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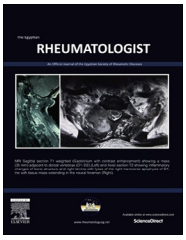

ORIGINAL ARTICLE

Correlation between synovial vascular endothelial growth factor, clinical, functional and radiological manifestations in knee osteoarthritis

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Abstract *Aim of the work:* To correlate between synovial vascular endothelial growth factor (VEGF), clinical, functional and radiological findings in knee osteoarthritis (KOA) patients.

Patients and methods: Twenty patients with primary KOA were clinically examined and the modified Ritchie articular index (RAI) recorded. The knees were examined and knee pain evaluated by the visual analog scale (VAS) and tenderness by the knee subscale of the RAI. The Western Ontario Mc Master scale (WOMAC) was recorded and the Kellgren–Lawrence grading used to assess radiographic severity. The synovial level of VEGF was assessed using ELISA.

Results: The mean age was 56.15 ± 7.77 years and body mass index 28.1 ± 4.04. All patients had knee effusion; 40% were bilateral and 60% unilateral. The mean duration of knee pain was 3.01 ± 1.43 years; duration of morning stiffness was 15.75 ± 3.72 min. The mean WOMAC was 44.22 ± 11.46 and modified RAI 5.45 ± 2.94. The mean knee subscale of RAI was 2.9 ± 1.16 and VAS for knee pain 5.7 ± 2.92. The mean synovial VEGF level was 693.71 ± 314.63 pg/ml. There was a significant increase in the synovial VEGF compared to the reference value ($p = 0.0001$). There was a significant correlation between the synovial VEGF and patients' age ($p = 0.04$), knee pain duration ($p = 0.025$), morning stiffness ($p < 0.0001$), modified RAI ($p = 0.0001$), knee subscale of RAI ($p < 0.0001$), VAS for knee pain ($p < 0.0001$) and WOMAC ($p = 0.0001$). There was a significant negative correlation between synovial VEGF and muscle

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strength grading ($p = 0.0001$) and a significant correlation with the radiological assessment ($p = 0.0001$).

Conclusion: Synovial VEGF significantly correlated with clinical manifestations, functional impact, as well as radiological changes of KOA.

1. Introduction

Osteoarthritis (OA) refers to failure of the joint accompanied by varying degree of joint pain, functional limitation and reduced quality of life [1]. Osteoarthritis is a disease with many associated comorbidities. In a study on Egyptian patients with primary OA, a higher risk of subclinical atherosclerosis was detected [2].

In a cohort of 180 Egyptian patients with knee osteoarthritis, joint pain and stiffness were the main symptoms and the visual analog scale (VAS) of knee pain ranged between 30 and 85%. They had functional impairment as assessed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). All the included patients were suffering from knee cartilage degradation on radiological assessment ranging between 2 and 3 as assessed by the Kellgren and Lawrence severity scale [3]. In another study on 20 patients with knee OA, 70% of patients had moderate OA (grade 2) and 30% had minimal OA (grade 1), according to the same scale [4].

Many factors have been implicated in the pathogenesis of OA. Osteopontin, a potential inflammatory cytokine, was estimated in Egyptian patients with knee OA and the synovial fluid level was found to be significantly higher than in the plasma level of the control and significantly correlated with the severity of knee pain [5,6]. Its synovial fluid levels also correlated with disease severity assessed according to the Kellgren–Lawrence grading [5]. Oxidative stress has also been implicated in the pathogenesis of OA [7]. The serum cartilage oligomeric matrix protein (COMP) level was also found to be an important marker of disease activity and cartilage destruction in knee OA patients [8]. The measurements of both hyaluronic acid and COMP were found to be of diagnostic and prognostic value in differentiating knee OA patients with early joint destruction. In combination with other biochemical markers as well as with the clinical and radiographic features, the clinical assessment of patients would remarkably improve [9].

Numerous studies have shown that inflammatory proangiogenic cytokines such as vascular endothelial growth factors (VEGFs) have been implicated in the pathogenesis of OA [10]. Inflammation can stimulate angiogenesis and angiogenesis can facilitate inflammation. Inflammatory cells such as macrophages that are present abundantly in chronically inflamed osteoarthritic synovium produce inflammatory mediators that induce angiogenesis in vivo. Inflammation results in hypoxia. Tissue hypoxia is a potent stimulator of angiogenesis. Angiogenesis through angiogenic factors such as VEGF facilitate plasma extravasation and inflammatory cell recruitment. Angiogenesis at osteochondral junction leads to endochondral ossification and the formation of osteophytes. Angiogenesis and joint damage further exacerbate inflammation. The newly formed vessel may become innervated and could be a source of pain. Through these mechanisms angiogenesis and inflammation can contribute to pain and joint damage in OA [11].

The aim of the present study was to assess the synovial fluid vascular endothelial growth factor (VEGF) levels in knee osteoarthritis (KOA) patients and correlate them with the clinical, functional and radiological findings.

2. Patients and methods

The following data were recorded for all included patients after they signed informed consent for inclusion into the study: Demographic data, weight and height to calculate body mass index (BMI) [12,13], history of knee(s) pain (Site of pain (right, left or bilateral), disease duration, relieving and aggravating factors, associated morning stiffness (in minutes), joint swelling, other joints involvement.). All patients had musculoskeletal examination including detailed knee joint examination [14], quadriceps muscle strength grading by Medical research council (MRC) [15], degree of tenderness assessed according to modified Ritchie articular index (RAI) and RAI sub-scale for both knees [16], visual analog scale (VAS) for knee pain was assessed [17] and the Western Ontario and Mc Master Universities (WOMAC) index score for detection of the functional capacity of lower limbs was calculated [18,19]. Radiological assessment with plain X-ray of both knees antero-posterior and lateral standing views were done and Kellgren and Lawrence grading criteria were used for assessment of radiographic severity of knee OA [20].

Synovial VEGF levels for patients were assessed using Enzyme-Linked ImmunoSorbent assay (ELISA). The reference value for synovial VEGF was taken after Fay et al. [21]. In their study collected synovial fluid from healthy joints of deceased donors ($n = 5$) was assayed by Enzyme-Linked ImmunoSorbent assay (ELISA) and the median VEGF level in healthy synovial fluid was 36 pg/ml [21]. The study was approved by the local university ethics committee and the study conforms to the provisions of the Declaration of Helsinki in 1995. All patients gave their informed consent prior to their inclusion in the study.

Statistical analysis: The data were analyzed statistically using the SPSS-17 (Statistical Package for Social Science version 17). Means and standard deviation were used to describe data distribution. Analysis of Variance (ANOVA or *F*-test) is used for comparison of more than 2 means. Least significant difference (LSD) is basically a *t*-test, used only when F value is significant to detect the presence of significance between each 2 groups. Spearman (nonparametric) rank correlation (rs) test was used to test correlation between 2 quantitative variables. The test was considered significant if the probability (*p*-value) was less than 0.05.

3. Results

Twenty patients suffering from primary knee OA were included in this study. They were eight males (40%) and twelve females (60%). The mean age of patients was 56.15 ± 7.77 years (ranged from 40 to 67). Five patients had normal weight (25%), eight were overweight (40%) and seven obese (35%); their mean BMI was 28.1 ± 4.04 (ranged from 20 to 31). Table 1 shows clinical, functional and laboratory disease characteristics of the patients. All patients had knee effusion, twelve had unilateral (60%) and eight had bilateral knee effusion (40%). Eight patients had unilateral flexion deformity (40%). Fifteen patients suffered from generalized OA (75%) where other joints were affected such as DIPs, lumbar and cervical vertebrae while only five patients suffered from just knee(s) OA (25%).

Table 2 shows comparison between patients and the reference value regarding the synovial VEGF levels. There was a statistically significant increase in the synovial VEGF in patients ($t = 14.16$, $p = 0.0001$). Table 3 shows the comparison between synovial VEGF levels among different muscle strength grading groups and radiological grading in the studied patients. A statistically significant increase of synovial VEGF level was present in those with a decreased quadriceps muscle strength grade compared to those with higher strength grades ($p < 0.01$). A statistically significant increase of synovial VEGF level was present with the increased radiological grading ($p < 0.01$).

There was a significant correlation between synovial VEGF and patient age ($r = 0.46$, $p = 0.04$). Whereas, there was no significant correlation between synovial VEGF and BMI ($r = 0.14$, $p = 0.56$). Table 4 shows a significant correlation

Table 1 Clinical and functional characteristics and synovial vascular endothelial growth factor (VEGF) among the studied patients with primary knee osteoarthritis.

Clinical characteristics	Minimum	Maximum	Mean ± SD
Duration of knee pain (years)	0.25	5	3.01 ± 1.43
Duration of MS (minutes)	10	20	15.75 ± 3.73
VAS for knee pain	2	10	5.70 ± 2.92
Knee tenderness[#]	1	5	2.90 ± 1.17
Modified RAI score	1	11	5.45 ± 2.95
WOMAC index score	24	62	44.22 ± 11.46
Synovial level of VEGF (pg/ml)	232	1151	693.71 ± 314.63

MS = morning stiffness, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, VAS = visual analog scale for pain, RAI = Ritchie articular index, VEGF = vascular endothelial growth factor.
[#] Knee tenderness assessed using knee sub-scale of modified RAI.

Table 2 Comparison between primary knee osteoarthritis patients synovial vascular endothelial growth factor (VEGF) and reference value.

	KOA patients ($n = 20$)	Reference value	t (p)
VEGF synovial (pg/ml)			
Range	232–1151	16–92	14.2 (0.0001)
Mean ± SD	693.7 ± 314.6	36.0 ± 19.14	

KOA: knee osteoarthritis, VEGF: vascular endothelial growth factor.

Table 3 Comparison of the synovial fluid vascular endothelial growth factor (VEGF) level among different muscle strength and radiological gradings in patients with primary knee osteoarthritis.

Parameter	Synovial VEGF in KOA patients ($n = 20$)		
	Mean ± SD	(Range)	F (p)
Muscle grading			
Grade 3	1008.1 ± 209.2	(542–1151)	12.42 (0.0001)
Grade 4	551.5 ± 223.6	(232–827)	
Grade 5	375.7 ± 39.7	(348–404)	
Radiological grading			
Grade 1	375.7 ± 39.7	(348–404)	12.7 (0.0001)
Grade 2	447.6 ± 208.6	(232–714)	
Grade 3	733.3 ± 101.6	(594–827)	
Grade 4	1008.1 ± 209.2	(542–1151)	

VEGF = vascular endothelial growth factor.

Table 4 Correlations between synovial vascular endothelial growth factor (VEGF) level and clinical and functional manifestations of the studied patients with primary knee osteoarthritis.

Clinical manifestations of the knee	Synovial VEGF *r* (*p*)
Duration of knee pain (years)	0.5 (0.025)
Morning stiffness duration (minutes)	0.82 (< 0.0001)
Tenderness by modified RAI	0.81 (0.0001)
Sub-scale of RAI for knee tenderness	0.73 (< 0.0001)
VAS for knee pain	0.84 (< 0.0001)
WOMAC index score	0.96 (0.0001)

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, VAS = visual analog scale for pain, RAI = Ritchie articular index, VEGF = vascular endothelial growth factor. $p < 0.05$ = significantly different.

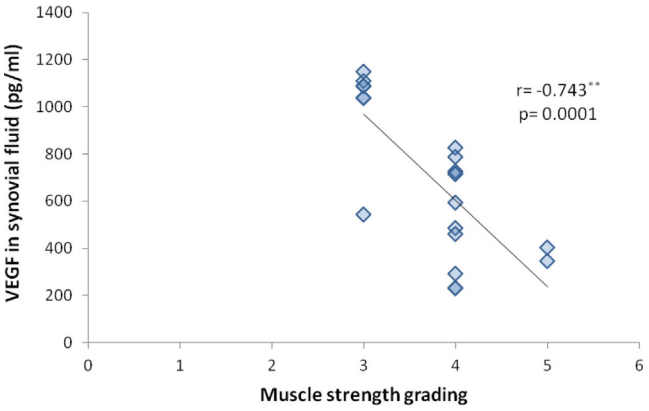

Figure 1 Correlation between synovial fluid vascular endothelial growth factor (VEGF) level and muscle strength grading in patients with primary knee osteoarthritis.

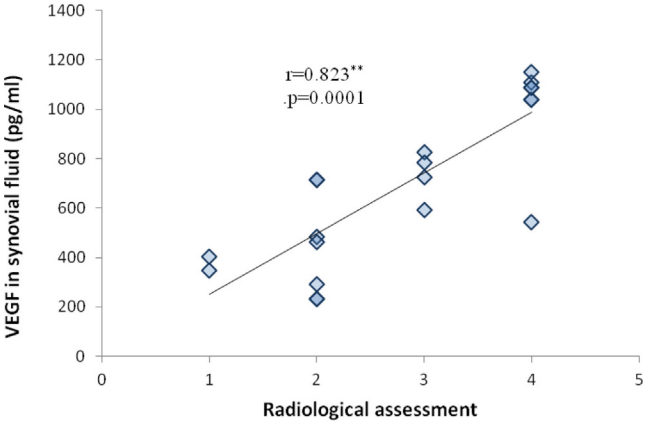

Figure 2 Correlation between synovial fluid VEGF level and radiological assessment in patients with primary knee osteoarthritis.

between the synovial VEGF level and the studied clinical and functional manifestations of the patients. There was a significant negative correlation between VEGF in synovial fluid and muscle strength grading ($p < 0.01$) (Fig. 1). There was a statistically significant positive correlation between synovial VEGF and radiological assessment ($p < 0.01$) (Fig. 2).

4. Discussion

The current study was carried out on 20 knee OA patients to highlight the role of VEGF in knee OA and its correlation with some variables which determine OA severity such as WOMAC index score for functional assessment, radiological assessment, degree of tenderness by RAI, VAS for pain assessment, duration of knee pain and morning stiffness.

In the current study, synovial fluid VEGF was significantly higher in OA patients compared to the reference value. This is according to Fay et al. [21] who found that the level of VEGF in synovial fluid from patients suffering from OA is 60-fold higher than healthy joints. They explained their results on the basis that inflammation in OA is known to be associated with activation of host angiogenesis where VEGF is one of the most potent proangiogenic stimuli of neovascularization [21,22].

In the current study, there was a significant correlation between synovial fluid level of VEGF and OA radiological grading. These results were in agreement with Rübenhagen et al. [23] and Klaus et al. [24]. Rübenhagen et al. [23] found that VEGF level in synovial fluid was correlated with radiological grading as assessed by Kellgren and Lawrence. In their study synovial fluid obtained from 82 patients, who had undergone total knee replacement surgery, was assayed by ELISA. Moreover, Klaus et al. [24] found a significant correlation between VEGF level in synovial fluid and radiographic damage of knee OA according to Ahlbaeck score. In contrast to this result with radiological grading, Anitua et al. [25] found no significant association between radiographic grading (Ahlbäck grading) and the levels of potential biomarkers in synovial fluid, including VEGF. This may be due to the different types of OA radiological scales and/or methods of statistical analysis used.

In the current study there was a significant correlation between synovial VEGF and VAS for pain assessment, the degree of tenderness as assessed by the modified Ritchie articular index and its subscale for knee tenderness. Pain and inflammation are often associated with increased tenderness. In this context VEGF acts as a pro-inflammatory cytokine by inducing adhesion molecules that bind leukocytes to endothelial cells, an initial and essential step toward inflammation [26]. Moreover, main events occurring in the cartilage during the pathogenesis of OA include an imbalance of metabolic and degradation signals, driven by cytokine cascades and the production of inflammatory mediators [27,28]. The close interdependence of angiogenesis and inflammation is often highlighted by angiogenic factors such as VEGF [29]. There are no previous studies which correlate between measured synovial fluid level of VEGF and degree of tenderness in patients with primary knee OA.

In the current study, there was an increase in synovial fluid VEGF level with decreasing quadriceps muscle strength grading. An important determinant of weakness in knee OA is arthrogenic muscle inhibition (AMI) – an ongoing neural inhibition that prevents the quadriceps muscles from being fully activated [30–32]. Being a direct cause of quadriceps weakness, AMI may contribute to muscle atrophy [32] and, in more

severe cases, can prevent effective quadriceps strengthening [33–35]. There is evidence suggesting that AMI is caused by a change in the discharge of sensory receptors from the damaged knee joint [32,35,36]. In turn, a change in afferent discharge may alter the excitability of multiple spinal reflex and supra spinal pathways that combine to limit activation of the quadriceps α-mono neuron pool [32]. An increase in knee joint mechanoreceptor and/or nociceptor discharge (as with acute swelling, pain or inflammation) leads to marked quadriceps AMI [37–39]. Therefore it can be assumed that increased synovial fluid level of VEGF (which was associated with increased joint pain and tenderness in the current study and hence inflammation) may indirectly (among other factors) account for decreased quadriceps muscle strength among the studied patients. There are no previous studies which correlate between measured synovial fluid level of VEGF and quadriceps muscle strength grading in patients with primary knee OA.

In the current study WOMAC score for functional assessment was increased with increasing synovial fluid level of VEGF. This implies that increased functional impairment can be aggravated by increasing OA severity as reflected by radiological grading, synovial inflammation and pain. There are no previous studies which correlate between measured synovial fluid level of VEGF and functional capacity in patients with primary knee OA as assessed by WOMAC index score.

In the present study there was a significant correlation between synovial fluid level of VEGF and patients' age. This was in agreement with Rübenhagen et al. [23].

In the current work, there was no significant correlation between synovial fluid level of VEGF and BMI. Obesity is an important aggravating factor for OA progression, but there are multiple factors other than obesity affecting the progression of OA such as aging, genetic factors, occupation, thigh muscle weakness and patients' life style [40]. In addition, the small sample size could also contribute to this result. There are no previous studies which correlate between measured synovial fluid level of VEGF and BMI of patients with primary KOA.

According to the present study results, it can be assumed that knee OA severity for studied patients was associated with synovial VEGF. This comes in accordance with Pfander et al. [41] who stated that the number of VEGF positive chondrocytes in cartilage samples correlates with OA severity, suggesting that ingrowing blood vessels may liberate pro-apoptotic signals in articular cartilage leading to apoptotic events in OA chondrocytes. In their study, OA severity was determined according to histochemical grading and 20 severe OA human cartilage samples were obtained from patients who had undergone total knee replacement, then specimens were prepared and scored according to Mankin histological scoring. The results of the present study were also in agreement with Tibesku et al. [42], who demonstrated that VEGF is synthesized by chondrocytes of the articular cartilage in knees of healthy rabbits after induction of OA because of anterior cruciate ligament (ACL) resection and significantly correlated with the degree of osteoarthritis.

In conclusion, synovial VEGF significantly correlated with clinical manifestations, functional impact, as well as radiological changes of knee osteoarthritis. A deeper understanding of the effects of biochemical parameters including VEGF on the initiation and progression of arthritic diseases will help us to find therapeutic targets to prevent and treat OA in the future.

Competing interest

None.

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