular endothelial growth factor; ANG: Angiopoietin; Tie-2: Tyrosine-protein kinase receptor for angiopoietin; Kruskal-Wallis test was used.

(p<0.05) (Table 3). REt was found to be significantly related to the number of swollen and sensitive joints, DAS28, Ritchie and HAQ scores (p<0.05). No correlations were detected between the levels of angiogenesis markers of the patients and clinical parameters (DAS28, Ritchie scores etc.). In group 1, VEGF value correlated positively with disease duration (p=0.024, r=0.355).

In the laboratory findings, we only found a positive correlation between anti-CCP and ANG1 (r=0.341, p=0.031). There was no significant correlation between REE and REt and laboratory findings (p>0.05) or angiogenesis markers (p>0.05).

Patients were studied in two subgroups: early (<2 years, n=21) and late (>2 years, n=19) disease periods.[25] There was a statistically significant difference between early and late disease periods for VEGF (386.5±231.5 and 675.3±338.9, respectively; p=0.003). There was no statistically significant difference between early and late disease periods for REE and REt (p>0.05) Significant correlation was found between REE value and serum VEGF level in late term patients (r=0.460) (p=0.047).

Rate of early enhancement and REt values showed a statistically significant difference between non-drug patients, monotherapy patients and combined therapy patients (p=0.024, p=0.027, respectively). The non-drug patients had significantly higher REE and REt values than patients who received monotherapy (p=0.007, p=0.016, respectively) and combined therapy (p=0.025, p=0.031, respectively). Comparison of clinical and angiogenesis factors according to the treatment type is given in Table 4.

DISCUSSION

Angiogenesis is an important pathogenetic process for synovitis persistence and disease activity in proliferative and destructive inflammatory synovitis such as RA. Displaying angiogenesis by imaging or biochemical markers may provide more objective data than the standard methods we are using today to monitor disease activity and response to treatment. In this study, we evaluated the levels of serum angiogenesis markers (VEGF, ANG1, ANG2 and Tie-2), conventional indexes (clinical, laboratory), and dynamic contrast-enhanced MRI parameters in patients with RA and in the control group simultaneously. We concluded that in RA patients, levels of REE, REt and serum VEGF were significantly higher than the control group. However, there was no correlation with serum angiogenesis marker (VEGF, ANG1, ANG2, Tie-2) levels and DAS28.

In order to evaluate the patients homogeneously, we divided them into two subgroups as early and late disease periods according to the disease duration. We found higher values of VEGF in late term patients. We correlated the serum angiogenesis markers REE and REt values into two subgroups. There was no correlation between patients in the early period while significant correlation was found between VEGF and REE values in late term patients. This correlation and our higher detection of VEGF in the late disease period may be an indication that the formation of unstable and permeable vessels formed by the increased VEGF effect in the vascular bed and this causes more and faster spread of contrast.

The Ballara et al.[20] study, which divided RA patients into early and late period categories, has demonstrated that patients in the early period had higher levels of serum VEGF compared to patients in the late period. In the literature, studies involving measurements of serum VEGF levels before and after DMARD and infliximab therapy have shown a decrease in serum VEGF levels as a correlation with improvement in clinical and laboratory disease activity markers after treatment and it was thought that VEGF levels could be a follow-up parameter.[4,5,21-24] However, we found that serum VEGF levels in patients with early period RA were lower than patients with late period (>2 years) RA. Similarly, a study by Ozgonenel et al.[25] including 40 RA patients and 38 controls have found that VEGF levels were higher in late period patients. They have stated that this was caused by poor disease control of late period RA patients in spite of DMARD treatment. In our study, a similar situation existed. Despite the medical care provided, a majority of the patients had medium and high activity according to DAS28, which supports this sentiment.

There is a limited number of studies in which serum levels of VEGF, ANG1, ANG2 and Tie-2 angiogenesis markers have been evaluated together, and compared with disease activity and activity in the synovial tissue detected by MRI. Westra et al.[26] have found that serum VEGF and ANG2 were higher in 176 newly diagnosed RA patients than healthy controls; particularly, ANG2 levels were shown to be correlated with disease activity. Clavel et al.[27] have observed 310 early arthritis patients with a mean disease duration of 3.1 months for one year, correlating serum VEGF, ANG1 levels with inflammation parameters and bone destruction. In our study, only serum levels of VEGF were significantly higher than the control group. ANG1 and ANG2 were higher than controls, while not statistically significantly. Also, there was no significant differences in Tie-2 serum levels.

When we examined the relationship between angiogenesis biomarkers and laboratory parameters, we found a significant correlation between anti-CCP and ANG1. ANG1, which is expressed from the invasive surface of the pannus, was found responsible for the cartilage matrix destruction that increased in culture. In a study of cell signaling mechanisms of ANG1 to determine the direct effects of ANG1 on cartilage destruction and synovium overgrowth, in addition to cytokines such as interleukin-1 alpha and TNF-alpha, the ANG1/Tie-2 signal was reported to be a factor responsible for destruction of the cartilage matrix in rheumatoid joint independent of angiogenesis.[28] The predictive value of anti-CCP in RA radiological progression has been demonstrated by several studies and it has been reported that more severe radiological damage develops in anti-CCP positive patients.[29] This correlation, which we have observed, suggests that ANG1 may be important for predicting erosive alterations and progression, while further research is needed in this regard.

Ejbjerg et al.[30] noted that mild synovitis or small bone erosions may be seen on MRI in healthy controls, while signal curves for synovitis and bone erosion on dynamic MRI are uncommon or absent. Histological studies have also shown that dynamic contrast-enhanced MRI is an effective method of showing inflammation of the stiffness ratio and disease activity.[31-33] In a study of Ostergaard et al.[34] including 17 patients with RA and 25 patients with osteoarthritis, dynamic contrast-enhanced MRI of knee joint stiffness ratio and microscopically graded synovial inflammation were found to be correlated. We also found a positive correlation between the clinical activity parameters of the patients such as the number of swollen and sensitive joints, DAS28, Ritchie and HAQ scores; and dynamic contrast-enhanced MRI REE and REt values. A higher correlation of REE with clinical and disease activity in RA suggests that it is more specific than REt; however, further work is needed in this regard. Our results support that dynamic MRI is a reliable method of delivering objective data to reflect disease activity in RA. The fact that there is no difference between REE and REt values in early and late disease periods may be due to synovial inflammation being affected by changes in disease activity independently of disease duration. In our study, REE and REt values were significantly higher in patients who did not receive medical treatment compared with patients receiving monotherapy and combined treatment. Although it is an expensive method as revealed in many studies, the efficacy of treatment was demonstrated with dynamic contrast-enhanced MRI measurements.[35-37]

This study has some limitations. Patients' data were not compared before and after treatment and only cross-sectional data were assessed. For this reason, it was not possible to evaluate the efficacy of treatment with these parameters. Moreover, our sample size was small and the patients consisted of a heterogeneous group.

In conclusion, our data suggest that serum VEGF was associated with RA disease duration, but not correlated with disease activity. Furthermore, serum VEGF level was found to be significantly correlated with REE value which evaluated synovial activity in late term patients. If larger series confirm that serum VEGF and ANG1 concentrations are predictive of joint damage, this may support a more aggressive treatment regime when high serum levels are detected. Also, monitoring of serum angiogenic markers may help to determine the suppression of vascular pannus formation and cartilage defect in future studies.

Declaration of conflicting interests

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