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Some Biochemical Changes in Serum and Synovial Fluid of Patients with Rheumatoid Arthritis

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Sixty cases were included in this study, divided into 2 groups; Group I (Control) (n = 20) and Group II (RA) (n = 40). Estimation of VEGF levels in serum (VEGFBL) and in synovial fluid aspirates of Knee joint in 11 RA patients (VEGFSF) using ELISA, in addition to different acute phase reactants and indices of disease activity. Plain x-ray of both hands to detect juxta-articular osteopenia and erosions. Serum VEGF showed a highly significant difference between Group I (Control) (165.4±46 pg mL^{-1}) and Group II (RA) (886.3±267.8 pg mL^{-1}) (p = 0.000). Serum CRP showed a highly significant difference between Group I (Control) and Group II (RA) (p = 0.000). Serum VEGF showed significant correlation with VEGF in Synovial Fluid (p = 0.012), Articular Index (AI) (p = 0.04), ESR (p = 0.01), Alkaline Phosphatase (ALKPASE) (p = 0.04) and CRP (p = 0.00, highly significant correlation). VEGF levels in synovial fluids (88.7±17.3 pg mL^{-1}) showed a significant correlation with VEGF in serum (VEGFBL) (p = 0.012) of the same RA patients, WBCs (p = 0.02) and CRP (p = 0.00, highly significant correlation). Serum VEGF is higher in RA patients than in controls. VEGF appears to play an active part in joint inflammation in early RA, however, in long-standing RA elevated VEGF serum levels may be an independent mark.

Key words: Rheumatoid arthritis, vascular endothelial growth factor (VEGF), angiogenesis

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease that results in progressive functional limitation, physical disability and premature death. RA extracts a considerable economic toll, particularly in terms of indirect costs related to lost productivity and premature mortality (Tugwell, 2000). It is characterized by peripheral joint inflammation, which results from the malign growth of synovial cells as a pannus overlaying and destroying cartilage and bone. One of the earliest observed features of RA is the development of a new vascular network within the synovium, which serves to promote the delivery of cells and nutrients to the invading pannus. The formation of new blood vessels involves a series of component steps, including activation of vascular Endothelial Cells (EC) by inflammatory mediators such as cytokines, degradation of the endothelial matrix by proteases, EC chemotaxis and development of new capillaries. However, an EC-selective mitogenic cytokine has been characterized, termed Vascular Endothelial Growth Factor (VEGF), which is emerging as a pivotal cytokine in the pathogenesis of RA (Paleolog, 1996).

Vascular Endothelial Growth Factor (VEGF), also known as vascular permeability factor, is a potent mitogen with a unique specificity for endothelial cells and a key mediator of aberrant endothelial cell proliferation and vascular permeability in a variety of human pathological situations, such as tumor angiogenesis, diabetic retinopathy, rheumatoid arthritis, or psoriasis (Siemeister *et al*., 1998). Maintenance of the invasive pannus in RA is an integral part of disease progression. The synovial vasculature plays an important role in the delivery of nutrients, oxygen and inflammatory cells to the synovium. VEGF is thought to contribute to the formation of synovial blood vessels which is integral to the development of arthritis in RA and blockade of VEGF activity might be of therapeutic benefit in RA (Miotla *et al*., 2000).

It is noteworthy that many of the antirheumatic drugs currently in clinical use or in trials apparently exert effects on the vasculature. Treatment of human RA with monoclonal antibody to TNF[alpha] significantly reduced serum VEGF in a time- and dose-dependent manner and correlated with alterations in disease parameters, such as C-reactive Protein (CRP) levels and swollen joint counts. The reduction in circulating VEGF levels may lead to decreased joint vascularity and swelling. It is possible that a combination of anti-TNF[alpha] antibody and anti-VEGF therapy may prove to be of greatest therapeutic benefit (Miotla *et al*., 2000).

Vascular Endothelial Growth Factor (VEGF) is an angiogenic mitogen that especially targets vascular endothelial cells and it also acts as an angiogenic mediator in RA (Kikuchi *et al*., 1998). VEGF is both an Endothelial Cell (EC)-selective mitogen and a modulator of changes in vascular permeability, both of which activities are of potential relevance in the pathogenesis of RA, although it is only recently that expression of VEGF in RA has been reported. It was also detected in synovial fluids from patients with active RA. Therefore, it is a potentially key mediator of the changes in the microvasculature which are observed as part of the early pathogenesis of RA. The selective effects of VEGF on EC proliferation and migration implicate this cytokine as a central mediator of neovascularization in RA. Understanding the mechanisms involved in neovascularization will allow the development of novel strategies for RA therapy, aimed especially at the treatment of early stages of the disease, prior to irreversible joint damage (Paleolog, 1996).

The aim of the present research is to estimate the serum levels of VEGF in RA patients and to correlate it with the clinical and laboratory features of disease activity in a trial to elucidate a relation between them.

MATERIALS AND METHODS

Subjects: This study was carried out on (40) cases, with age ranged between 21-57 years old who provisionally diagnosed as Rheumatoid arthritis, fulfilling the American College of Rheumatology (ACR) criteria (Arnett *et al*., 1988), from those attending the outpatient clinic of Rheumatology and rehabilitation Faculty of Medicine-Cairo University, over a period of 13 months (January 2003 to January 2004). Another group of 20 healthy normal persons of the same matched age and sexes with no history of Rheumatoid arthritis were collected as control group. Both cases and controls was conducted for complet history, full clinical and neurological examination, Ritchie Articular index score (Ritchie *et al*., 1968) and disease activity measurement by (Mallaya and Mace, 1981) were done.

Radiological assessment: Plain x-ray of both hands, postero-anterior view was done for detection of juxta-articular osteopenia and erosions.

Biochemical analysis: Fasting venous blood samples were taken for estimation of Complete Blood Count (CBC), Erythrocyte sedimentation rate (ESR), Liver function tests, Kidney function tests, Serum rheumatoid factor by the Latex method. Estimation of serum C-reactive Protein

(CRP) by using a commercial assay kit purchased from Randox Laboratories Limited, Ardmore, Diamond Road, Crumlin, Co. Antrim, United Kingdom. Estimation of VEGF levels in serum and in synovial fluid by using the Oncogene Research Products, Human VEGF Enzyme-linked Immunosorbent Assay (ELISA), Catalog number QIA51.

Statistical evaluation: The statistical analysis of the data was done according to the SPSS software, standard version, release 9.0.0.

RESULTS

Regarding the levels of CRP and VEGA among cases with Rheumatoid arthritis, (35.4±13.5 mg L^{-1} and 886.3±267.8 pg mL^{-1}), there was a highly significant difference as compared with their levels in control group (5 mg L^{-1}±2 and 165.4±46 pg mL^{-1}), respectively (Fig. 1). While VEGF level in synovial fluid was estimated in 11 patients who had knee effusion, was 88.7±17.3 pg mL^{-1}.

Regarding the Means of the Grades of Disease Activity (MGDA) according to Mallaya and Mace (1981) three patients had MGDA II (7.5%), 32 had MGDA III (79%) and 5 had MGDA VI (12.5%) (Fig. 2).

Clinically twenty one patients (21), showed joint deformity (52.5%), while 19 had no deformities (47.5%). Regarding radiological erosion in carpal bones, it was evidenced in 30 patients (75%), while it was absent in 10 (25%). Also, radiological Osteopenia was qualitatively diagnosed in 39 patients (97.5%) and absent in 1 patient only (2.5%) (Fig. 3).

Regarding the correlations between Levels of serum VEGF with other different variables among cases with Rheumatoid Arthritis, we found that serum VEGF showed significant correlation with VEGF in synovial fluid (Fig. 4), articular index (Fig. 5), ESR (Fig. 6) and highly significant correlation with CRP (Fig. 7).

On the other hand the correlations between Levels of VEGF in Synovial Fluid with other different variables among cases with Rheumatoid Arthritis, we found that VEGF of the synovial fluid showed highly significant correlation with CRP (Fig. 8) and significant correlation with WBC_s (Fig. 9).

Regarding the correlation between clinical findings and levels of serum and synovial fluids VEGF, can be summarized in the Table 1.

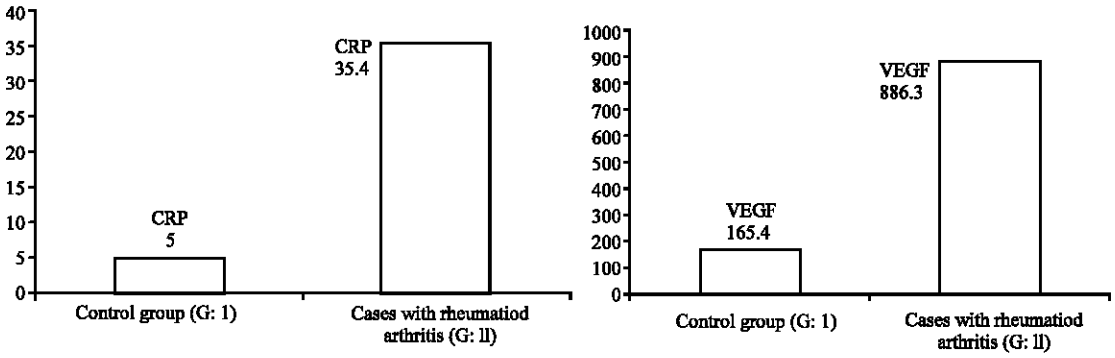

Fig. 1: Levels of CRP and VEGF among both groups

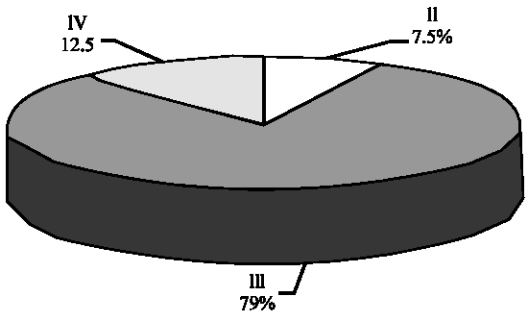

Fig. 2: The MGDA ratio among cases with RA

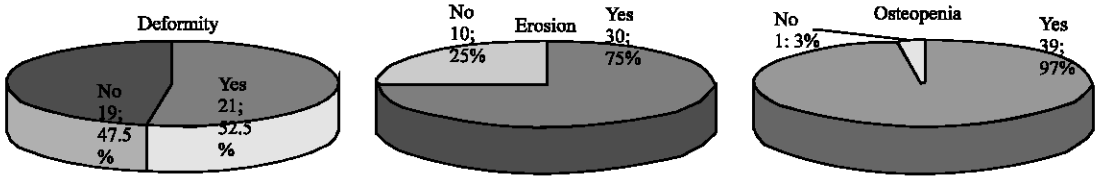

Fig. 3: The ratio of Deformity, Erosion and Osteopenia among cases with RA

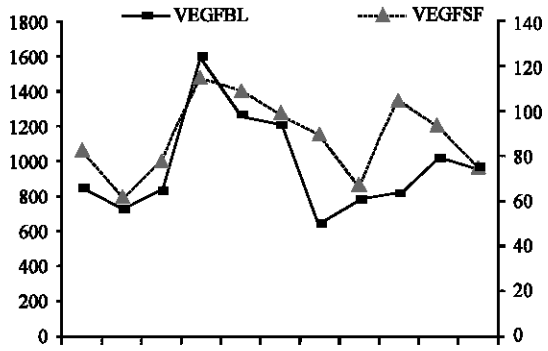

Fig. 4: The significant correlation between serum VEGF levels (VEGFBL) and synovial fluid VEGF levels (VEGFSF) among cases with knee effusion (p = 0.012)

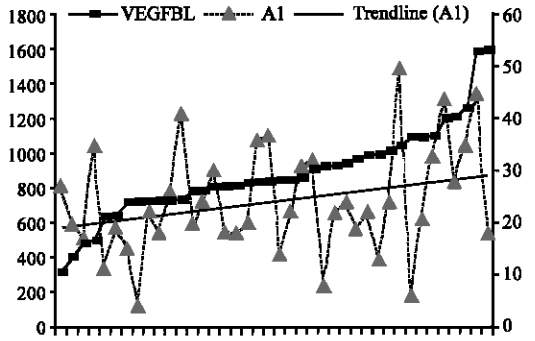

Fig. 5: The significant correlation between Serum VEGF levels (VEGFBL) and articular Index (AI) among cases with Knee Effusion (p = 0. 04)

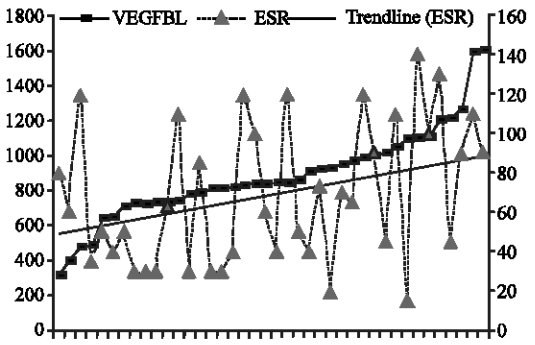

Fig. 6: The significant correlation between Serum VEGF levels (VEGFBL) and ESR among cases with RA (p = 0.01)

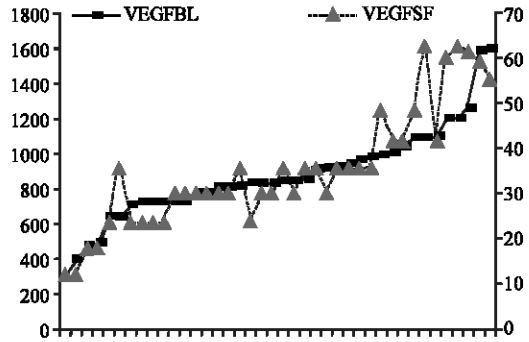

Fig. 7: The highly significant correlation between Serum VEGF levels (VEGFBL) and CRP levels among cases with RA (p = 0.001)

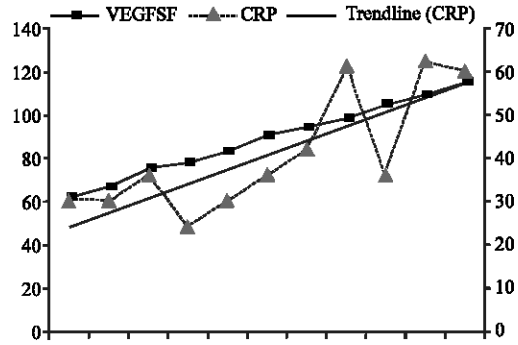

Fig. 8: The highly significant correlation between VEGF in Synovial Fluid (VEGFSF) and CRP among cases Knee Effusio (p = 0.001)

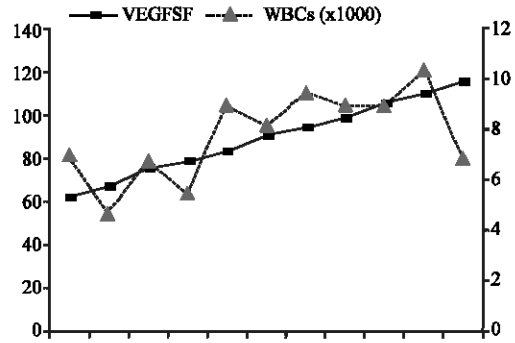

Fig. 9: The significant correlation between VEGF in Synovial Fluid (VEGFSF) and WBCs among cases with RA (p = 0.02)

Table 1: Descriptive Statistics of VEGF (Serum and Synovial Fluid) Levels according to Different Clinical variables among cases with RA

Parameters		Variable	N	Min	Max	Mean	SD
MGDA	II	VEGFBL	3	649	1100	826.33	240.43
		VEGFSF	1	90	90	90	.
	III	VEGFBL	32	402	1608	903.81	268.64
		VEGFSF	9	62	115	89.77	18.96
	IV	VEGFBL	5	315	1108	810.4	314.95
		VEGFSF	1	78	78	78	.
Deformity	Yes	VEGFBL	21	480	1598	927.38	269.65
		VEGFSF	7	62	115	90.85	18.79
	No	VEGFBL	19	315	1608	840.94	265.64
		VEGFSF	4	67	105	85	16.3
Erosion	Yes	VEGFBL	30	315	1608	901.26	286.94
		VEGFSF	10	62	115	90.9	16.61
	No	VEGFBL	10	402	1108	841.5	206.68
		VEGFSF	1	67	67	67	.
Osteopenia	Yes	VEGFBL	39	315	1608	892.53	268.46
		VEGFSF	11	62	115	88.72	17.33
	No	VEGFBL	1	644	644	644	.
RF	+ve	VEGFBL	38	315	1608	879.23	273.07
		VEGFSF	11	62	115	88.72	17.33
	-ve	VEGFBL	2	992	1050	1021	41.01

DISCUSSION

Joint destruction in RA is caused by hyper vascularized pannus which invades cartilage and bone. Angiogenesis is recognized as a key event in the formation and maintenance of the pannus, which is regulated by a delicate balance of angiogenesis inducers, including VEGF and different angiostatic agents. Pannus growth in RA is critically dependent upon accompanying neovascularization. VEGF is a potent angiogenic promoter, which is thought to play a crucial role in synovial angiogenesis in RA (Strunk *et al*., 2004a, b). Although many pro-angiogenic factors have been demonstrated to be expressed in RA synovium, the potent pro-angiogenic cytokine VEGF has been demonstrated to have a central involvement in the angiogenic process in RA. The additional activity of VEGF as a vascular permeability factor may also increase oedema and hence joint swelling in RA (Afuwape *et al*., 2003a).

VEGF is detectable in serum, synovial tissue and synovial fluids of patients with RA (Gudbjörnsson *et al*., 2004). A number of studies have reported that VEGF concentrations are higher in the serum of RA patients than in healthy controls or patients with osteoarthritis (Kikuchi *et al*., 1998; Ballara *et al*., 2001; Sone *et al*., 2001; Nakahara *et al*., 2003; Strunk *et al*., 2004b), which is agreed with our results.

The source of VEGF in the serum is unclear. *In vitro*, human peripheral blood mononuclear cells have been shown to release VEGF in response to cytokines expressed in RA synovium, such as TNF-α (Drouart *et al*., 2003). Release of VEGF from platelets has also been reported by Nagashima *et al*. (2000). Serum VEGF might therefore be derived from platelets, synovial-fluid neutrophils, inflamed synovial tissue or other sources (Taylor, 2002).

In this study serum VEGF (VEGFBL) showed a significant correlation with VEGF in Synovial Fluid (VEGFSF) in the RA group, which is agreed with study done by Lee *et al*. (2001) who stated that serum VEGF concentration was significantly higher in RA patients than in osteoarthritis patients or normals. Other different studies concluded that serum VEGF levels and VEGF expression were significantly elevated in RA patients relative to controls and correlated with disease activity (Paleolog and Fava, 1998; Taylor, 2002; Afuwape *et al*., 2003b).

In the present study serum VEGF levels (VEGFBL) showed a significant correlation with Articular Index (AI), Erythrocyte Sedimentation Rate (ESR), Alkaline Phosphatase and a highly significant correlation with C-reactive protein (CRP), which is agreed with study done by Sone *et al*. (2001), they found that mean serum VEGF concentration in RA Patients was significantly higher than controls and VEGF levels showed a significant correlation with articular index (AI) and Lansbury's activity index (LI) as well as with ESR and CRP only in stages I and II of disease progression. Serum VEGF levels may therefore be valuable as a marker of disease activity in patients with early RA. While on the other hand study done by Drouart *et al*. (2003), stated that in the RA patients, serum VEGF was not correlated with ESR, CRP or platelet count.

Ballara *et al*. (2001) reported that serum VEGF concentrations at presentation with early RA correlate highly significantly with development of radiographic damage over the subsequent year. Collectively, these findings implicate vascular pannus in the erosive phase of disease.

Although, in the present research, both serum and synovial fluid VEGF levels in RA patients with deformity were higher than in those without deformity (Table 1), yet this difference was not statistically significant. Similarly, both serum and synovial fluid VEGF levels in RA patients with subjective evidence of radiological erosion were higher than in those without also this difference was not statistically significant. As for juxta-articular osteopenia, serum VEGF levels in RA patients with osteopenia were higher than that in the only patient without.

Ballara *et al*. (2001) and Kikuchi *et al*. (1998) concluded that serum VEGF concentrations were significantly higher in patients with early RA than in patients with self-limiting arthritis. Improvement in the clinical symptoms of RA was associated with a reduction in serum VEGF levels. These findings implicate VEGF in

the persistence of inflammatory arthritis and support the hypothesis that expansion of the synovial vasculature is important for the development of joint destruction in RA. Also Lu *et al.* (2000), stated that VEGF levels correlated with the degree of neovascularization and arthritis severity. They suggested that VEGF plays a crucial role during an early stage of arthritis development, affecting both neovascularization and the progression of synovitis.

Pinheiro *et al.* (2001) measured serum VEGF levels in patients with long-standing RA. Serum levels of VEGF in RA patients were significantly higher than in healthy controls. VEGF levels showed no correlation with CRP, SAA amyloid protein, or the disease activity score. This may explain the absence of significant correlation between serum VEGF levels (VEGFBL) and mean grade of disease activity (MGDA). In our study, where mean serum VEGF level in RA patients with MGDA II was lower than in those with MGDA III and MGDA IV. Similarly, mean synovial fluid VEGF level in RA patients with MGDA II, III, IV were decreased in RA patients. These results also agree with the work of Kolopp-Sarda *et al.* (2001) they suggested that, contrary to the results reported in patients with early onset RA, where VEGF appears to play an active part in joint inflammation, in long-standing RA elevated VEGF serum levels may be an independent marker.

Andreakos *et al.* (2003) demonstrated that VEGF is involved in the inflammatory, angiogenic and destructive processes in the RA joint.

Many studies elicited the high levels of VEGF in synovial fluids of RA patients indicating that VEGF have an important role in the pathogenesis of RA. VEGF Levels were highest in RA SFs than in SFs from patients with other forms of arthritis (Fava *et al.*, 1994). Additionally, Synovial fluid VEGF was higher in RA) compared with OA or other arthritides (Koch *et al.*, 1994).

Walsh *et al.* (1998), showed that the balance between angiogenesis and vascular regression in rheumatoid synovitis may be determined by the focal expression of angiogenic and endothelial survival factors. VEGF is strongly expressed in the hypertrophic synovial lining of RA joints. The increased vascular permeability in RA may contribute to the development of tissue edema and joint stiffness (Paavonen *et al.*, 2002). VEGF-mRNA was expressed in all RA synovial tissues. VEGF protein was localized in many synovial lining cells, endothelial cells and stromal cells surrounding microvessels in RA synovial tissues (Wauke *et al.*, 2002). Yamashita *et al.* (2002), showed that VEGF was up-regulated in the synovial tissue of patients with RA. VEGF protein was strongly increased in rheumatoid synovium and localized at the synovial surface (Pufe *et al.*, 2001).

In RA, the capacity of synovial fibroblasts in the hypoxic environment to secrete large amounts of VEGF in response to cytokines probably contributes significantly to angiogenesis in the synovium (Berse *et al.*, 1999). Also, hypoxic conditions in RA synovium, which are likely to be transient and episodic, may contribute to the persistence of synovitis by inducing VEGF (Hitchon *et al.*, 2002).

In present study, we estimated VEGF levels in synovial fluids of 11 patients with RA and it showed a significant correlation with VEGF in serum (VEGFBL) of the same RA patients.

Enomoto *et al.* (2003), demonstrated that VEGF and its receptors are expressed in OA cartilage. Also, Pfander *et al.* (2001), showed that VEGF is expressed by articular chondrocytes in normal and OA human knee cartilage. Infrapatellar fat pads were found to contain various levels of bFGF, VEGF, TNF alpha and IL6. The expressions of both bFGF and VEGF were localized in immature adipocytes, interstitial undifferentiated mesenchymal cells and vascular endothelial cells. Although synovial cells and articular chondrocytes are thought to be primary sources of cytokines found in knee synovial fluids, the results suggest that they may also originate from this fat pad (Ushiyama *et al.*, 2003).

In previous studies it has been shown that patients with RA had higher synovial fluid VEGF concentrations than patients with OA. Gudbjörnsson *et al.* (2004), were interested to find out whether synovial fluid VEGF could be used as a marker for RA in discriminating between different forms of inflammatory arthritis. However, they found no significant difference in VEGF levels in synovial fluids from patients with different subsets of inflammatory arthritis. This might reflect the heterogeneity of inflammatory arthritis as in clinical practice, patients present with different disease activity, duration and treatment.

Additionally, the research of Giatromanolaki *et al.* (2003), revealed that VEGF was persistently increased in RA more than in OA, suggesting a relative failure of the HIF-alpha pathway to effectively produce a viable vasculature for OA, which is consistent with the degenerative nature of OA, in contrast to the proliferative nature of RA.

In this research, we have not estimated the level of VEGF in synovial fluid of controls due to the technical difficulties to aspirate synovial fluid from normal, non inflamed, joints. Additionally, we have not included patients with joint effusion caused by OA or other forms of arthritis due to the proved presence of VEGF and its role in their pathogenesis, accordingly, these patients cannot be considered controls.

In RA, VEGF is synthesized and released by a large number of subsynovial macrophages, neutrophils, mast cells, fibroblasts surrounding microvessels, vascular smooth muscle cells and synovial lining cells and may stimulate endothelial proliferation in a paracrine manner via VEGF receptors (Yamada *et al*., 1998; Kasama *et al*., 2000). Once expressed, VEGF plays a crucial role in the neovascularization of the pannus and the progressive joint destruction associated with RA. (Kasama *et al*., 2001).

Bottomley *et al.* (2000) investigated VEGF production from Peripheral Blood Mononuclear Cells (PBMC) of RA patients and healthy controls in response to stimulation by different cytokines and SF. RA patients had significantly higher spontaneous production of VEGF compared with controls and monocytes were identified as the predominant cellular source, emphasizing the importance of monocytes as a source of VEGF in the pathophysiology of RA. Several cytokines known to be present in SF can modulate the level of VEGF secretion, but the predominant effect of SF in VEGF up-regulation is shown to be dependent on TNF-alpha.

Furthermore, serum VEGF concentrations correlate with individual and composite measures of RA disease activity, including acute phase markers and counts of swollen and tender joints (Ballara *et al*., 2001; Sone *et al*., 2001; Lee *et al*., 2001). Latour *et al.* (2001), determined whether the VEGF level in rheumatoid synovial tissue is a marker for disease severity. VEGF labeling was seen on endothelial cells and macrophages in all synovial biopsies and was significantly correlated with score progression during the 10-year follow-up, but was not correlated with the joint count, radiological stage of the biopsied joint or progression of this stage, scores, presence of rheumatoid factor or presence of extra-articular manifestations. They suggested that the amount of VEGF in the rheumatoid synovium may be a marker for joint destruction in patients with RA.

Rheumatoid SF neutrophils were found to contain significantly larger amounts of both VEGF protein and its mRNA than peripheral blood neutrophils from either RA patients or healthy controls. Level of VEGF in RA SF was significantly higher than in OA. VEGF Levels also correlated with RA disease activity. Thus, SF VEGF may be considered an indicator of both local and systemic inflammation of RA, contributing to the neovascularization seen during RA synovitis (Kasama *et al*., 2000). In primary inflammatory arthropathy patients, SF VEGF level correlated significantly with SF total leucocyte and neutrophil count. (Bottomley *et al*., 2000).

In present study, the levels of VEGF in Synovial Fluid (VEGFSF) showed significant correlation with VEGF in Blood (VEGFBL) as mentioned above, also with white blood cells count in peripheral blood (WBCs) and a highly significant correlation with C-reactive protein (CRP)) as one of the acute phase markers going hand in hand with the results of (Ballara *et al*., 2001; Sone *et al*., 2001; Lee *et al*., 2001).

In a study of RA patients, serum VEGF concentrations were higher in patients with early RA than in patients with long-standing, treated RA. (Ballara *et al*., 2001). This was also elicited by the study of Kolopp-Sarda *et al*., 2001), who tried to appreciate the evolution of serum angiogenic and/or adhesion molecules levels during a long term follow-up of RA patients. Serum levels of VEGF in samples collected over 6 years in RA patients with monitored clinical parameters of disease activity and severity. The levels of VEGF were normal or lower than normal. No statistically significant time effect was noted. No effect either was noted as related to the therapeutic agents taken by the patients.

Similarly, in this research, no significant correlation was found between serum VEGF levels (VEGFBL) and disease duration and specific treatment intake.

VEGF is involved in the pathogenesis of RA and measurement of serum concentration of VEGF is a noninvasive, useful method for monitoring the disease activity of RA (Harada *et al*., 1998). Gudbjörnsson *et al.* (2004), had an opinion that an inflammation marker should be included in angiogenic peptide studies on patients with inflammatory disorders.

Vascular pannus in the erosive phase of disease strongly suggests that proangiogenic molecules such as VEGF are targets for novel therapies in RA. It seems likely that serological and imaging measures of vascularity in RA will become useful tools in the assessment of disease activity and response to therapy (Andreakos *et al*., 2003).

In a trial to detect angiogenesis in RA by highly advanced imaging techniques rather than estimation of serum VEGF levels (Strunk *et al*., 2004b), showed that qualitative Doppler sonographic estimation of the intensity of intra-articular synovial blood flow did not correlate with the actual serum VEGF level of the same patient.

Angiogenesis, the process that leads to the formation of new blood vessels or neovascularization, continues to be a topic of major scientific and public interest. As knowledge of the molecular mechanisms that regulate neovascularization continues to emerge, there is increasing hope that new discoveries will lead to newer therapies that target angiogenesis as a reliable option for

disease therapy. For example, it may be possible to develop strategies that, on the one hand, are designed to limit angiogenesis for the treatment of chronic diseases such as cancer or RA and, on the other, to promote angiogenesis in the ischemic heart or diabetic limb. With the emergence of tissue engineering as a discipline, it has become increasingly clear that long-term success in organ and tissue reconstruction will depend on the ability to develop a stable, renewable supply of blood vessels. Recent discoveries in the field of angiogenesis have influenced the development of novel therapies, forced a reconsideration of conventional therapies and revolutionized approaches to organ and tissue reconstruction (Polverini, 2002).

Inhibition of angiogenesis, as an adjunct to existing therapy of RA, or even as a stand-alone treatment, would not only prevent delivery of nutrients to the synovium, but could also lead to vessel regression and possibly reversal of disease. Thus, VEGF blockade may be an effective therapeutic adjunct for the treatment of RA. (Afuwape *et al*., 2003a).

Ballara *et al*. (2001), observed that RA patients with persistent disease activity despite conventional therapy have relatively high serum VEGF concentrations at first presentation. These observations suggest early introduction of a more aggressive therapeutic regime in patients with highly elevated serum VEGF concentrations early in their disease course. 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 disease evolution (Taylor, 2002).

Angiogenesis is at least partly responsible for the symptoms and signs observed in inflammatory arthritis. Angiostatic therapy of arthritis is tempting, but no major human clinical trials of angiostatic agents in rheumatology have yet been initiated, in contrast to several studies in oncology and ophthalmology. That's why (Gudbjörnsson *et al*., 2004) have the concept of angiogenesis as an important pathogenic mechanism in inflammatory arthritis and increase the surge for clinical trials of angiostatic agents in inflammatory arthritis.

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