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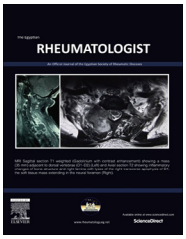

ORIGINAL ARTICLE

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.