

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. 30 patients with Rheumatoid arthritis were enrolled in our 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 could be used as a marker for rheumatoid arthritis.

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

1. Introduction

Rheumatoid arthritis (RA) is one of the most common chronic inflammatory autoimmune diseases. It primarily affects the joints, and 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).

Vascular endothelial growth factor (VEGF) is one of the most potent agents that favoring synovial angiogenesis and progression of joint inflammation in RA. An elevated level of VEGF is found in both serum and synovial fluid of RA patient (3).

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 endothelial cells (4).

Musculoskeletal ultrasound (MSUS) is included in the European League Against Rheumatism (EULAR) recommendations as a valuable imaging tool in patients with rheumatoid arthritis (RA). It can be used in establishing diagnosis of RA (5).

2. Aim of the work

There for the aim of our study was to measure serum level of vascular endothelial growth factor (VEGF) in Rheumatoid arthritis patients, and to correlate its level with grey scale ultrasound findings.

3. Patients and Methods

3.1 Patients Selection:

Thirteen RA patients, Diagnosed according to ACR/EULAR classification criteria for RA 2010, collected from the Rheumatology, Rehabilitation and

Physical medicine outpatients 'clinic and inpatients' department of Benha University Hospitals, along with twenty healthy ages and sex matched volunteer controls.

3.2. History

History taking included; personal history, analysis of the complaint, present history and review of other body systems specially musculoskeletal complaints, chest complaints, ocular complaints and GIT complaints; past history of medical diseases, drug allergy, previous history of Raynaud's phenomenon, and previous admission to hospitals and family history of similar condition or other rheumatologic, endocrinal or metabolic diseases in the family was also obtained.

3.3. Examination

Clinical examination included general examination including vital data; eyes examination for evidence of conjunctivitis, iritis, scleritis, episcleritis or dryness; skin examination for subcutaneous nodules, skin rash, vasculitic skin lesions; locomotor system examination as follows: inspection of the overlying skin, swellings and muscle wasting, palpation for hotness and tenderness, both active and passive movement were tested, assessment of motion of each joint for stability of movement and for the presence of associated complications.

3.4. Investigations

Serum Vascular endothelial cell growth factor (VEGF) concentrations were measured by ELISA.

3.5. Radiological assessment:

Grey scale ultrasound was done for joint assessment.

4. Statistical analysis

All statistical analyses were conducted using STATA/SE version 11.2 for Windows (STATA Corporation, College Station, Texas).

The Spearman correlation coefficient (rho) was used to test for the correlation between VEGF and grey scale ultrasound findings parameters.

Statistical significance was considered at $P < 0.05$.

5. Results

Serum Vascular endothelial cell growth factor (VEGF) concentrations were elevated among RA patients.

Table (1) Correlations between serum VEGF level and MSUS findings in RA patients.

MSUS (no.=30)	No.	VEGF conc.		X ²	P	
		Mean ±SD	Range			
Synovial effusion grades	1	10	491.36±189.00	285.84-793.65	13.60	0.001 (s)
	2	12	730.64±242.63	321.54-1124.26		
	3	8	1049.25±282.12	397.58-1282.23		
Synovial hypertrophy grades	0	1	352.77±0	352.77	10.58	0.01 (S)
	1	7	462.20±188.21	285.84-793.65		
	2	18	799.85±305.17	316.98-1282.23		
	3	4	1022.46±116.96	934.35-1191.62		
Bone erosion grades	0	7	461.97±188.36	285.84-793.65	16.73	0.0008 (HS)
	1	4	386.70±112.72	316.98-553.93		
	2	13	870.23±247.99	462.85-1282.23		
	3	6	996.95±230.02	576.21-1195.24		

6. 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 (6).

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 (7).

Angiogenesis in the synovial membrane of RA patients is a critical early step in the disease's pathogenesis and persistence, 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 (8).

The blood markers ESR and CRP have been widely used for RA assessment. However, they do not always precisely reflect the disease activity (9).

Vascular endothelial growth factor is expressed in the joints of RA patients. It is synthesized and released by different cell types. Several investigations found correlations between serum VEGF levels and laboratory and clinical disease activity variables or the development of radiographic damage (8).

Similar results were observed by the study of Strunk et al. (4). They found that highly statistically significant difference between the both study groups.

This result is inconsistent to the results of some of the individual studies like (e. g., Paradowska et al.) (11).

Furthermore, Taylor, (11) established that serum VEGF concentrations were higher in patients with early RA than in patients with long-standing, treated RA.

The level of inflammation in the biopsy retrieved (n = 197, rho = 0.43, 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 (12).

Musculoskeletal ultrasound (MSUS) is available, non-invasive, and relatively inexpensive bedside imaging method with high patient acceptability (13).

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 (14).

Taşmas et al., (15) found synovial hypertrophy in only 75% of patients.

Nakagomi et al., (16) and Minowa et al., (17) 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."

In our study, there was a highly significant positive correlation between serum vascular endothelial growth factor (VEGF) level and grey scale ultrasound findings.

Yasushi et al., (18) admitted that synovial vascularity was positively correlated with VEGF and remained even when treated patients with rheumatoid arthritis; but synovial echogenicity was also significant and inversely correlated with VEGF.

Moreover, Jiâ-Won et al., (19) proved that serum VEGF concentration was higher in patients with moderate to severe synovial hypertrophy on GSUS, concentrations were significantly associated with the presence of active synovitis could represent synovial proliferation.

7. Conclusion

Vascular endothelial growth factor concentrations were elevated in the sera of patients with RA and could be used as a marker for rheumatoid arthritis.

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