Correlation between Vascular Endothelial cell Growth Factor (VEGF) and Muscular ultrasonography findings in Rheumatoid arthritis
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Abstract
Background: Vascular endothelial growth factor (VEGF) is expressed in the joints of RA patients, it is synthesized and released by different cell types, such as subsynovial macrophages, fibroblasts surrounding microvessels, vascular smooth muscle cells and synovial lining cells. Several investigations found correlations between serum VEGF levels and laboratory and clinical disease activity variables or the development
of radiographic damage, also musculoskeletal ultrasound (MSUS) is available, non-invasive, and relatively inexpensive bedside imaging method with high patient acceptability. This technique is more sensitive and reproducible than clinical evaluation in assessing joint inflammation, so we measured the serum vascular endothelial growth factor (VEGF) level in rheumatoid arthritis patients, assessment of musculoskeletal ultrasound
(MSUS) findings in rheumatoid arthritis patients and to correlate between serum level of vascular endothelial growth factor and musculoskeletal ultrasound findings in rheumatoid arthritis patients, in our study, 30 patients with Rheumatoid arthritis were enrolled in this study, they were collected from the Rheumatology, Rehabilitation and physical medicine outpatients' clinic and inpatients' department of Benha University Hospitals
and 20 apparently healthy volunteers with a comparable age and sex of patients were included in the study as a control group.

Conclusion: Vascular endothelial growth factor concentrations were elevated in the sera of patients with RA and correlated with individual and composite measures of the disease activity. Musculoskeletal Ultrasonography represents Sensitive, noninvasive method for visualizing
synovial vascularization in RA, such as power Doppler sonography, and so emerging as clinically important tool in the assessment of disease activity and hold promise as novel mean of evaluating the response of patients to therapy. As arresting structural damage to joints becomes a realistic goal in the management of RA, vascular imaging and serologic markers may be more sensitive than disease activity scores in determining at an
early stage of treatment which patients are responding satisfactorily.

Keywords: Vascular Endothelial Growth factor, Muscular ultrasonography, Rheumatoid arthritis.

1. Introduction

One of the most common chronic inflammatory autoimmune diseases is rheumatoid arthritis. It primarily affects the joints, it manifests as synovitis of
multiple joints and may eventually progress to joint destruction. Abnormal synovial proliferation due to cellular recruitment, angiogenesis, and most importantly pannus formation is the pathologic hallmarks of RA. Upregulation of multiple proinflammatory and angiogenic mediators in hypoxic RA synovium initiates and promotes
synovial inflammatory process in RA (1). However it should be thought of as a syndrome with extra-articular symptoms including rheumatoid nodules, lung involvement or vasculitis, and systemic comorbidities (2).

A combination of angiogenic promoters, and down-regulation of inhibitors drives up-regulation of a process that called angiogenesis which
including formation of new microvessels from the preexisting vasculature consists of multiple processes such as degradation of vascular basement membranes and surrounding extracellular matrix as well as migration and proliferation of endothelial cells (3). Vascular endothelial growth factor (VEGF) is one of the most potent agents that
favoring Vascular synovial endothelial angiogenesis growth and factor may progression also play a of joint critical role inflammation in the in RA. An chronic elevated edema and level of swelling VEGF is typical of found in both rheumatoid serum and arthritis as synovial well as in fluid of RA producing patient (4). the
chondrolytic and osteolytic fragments that can be found in rheumatoid arthritis joint effusions, VEGF stimulates pannus formation, and as the pannus grows more VEGF is produced, forming a vicious circle. In patients with RA, moreover, VEGF and its receptor have been shown expressed in the synovial tissue of
inflamed joints (5).

It is considered that high levels of VEGF may be associated with accelerated atherosclerosis and increased risk of cardiovascular disease (CVD) in patients with rheumatoid arthritis (6). Musculoskeletal ultrasound (MSUS) is included in the European League Against Cardiovascular Disease (ELCVD).
Rheumatism (EULAR) recommendations as a valuable imaging tool in patients with rheumatoid arthritis (RA). It can be used in establishing diagnosis of RA, as a predictor of progression from undifferentiated arthritis to clinical RA, for detection of structural damage, as a predictor for disease outcome, for monitoring the effect of treatment and for
assessment of remission (7).

Musculoskeletal ultrasound allows visualization of inflammation of the synovial membrane and erosions at the very early stage of the disease as ultrasonography can directly demonstrate joint inflammation, including synovial hypertrophy, using grayscale (GS), and increased...
blood flow and vascularization demonstrate using power Doppler techniques (PD) (8).

2. Aim of the work

Therefore the aim of our study was measurement of Serum level of vascular endothelial growth factor (VEGF) in Rheumatoid arthritis patients, assessment of Musculoskeletal Ultrasound (MUS).
findings in Rheumatoid arthritis and Correlation between Serum level of VEGF and Musculoskeletal U/S Findings.

3. Patients and Methods

2.1 Patients Selection:

Thirteen RA patients, Diagnosed as RA as per ACR/EULA classification criteria for RA 2010, collected from the rheumatology, rehabilitation and physical
medicine outpatients’ clinic and inpatients’ department of Benha University Hospitals at the period between August 2019 and August 2020 were enrolled in this study, along with 20 healthy ages and sex matched volunteered controls. The study was approved by the Ethics Board of Benha University and an informed written consent was taken from...
each participant in the study.

2.2 Inclusion criteria

All patients are males at or above the age of 18 years old. All patients have unilateral inguinal hernia either primary or recurrent.

2.3 Exclusion criteria

Patients will be excluded from the study if they have: Infectious disorders like; septic arthritis, viral arthritis, or fungal arthritis. Also,
patients with inflammatory arthritis like; SLE, and inflammatory bowel disease with arthritis will be excluded, patients with malignancy, gouty arthritis, endocrinal diseases like; hyperthyroidism or hypothyroidism or patients with metabolic disorders were excluded from this study.

2.4 History

Clinical history taking included; personal history
including analysis of the age, occupation, and special habits of medical importance particularly smoking; complaint and its duration; history of present illness including
drug allergy, previous diseases in the family.
history of Raynaud's phenomenon, 2.5Examination
and previous Clinical examination
admission to included general examination
hospitals and
family examination
history of including vital data;
similar eyes
condition or examination
or metabolic conjunctivitis
rheumatological for evidence
endocri

iritis, scleritis, episcleritis or dryness; skin examination for subcutaneous nodules, skin rash, vasculitic skin lesions; locomotor examination Joints of the body are examined thoroughly as follows: inspection of the overlying skin for any deformities, swellings and muscle wasting, palpation for hotness and tenderness, both active and passive movement were tested,
assessment of motion of each joint, stability of movement and for the presence of complications whenever required for patients including complete blood picture, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, serum anti cyclic citrullinated antibodies were requested for
Vascular endothelial cell growth factor (VEGF) concentration will be measured in serum using a commercially available ELISA kit (SunRed Biotechnology Company) according to the manufacturer’s protocol.

Préparation

II)
Five ml of venous blood were withdrawn from each patient and control subject under study, Serum was extracted as soon as possible after Specimen collection, blood coagulation occurred at room temperature 10-20 min, then centrifugation was done for 20-min at the speed of 2000-3000 r.p.m., the supernatant was removed.
Specimens were kept in -20 °C to preserve.

27) Principle of the procedure:
The kit uses a double-antibody sandwich enzyme linked immunosorbent assay (ELISA) to assay the level of human (VEGF) in serum samples. Serum samples were added to monoclonal antibody enzyme well which is pre-coated with the kit.
human (VEGF) monoclonal antibody, incubation; then, VEGF antibodies labelled with biotin were added, and combined with Streptavidin-HRP to form immune complex. Incubation was carried out and then washing again to remove the uncombined enzyme. Then Chromogen Solution A, B, were added. The colour of the
liquid changed into the blue, and at the effect of acid, the colour finally became yellow. The chroma of colour and concentration of the human (VEGF) of sample were correlated.

29) Clinical assessment of disease activity Rheumatoid arthritis disease activity was assessed using the modified disease score.
of joint count (DAS-28) DAS-28
The final score is calculated and graded as:
Remission = DAS-28 < 2.6
Low activity = DAS-28 scoring 2.6 – 3.2
Moderate activity = DAS-28 scoring 3.2 – 5.1
High activity = DAS-28 Scoring >5.1

Assessment of functional status using the health assessment questionnaire (HAQ).
31) Radiological assessment: evaluates the same 32 locations for
1) Plain X-rays for both the presence (1) or absence (0)
hands: of erosions. The Larsen postro-
view; the bone erosion score range is
of RA 0–160.
patients will be evaluated by Larsen score, the Larsen score
2) Musculoskeletal Ultrasonography (MSUS) and power
patients will be evaluated by Larsen score, the Larsen score
and power Doppler
examination (PD): Ultrasound was performed by a commercial available Logiq e real-time scanner (General Electric Medical Systems, Milwaukee, Wisconsin, USA) on the same day as clinical assessments using with a high frequency (8-13 MHz) linear transducer; the MSUS assessment included 12 synovial sites in 6 joints for
joint effusion, joint proliferation, bone erosion and power Doppler signal.

3. Patients permission and education (informed consent):

All patients had given permission to take part in the study. Patients were educated about the procedure to be performed.
**Table 1: Clinical characteristics of the RA patients group**

<table>
<thead>
<tr>
<th>Characteristics (no.=30)</th>
<th>Mean ±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (years)</td>
<td>5.84±4.24</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-15</td>
</tr>
<tr>
<td>MS (hours)</td>
<td>0.71±0.36</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-1.5</td>
</tr>
<tr>
<td>No. of tender joints</td>
<td>4.33±2.72</td>
<td>1-14</td>
</tr>
<tr>
<td>No. of swollen joints</td>
<td>2.7±1.93</td>
<td>0-10</td>
</tr>
<tr>
<td>VAS score</td>
<td>3.73±2.13</td>
<td>0-10</td>
</tr>
<tr>
<td>Extra-articular manifestations (%)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>DAS score</td>
<td>4.64±0.82</td>
<td>3.1-6.5</td>
</tr>
<tr>
<td>HAQ score</td>
<td>1.39±0.46</td>
<td>0.2-1.9</td>
</tr>
</tbody>
</table>

4.Discussion Rheumatoid arthritis (RA) is a chronic, autoimmune,
multisystemic, inflammatory, progressive condition of unclear etiology that causes joint pain, swelling, stiffness, and synovial joint destruction, resulting in serious impairment and premature mortality (9).

It is estimated that it affects between 0.5% and 1.0% of the world’s Adult population and affects women more than men. Up to 90% of patients with aggressive
synovitis have radiologic evidence of bone erosion within 2 years of diagnosis, despite treatment (10).

Angiogenesis is in the synovial membrane of RA patients is an early step in the disease's pathogenesis and persistence, vascular endothelial growth factor (VEGF) is the most endothelial-cell-specific factor that induces vascular permeability and progression.
of joint inflammation in rheumatoid arthritis, as it is proved that an elevated level of VEGF is found in both serum and synovial fluid of rheumatoid arthritis patient (4).

In RA synovium, VEGF expression is upregulated in macrophages and fibroblasts and it has demonstrated protein expression in synovial endothelial cells by immunohistochemistry. Furthermore, this induction
of VEGF is significantly inhibited by anti-integrin antibodies (11).

As regard clinical characteristics of rheumatoid arthritis group disease duration ranged from 4 months to 15 years with (Mean ± SD 5.84±4.24), morning stiffness duration ranged from 0.25 hours to 1.5 hours with (Mean ± SD 0.71±0.36), and extra-articular manifestations were positive in 36.67% of patients.
In our study, the number of tender joints ranged from 1 joint to 14 joints (Mean $\pm$ SD 4.33$\pm$2.72), and the number of swollen joints ranged from 0 joint to 10 joints (Mean $\pm$ SD 2.7$\pm$1.93).

In RA treatment, assessing health-related quality of life (HRQoL) and functional status has become an important complement to clinical, laboratory, and functional indicators in
evaluating patients and the Health Assessment Questionnaire (HAQ) is considered one of the tools that have been proposed to evaluate the HRQoL and disability in patients with RA (12). The HAQ-VAS Pain Scale obtained information on how RA patients felt pain, it horizontal VAS with endpoints labeled from zero (no pain) to one hundred (worst pain) (13). So in our study we
assessed Health Assessment Questionnaire for Rheumatoid Arthritis. The HAQ and Visual Analogue Scale (VAS), the HAQ was ranged from 0.22-1.96 (Mean ± SD 1.39±0.46), and the VAS was ranged from 0 to 10 (Mean ± SD 3.73±2.13). Our results showed that Disease activity score (DAS) ranged from 3.1-6.55 (Mean ± SD 4.64±0.82). This result was in agreement with Joharatnam.
et al., (14). All participants had DAS28 scores >3.1, consistent with active RA, and eight participants (16%) displayed high disease activity (DAS28 > 5.1).

Although laboratory tests for the RA-related autoantibodies rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) are abnormal (seropositive) in many patients with RA, values are normal (seronegative) in about one
third of patients with rheumatoid arthritis (15).

In our study, RF titer ranged from 8 to 128 with (Mean ± SD 35.04±32.08 IU/ml), also ACCP titer positivity Mean 13, also it was positive in 13 (43.33%) of patients, and negative in 17 (56.67%). The blood markers ESR and CRP have been widely used for RA assessment. However, they do not always precisely reflect the disease activity or
treatment response, but DAS28 has been widely used for RA assessment, it is also based on ESR or CRP measurement (16).

According to laboratory parameters in our study, the inflammatory markers represented in ESR and CRP have a highly significant difference (increase) in RA patients than healthy group as ESR in RA patients Mean ±SD was (89.53±36.32), with range (17-145) and P was
(<0.001 %), while CRP in RA patients Mean ±SD was (24.2±16.48) with range (8-96) and p was (<0.001).

Jiâ-Won et al. (17) admitted that the concentration of blood levels of ESR and CRP were significantly high as markers for systemic inflammatory responses in RA.

As regard other laboratory parameters in our study, platelets count showed non-
significant difference between patient and control groups $p (0.44\%)$, while hemoglobin concentration showed a significant difference in between them $p (0.04\%)$.

In our study, there was a broad range of serum VEGF levels in RA patients and control groups. In the RA group (285.84 to 1282.23 pg/ml) with Mean $\pm$SD (735.84$\pm$316.77 pg/ml), while in the healthy group
ranged from (87.46 to 310.22 pg/ml) with Mean ±SD (195.53±66.94 pg/ml), so there was a highly significant difference (increase) between patients and control group (p<0.001). Vascular endothelial growth factor is expressed in the joints of RA patients. It is synthesized and released by different cell types, such as subsynovial macrophages, fibroblasts surrounding vascular microvessels,
smooth muscle cells and synovial lining cells. Several investigations found correlations between serum VEGF levels and laboratory and clinical disease activity variables or the development of radiographic damage (11). Similar results were observed by the study of Strunk et al. (3). They found that highly statistically significant difference between the both study groups with a
broad range of serum VEGF levels in both groups from (211 to 1974 pg/ml) in the RA group with (mean = 795 pg/ml), and from (70 to 1090 pg/ml) in the healthy controls with (mean = 569 pg/ml), (p=0.04).

Also, the meta-analysis of Lee and Bea, (18) revealed that VEGF levels were significantly higher in the RA group than in the control group (SMD = 1.480, 95% CI=0.71–2.241, p<0.05).
A meta-analysis by Jiâ-Won et al., (17) revealed that VEGF levels were significantly higher in the RA group than in the control group (SMD = 1.480, 95% CI = 0.71–2.241, p = 1.4 × 10^{-4}).

In addition, Westra et al., (19) stated that patients with RA had higher levels of VEGF at disease onset compared with healthy controls. This result is contradictory to the results of some of the individual
studies like (e. g., Paradowska et al, (20) and to some published functional assays (e. g., Rueda et al, (21) they stated that no significant difference in VEGF levels was found between patients and control groups.

Contrary, Han et al., (22) demonstrated that the frequency of the 936 T allele, which has been associated with lower production of VEGF, was significantly increased in
RA patients compared with controls (22.7 vs 13.4%, P = 0.002).

Our results show correlation between serum level of VEGF and clinical characteristic of rheumatoid arthritis patients including disease duration with a significant positive correlation (Rho=0.39), morning stiffness with a significant positive correlation (Rho= 0.36), and in our study there was a highly...
significant positive correlation between serum VEGF and number of tender joints (Rho=0.84), (p<0.001), the number of swollen joints have a highly significant positive correlation with serum VEGF concentration and there was a highly significant positive correlation between VEGF concentration and DAS in RA patients (Rho=0.87), (p<0.001).

Furthermore, Taylor, (23)
established that serum VEGF concentrations correlate with individual and composite measures of RA disease activity, including acute phase markers and counts of swollen and tender joints. And serum VEGF concentrations were higher in patients with early RA than in patients with long-standing, treated RA. A meta-analysis of the correlation coefficients by Jiâ-Won et al., (17)
showed a significantly positive correlation between circulating VEGF levels and RA disease activity (correlation coefficient = 0.66, 95% CI = 0.281–0.446, p < 1.0 × 10⁻⁸). Also, Lee and Bea, (18) meta-analysis was in agreement with our results, as it showed a significantly positive correlation between circulating VEGF levels and RA disease activity (correlation coefficient = 0.66, 95% CI
correlation coefficient $= 0.497$, 95% CI $= 0.389$–$0.591$, $p < 1.0 \times 10^{-8}$, respectively. Ozgonenel et al., (24) assessed serum VEGF levels in RA patients and correlated VEGF production with disease activity. Serum VEGF was not only associated with high disease activity indicated by DAS28, but also with high-grade systemic inflammation observed in
active RA has indeed been associated with the perpetuation of synovial angiogenesis including VEGF mediated neovascularization (25).

According to our study there was highly significant positive correlation between serum VEGF and laboratory parameters represented as ESR, CRP and RF (p<0.001), (p<0.001) and (p<0.0001) respectively.

Our results were
supported by study of Orr et al., (26) as it reported that in RA patients, although a statistically significant positive correlation was observed between CRP and the level of inflammation in the biopsy retrieved (n = 197, \( \rho = 0.43, \text{ CI } 0.30–0.54, \ p < 0.0001 \)), there was a histological evidence of inflammation in the synovium in 49.4% of the patients who had a normal CRP. A positive correlation was also observed
between ESR and the level of inflammation in the biopsy retrieved (n = 188, rho = 0.29, CI 0.15–0.42, p < 0.0001).

In accordance with our results, study of Świdrowska et al., (27) found that serum VEGF levels correlated significantly with C-reactive protein and erythrocyte sedimentation ratio.

On the other side, Ozgonenel et al., (24) proved that Serum VEGF
levels could be correlated with systemic inflammation indicated by erythrocyte sedimentation rate (ESR) but not with rheumatoid factor.

In the study of Strunk et al., (3) they compared local intra-articular synovial hyperaemia of one symptomatic joint (wrist) with the immediate serum VEGF level of the same patient as a parameter of systemic disease or angiogenic activity.

Moreover,
blood centrifugation leads to efflux of VEGF from thrombocytes, which may have contributed to the wide range of VEGF concentrations measured. A significant reduction of serum VEGF levels could be determined with a delay of 1 week after the decrease of Doppler activity, but no correlation was found between both parameters (rho: $P = 0.7$; $r = -0.03$).

In our study, we
found a highly significant statically difference in VEGF concentration between RA patients and controls.

Musculoskeletal ultrasound (MSUS) is available, non-invasive, and relatively inexpensive bedside imaging method with high patient acceptability. This technique is more sensitive and reproducible than clinical evaluation in assessing joint inflammation (28).
The greater resolution of superficial musculoskeletal structures offered by high-frequency transducers has promoted an increasing use of MSUS in rheumatic diseases. Several studies have demonstrated that high-frequency MSUS is accurate for detecting joint effusion and synovitis. Compared with magnetic resonance imaging (MRI) and direct arthroscopic visualization, Power Doppler (PD)
detect flow from small vessels and low velocity flow at the microvascular level. PD detects indirect signs of increased vascularization associated with soft tissue musculoskeletal inflammatory and infectious diseases and enteritis in spondyloarthropathies (29).

When rheumatoid arthritis patients were examined by musculoskeletal ultrasound a high increase in the positive results of RA
Bone erosions were detected, this indicated that US has modest diagnostic efficacy when used as a screening imaging test for RA bone erosion (30).

In our study we used patient’s musculoskeletal ultrasonography MSUS score by 6 joint score ranged from 6 to 54 with (Mean ±SD 32.2±13.32), X-Ray score by Larsen score ranged from 7 to 152 with (Mean ±SD 65.27±43.57), and musculoskeletal
tal ultrasonography findings including Synovial hypertrophy which has the highest percentage among our study group 60%, bone erosions were 43.33%, Synovial effusion was 40%, and power Doppler signal was 33.335%.

Támas et al., (31) examined 100 patients with at least one clinically swollen joint, and found synovial hypertrophy in only 75% of patients. Nakagomi et al., (32) and Minowa
et al., (33) evaluated the use of MSUS according to the 2010 criteria for RA and found MSUS very useful, they showed that joints with a GS score 1 were defined as having “GS 1 ultrasound synovitis,” and joints with a GS score 2 or a PD score 1 were defined as having “GS 2/PD 1 ultrasound synovitis.”

Our results were supported by study of Ali et al., (36) it found that DAS is always positively
and highly significantly correlated to disease severity both by total US gray scale count and total US PD score count and highly significantly correlated to total US PD joint number at any time during follow up of their patients. They also found that number of tender and swollen joints is always
positively and significantly correlated to total US PD joint number and US gray scale number at start. Furthermore, Kurosaka et al. (34) showed an association between VEGF and PD sum scores in patients with RA. Our results showed that as regard correlations between serum Vascular Endothelial Growth Factor (VEGF) level and musculoskeletal
ultrasonography (MSUS) gray scale findings in rheumatoid arthritis patients, bone erosions had the most highly significant positive correlation with serum VEGF level (p=0.0008), then synovial effusion which had a significant positive correlation with serum VEGF level (p=0.001), and Synovial hypertrophy which showed the least one (p=0.01).

In the study of Yi et al., (35) synovial
thickening was detected with a positive rate of 38.8%, Joint effusion was with a positive rate of 27.2%, Doppler signal, showed a positive rate of 24.1%, there was statistical significance in the positive rate of synovial thickening, joint effusion and synovial angiogenesis between different genotypes of VEGF rs833070 and rs3025030 (P<0.05). In our study, there was highly significant
positive correlation between power Doppler grades and VEGF concentration (p<0.0001%), and there was a highly significant positive correlation between serum vascular endothelial growth factor (VEGF) level and radiological scores of the rheumatoid arthritis patients’ group as X-Ray grades (p<0.0001%), and musculoskeletal ultrasonography (MSUS) (p<0.001%).
Yasushi et al., (39) admitted that synovial vascularity was positively correlated with VEGF (p < 0.05) and remained even when treated patients with rheumatoid arthritis; but synovial echogenicity was also significant and inversely correlated with VEGF (p < 0.05).

Moreover, Jiâ-Won et al., (17) proved that serum VEGF concentration was higher in patients with moderate to severe synovial
hypertrophy on GSUS and in patients with increased vascularity on PDUS than in those without, these higher concentrations were significantly associated with the presence of active synovitis could represent synovial proliferation and hypervascula rity on US and reflect the systemic inflammatory status of RA assessed by TJC, SJC, ESR, CRP, and DAS28. Our results were
supported by study of Sallam et al., (40) as they reported that Radiological evaluation of rheumatoid patients in the study by Power Doppler ultrasonography (PDUS) revealed that there is a significant association between VEGF gene polymorphisms and high PDUS grading. Also, this was in harmony with Chinese study results that held by Yi et al., (35) that detected significant association between
VEGF gene polymorphisms and PDUS.

It was reported that serum VEGF concentrations at early presentation of RA had highly significantly positive correlation with development of radiographic damage over the subsequent year as assessed in radiographs of the hands and feet by the van der Heijde modification of Sharp's method. They have also observed that RA
patients with persistent disease activity despite conventional therapy had relatively high serum VEGF concentrations at first presentation. It might also be speculated that, in the future, serial serum measurements of angiogenic markers may help to determine whether vascular pannus, with its potential to cause cartilage and bone destruction, is adequately suppressed at any given stage of
5. Conclusion

Vascular endothelial growth factor concentrations were elevated in the sera of patients with RA and correlated with individual and composite measures of the disease activity. Musculoskeletal ultrasonography represents a sensitive, noninvasive method for visualizing synovial vascularization in RA, such as
Power Doppler sonography, and so emerging as clinically important tool in the assessment of disease activity and hold promise as novel mean of evaluating the response of patients to therapy. As arresting structural damage to joints becomes a realistic goal in the management of RA, vascular imaging and serologic markers may be more sensitive than disease activity scores in
determining at an early stage of treatment which patients are responding satisfactorily.

6. References


angiogenic factors in rheumatoid arthritis.


[9] Al-Jabi, S. W., Seleit, D.

[10] Aletaha, D., and Smolen, J. S. Diagnosis and


[12] Van Vollenhoven R. Rheumatoid arthritis:


[14] Joharatnam, Nalinie; McWilliam, Daniel


Angiogenic cytokines can reflect the synovitis severity.


Paradowska-Gorycka, A., Pawlik, A.

functional variants in rheumatoid arthritis.


[25] Szekanecz, Zoltán; and Koch, Alisa E. VEGF as


[27] Świdrows

[28] Elsaman, A. M., Mostafa, E. S., Radwan, A. R. Ankle evaluation in active rheumatoid arthritis by ultrasound: a cross-
sectional study.


[31] Ta˘mas¸ MM, Rednic N, Felea I, and Rednic

Criteria for Rheumatoid Arthritis to Predict the Requirement for Methotrexate Treatment.

Minowa, Kentaro; Ogasawara, Michihiro; Murayama, Go; et al. Predictive grade of ultrasound synovitis for diagnosing rheumatoid arthritis.


[33]
