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Plasma Vascular Endothelial Growth Factor (VEGF) profile and the association with synovial inflammation in knee osteoarthritis

Elysanti Dwi Martadiani,[1*] I Ketut Siki Kawiyana,[2] Sianny Herawati,[3] Anastasia Tjan[1]

ABSTRACT

Background: Osteoarthritis (OA) pathophysiology is affected by the inflammatory process of the synovium, which in turn plays a role in the prevention of disease progression. It is believed that vascular endothelial growth factor (VEGF), an essential growth factor for vascular endothelial cells, is engaged in synovial inflammatory process that occurs in knee OA, but the association between circulating VEGF levels with synovial inflammation in knee OA is not well known.

Objectives: This study aimed to identify plasma VEGF profile and its association with synovial inflammation in knee OA patients.

Methods: a consecutive cross-sectional study of primary knee OA patients with or without synovial inflammation was employed. All research materials from history taking, physical examination, to imaging analysis such as ultrasound as well as measurement of plasma VEGF levels using ELISA were done and analyzed using T-test, Spearman correlation test, Pearson correlation test, and multiple linear regression analysis.

Results: There was significant increase of circulating plasma VEGF level in knee OA patients with synovial inflammation ($p < 0.05$). Synovial inflammation was proven associated with high level of plasma VEGF level and influenced by overweight and degree of knee OA variable ($p < 0.05$), but did not associate with the existence of OA in other joints, consumption of OA therapy, hyperuricemia or diabetes mellitus ($p > 0.05$).

Conclusions: Plasma VEGF levels higher in knee OA with synovial inflammation than without synovial inflammation, and there was an association between high plasma VEGF levels with the occurrence of synovial inflammation in knee OA.

Keywords: *knee osteoarthritis, synovial inflammation, vascular endothelial growth factor*

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[1]Diagnostic Radiology Department, Udayana Faculty of Medicine/Sanglah Hospital-Denpasar
[2]Orthopaedic and Traumatology Department, Udayana Faculty of Medicine/Sanglah Hospital-Denpasar
[3]Clinical Pathology Department, Udayana Faculty of Medicine/Sanglah Hospital-Denpasar

[*]Corresponding to:
Elysanti Dwi Martadiani, Diagnostic Radiology Department, Udayana Faculty of Medicine/Sanglah Hospital-Denpasar
elysantidm@gmail.com

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INTRODUCTION

Knee osteoarthritis (OA) is the most common chronic arthritis, which caused pain and daily activities limitation, ergo decreasing quality of life. Various elements are involved in disease mechanism, which is why its pathogenesis is not fully understood, and need further research to uncover.

Pathological processes that occur in the knee (OA), besides involving joint cartilage and the entire joint component, includes inflammation of the synovial membrane. Recent developments of knee OA pathogenesis are mostly focused on synovial inflammation because it is strongly associated with joint pain as well as damage rate of joint cartilage.[1,2] Because synovial inflammation presents in the early stage of knee OA,[3] it could become the potential target management for knee OA.

Instead of synovial biopsy that is invasive for the patient, ultrasound can perceive synovial inflammation accurately. Ultrasound is a safe, sensitive and affordable modality of choice to evaluate synovial inflammation in knee OA. It has a good validity in detecting and characterizing synovial conditions such as thickening, joint effusion or both.[4,5]

Synovial thickening as inflammation indicator is thought to be associated with the increase of mitogenic activity in synovium, which supported by the escalation of angiogenesis process in synovium. Vascular endothelial growth factor (VEGF), also known as vascular permeability factor (VPF), is a strong angiogenesis factor,[6] which acts as a proinflammatory mediator in the pathogenesis of rheumatoid arthritis (RA) and protects rheumatoid synoviocyte from apoptosis, resulting in synovial hyperplasia.[7] The role of VEGF in synovial inflammation evoking synovial hypertrophy and joint effusion in ultrasound still cannot be explained. Hence this unclear correlation accounts for this study, which purposes to explore the plasma VEGF profile in patients with knee OA, as well as their association with synovial inflammation. Expectantly, the results could improve the understanding of synovial inflammation mechanism in knee OA and its therapeutic

of choice bypassing VEGF pathway of synovial inflammation.

MATERIALS AND METHODS

Research Subject and Design

A cross-sectional study of primary knee OA patients with or without synovial inflammation was employed. Inclusion criteria was men or women aged ≥50 years with primary right and left knee OA. Other joint diseases such as rheumatoid arthritis, septic arthritis, pseudogout, and acute gouty arthritis were excluded, knee OA that accompanied by a tumor or malignancy was also not included.

OA diagnosis is made based on the American College of Rheumatology (ACR) OA criteria. Kellgren and Lawrence (KL) classification was used to appoint degree of severity of knee OA, which mild was ascribed for KL 1-2, while KL 3-4 was severe. Hip, shoulder, ankle or other OA other than the knee, were diagnosed based on radiographic findings according to ACR criteria as well as diagnostic criteria used in previous studies.[8-11] Synovial inflammation was stated with presence or not. Inflammation of the synovium was established if it met both clinical and ultrasound criteria. Clinical criteria for synovial inflammation of the knee are joint pain, swelling and the presence of joint function disorder.[12,13] Ruling out synovitis from ultrasound scanning can be achieved by finding minimal one out of two criteria; (1) presence of diffuse or nodular type of synovial thickening, and or (2) the presence of joint effusion. Ultrasound examination was performed with Sonoace 8000® (Medison), linear transducer, 7,5-10 megahertz (MHz) frequency, B-mode program, by one radiologist on the suprapatellar recess, medial and lateral compartment of the knee. Synovial thickening assessed if the measurement equal or greater than 4 mm (≥ 4 mm) whereas effusion depth of 4 mm or more was indicated as joint effusion.[4]

Pseudogout imaging of the knee appears as joint inflammation with chondrocalcinosis. ACR/EULAR 2010 was used as the criteria for diagnosing rheumatoid arthritis, while ACR 1977 for diagnosing gouty arthritis. Elevation of uric acid serum greater than 7 mg/dl is identified as hyperuricemia. According to American Diabetic Association 2017, diabetes mellitus (DM) was described as the elevation of fasting blood glucose greater than 126 mg/dL. In this study, if the subject had a history of DM, he/she classified as positive DM.

The independent variable of this study was plasma VEGF levels. The dependent variable was synovial inflammation in knee OA. Confounding variables were overweight, the degree of knee OA, the existence of OA in other joints, accept OA therapy, hyperuricemia and DM.

Laboratory and Radiographic Evaluation

All laboratory results, primarily white blood cell count to rule out the presence of acute infection, erythrocyte sedimentation rate to exclude chronic infection, uric acid and fasting blood glucose levels to determine the presence of hyperuricemia or DM were collected. The peripheral blood sample was centrifuged and processed to separate the plasma and analyzed to obtain VEGF level using enzyme-linked immunosorbent assay (ELISA) method at Clinical Pathology Laboratory of Sanglah Hospital Denpasar, using human VEFG kit from Quantikine, R & D System, Inc (United States). The unit used is pg/mL, and high level of VEGF is defined when it exceeds the median value. All laboratory examination was completed under the supervision of a clinical pathologist.

Imaging analysis of the knee was performed on weight-bearing position, anterior-posterior and lateral view in extension knee. It was read by a radiologist and was classified based on Kellgren and Lawrence criteria. Imaging findings also determine knee OA severity and assess other joint involvement of OA instead of the knee, based on the patient history taking. Knee ultrasound was done to observe any synovial thickening, joint effusion or both.

Data Collection

Subjects of the study were derived from consecutive sampling of knee OA population at Sanglah Hospital. The degree of knee pain and oral medication history within three days prior, history of other diseases, the presence of pain in other joints outside the knee, and history of tumor or malignancy were recorded through history taking. Body mass index (BMI) and the presence of clinical synovial inflammatory symptoms in the knee joint which includes joint pain, joint swelling, joint effusion testing, and joint function disorder were collected. Assessment of joint function disorders was based on physical examination which was described by a limited range of active and passive knee joint motion and classified into four functional class (FC). Functional class (FC) I was described as normal joint function without or with symptom, FC II was defined as the presence of joint function disturbance but able to do normal activity without other person aid/device to

do the activity, FC III was ascribed as the presence of activity disorder and need special device to do the activity, and FC IV was characterized as over-all dependency. Functional class I represented subjects without joint function disorder and FC II-IV characterized subjects with joint function disorder.

Subsequently, after all examinations had been completed, in the form of history taking, physical examinations, laboratory and radiology evaluations, they were collected as research materials.

Statistical Analysis

Statistical analysis was conducted to know the influence of confounding variable on the dependent variable. Descriptive study was done to determine the characteristic of the variable. Numerical data presented as mean ± SD if the data were normally distributed and median (minimum-maximum) if the data were not normally distributed. T-test analysis was conducted to signify the difference between the degree of knee pain, mean synovial thickening, mean of joint effusion depth, and plasma VEGF levels between knee OA with or without synovial inflammation. Spearman correlation test was applied to assess the association of plasma VEGF level with the presence of synovial inflammation, followed by multiple linear regression test to control various confounding variables. Confidence interval used was 95% with a significant level of $p < 0.05$. All statistical analysis were completed using computerized statistical programme.

Ethical Issues

Ethical feasibility had been approved by research ethics committee of Udayana Faculty of Medicine-Sanglah Hospital Denpasar No. 38/UN.14.2/KEP/2018.

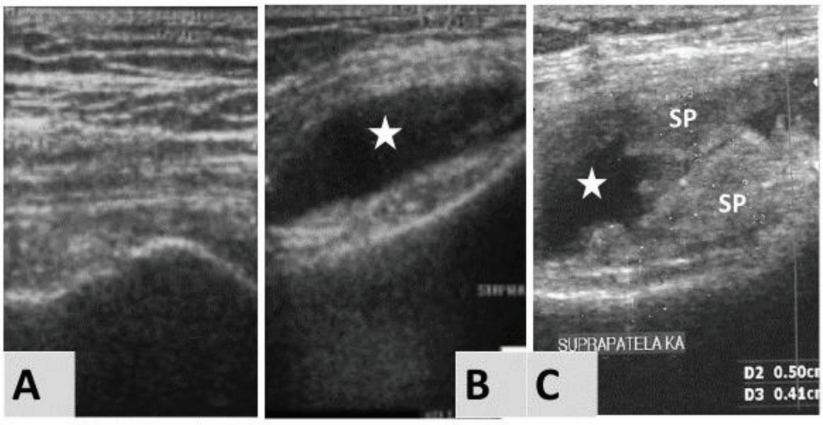

Figure 1 Knee ultrasonography result. A. Without synovial inflammation; B. Joint effusion (star) without synovial thickening; C. Joint effusion (star) with synovial thickening (SP)

RESULTS

There was a total of 70 subjects who met the inclusion and exclusion criteria in this study. Baseline characteristics of all subjects were listed in Table 1, included radiographic interpretation of the knee joint. None of the subjects had diagnosed as rheumatoid arthritis, septic arthritis nor malignancy. Characteristic of both criteria of synovial inflammation (ultrasound and clinical findings) of the knee OA were listed in Table 2. Ultrasound manifestation of synovial inflammation was shown in Figure 1.

Pain severity of the patients with synovial inflammation was significantly higher than in subjects without synovial inflammation ($p < 0.05$). The mean synovial thickness and joint effusion depth in knee OA patients with synovial inflammation were significantly greater ($p < 0.0001$ for both mean synovial thickness and joint effusion depth) compared to knee OA without synovial inflammation.

The mean VEGF plasma level was 180.05 ± 122.31 pg/ml, with a median value of 159.96 pg/ml. VEGF levels were categorized as high if they have values above the median value. High plasma VEGF levels were present in 35 (50%) subjects. The mean rate of VEGF in knee OA patients with synovial inflammation was significantly higher than in knee OA patients without synovial inflammation ($p = 0.014$), as seen in Table 3.

Spearman correlation test showed an association between independent variables (plasma VEGF levels) and dependent variables (synovial inflammation) of knee OA ($r = 0.289$; $p = 0.015$) (Table 4). The true association of high plasma VEGF levels and synovial inflammation still cannot be explained by Spearman's correlation analysis. It was assumed to be affected by other confounding variables which involved in synovial inflammation, such as OA oral medication, hyperuricemia, DM, overweight, and degree of knee OA and OA in other joints. Multiple linear regression analysis was performed to determine the relationship of these confounding variables with synovial inflammation occurrence. Multiple linear regression analysis proved that high level of plasma VEGF is associated with synovial inflammation despite all existed confounding variables, with significant influence of overweight and degree of knee OA (Table 5).

DISCUSSION

This study proved significant differences in plasma VEGF levels in knee OA patients with or without synovial inflammation, in which mean VEGF levels in knee OA patients with synovial inflammation was

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Table 1 Baseline characteristics of 70 subjects with knee OA

Parameters	Value
Age (years), mean ± SD	62.71 ± 7.48
Male, n (%)	22 (31 %)
Female, n (%)	48 (69 %)
History of knee OA medication, n (%)	7 (10%)
Relating diseases, n (%)	
DM	9 (13%)
Hyperuricemia	7 (10%)
Tumor/malignancy	0 (0%)
OA of other joints	14 (20%)
BMI (kg/m^2), mean ± SD	24.99 ± 3.66
Laboratory results, mean ± SD	
Uric acid (mg/dL)	5.56 ± 1.45
BSN (mg/dL)	97.75 ± 17.89
White blood cells (x10^9/L)	6.95 ± 1.64
Erithrocyte sedimentation rate (mm/hour)	2.29 ± 2.9
Radiographic results, n (%)	
Mild knee OA (KL 1-2)	47 (67%)
Severe knee OA (KL 3-4)	23 (33%)

OA: Osteoarthritis, DM: Diabetes mellitus, BMI: Body mass index, KL: Kellgren and Lawrence, SD: Standard deviation

Table 2 Clinical and ultrasound features of the synovial inflammation of the knee

Synovial inflammation features	Value
A. Clinical features of synovial inflammation	
Pain severity (VAS), mean ± SD	
Knee OA with synovial inflammation	
Right knee	6.69 ± 1.15
Left knee	6.58 ± 1.23
Knee OA without synovial inflammation	
Right knee	2.87 ± 1.03
Left knee	2.71 ± 0.79
Joint swelling, n (%)	54 (77%)
Positive effusion test, n (%)	41 (58.6%)
Disturbance of knee function, n (%)	51 (73%)
Normal knee function, n (%)	19 (27%)
Simultaneous sign of clinical synovial inflammation, n (%)	51 (73%)
B. Ultrasound characteristic of synovial inflammation	
Positive ultrasound findings, n (%)	59 (84%)
Negative ultrasound findings, n (%)	11 (16%)
Synovial thickness (mm), mean ± SD	
Knee OA without synovial inflammation	0.53 ± 0.68
Knee OA with synovial inflammation	2.28 ± 1.50
Effusion depth (mm), mean ± SD	
Knee OA without synovial inflammation	1.56 ± 1.40
Knee OA with synovial inflammation	4.10 ± 2.04

VAS: Visual analog scale, OA: Osteoarthritis, SD: Standard deviation

higher than patients without synovial inflammation ($p < 0.05$). Several studies have proven that VEGF levels in both plasma and synovial fluid in OA patients were significantly higher than controls.[14,15] The difference in their study with this study is that this study emphasizes plasma VEGF levels found in synovial inflammation in knee OA populations, not between knee OA patients with normal subjects.

The relationship of synovial inflammation and synovial thickening which could be detected in ultrasound is might be caused by angiogenesis of the synovium, which is could occur at various stage of OA.[3,16] Vascular endothelial growth factor is considered a potent proangiogenic factor that plays at the beginning of angiogenesis through induction of increase proliferation and migration of endothelial cells.[17] There is an increase in both VEGF and intercellular adhesion molecule-1 (ICAM-1) in inflamed synovium, indicating neovascularization in the synovium.[3,13] Synovial lining cells of OA patients may secrete VEGF which assumed its contribution to inflammation and angiogenesis presence in OA patients. Macrophage infiltration is associated with synovial angiogenesis, in which macrophages are the dominant cells in expressing VEGF in the synovium.[17] Pannus is an inflammatory vascular tissue, which is formed by neovascularization, infiltration of inflammatory cells in the synovium and synoviocyte hyperplasia. The formation of these new blood vessels contributes to infiltration of inflammatory cells as well as the growth and survival of synovial cells. Together with the progression of the disease, pannus in OA may resemble the pannus found in arthritis rheumatoid[18] and can be noticed by ultrasound.

Synovial inflammation will change synovial membrane permeability and lymphatic system in sub-synovium, resulting in an imbalance of osmotic pressure between plasma and joint space.[19] The increased vascular permeability of the synovial membrane is also affected by the increased production of VEGF, therefore vascular protein leakage and fluid transfer into joint space make an effusion on the joint. On the other hand, VEGF is also a macrophage's and mast cell's stimulator, in which mast cell's activation is associated with histamine release.[16] In inflamed OA, there are histamine release, prostaglandins, leukotriene and nitric oxide, and might contribute to joint effusion through increased vascular permeability.[20]

Significant correlation was found between high plasma VEGF level and synovial inflammation ($r = 0.289$; $p = 0.015$). This result was confirmed by multiple linear regression tests that proved even after involving other confounding variables, the high plasma VEGF concentrations remained significantly

Table 3 Plasma VEGF profile level on knee AO with and without synovial inflammation

	Knee OA with synovial inflammation	Knee OA without synovial inflammation	Mean difference	*p-value*
Plasma VEGF level (pg/ml), mean ± SD	129.24 ± 18.10	77.46 ± 17.77	80.178	0.014

VEGF: Vascular Endothelial Growth Factor, OA: Osteoarthritis

Table 4 Correlation of plasma VEGF level with synovial inflammation on knee OA

Variable	r	*p-value*
Plasma VEGF level	0.289	0.015*

**Spearman's rho, VEGF: Vascular Endothelial Growth Factor, OA: Osteoarthritis*

Table 5 Multiple linear regression analysis result of synovial inflammation with plasma VEGF level and other confounding variables

Variables	B	95% CI	*p*-value
High plasma VEGF levels	0.216	0.020-0.411	0.031*
Consumption of OA therapy drugs	0.014	-0.330-0.375	0.080
Overweight	0.308	0.100-0.515	0.004*
The presence of OA outside the knee joint	0.110	-0.128-0.348	0.924
Hyperuricemia	0.057	-0.257-0.371	0.363
DM	0.075	-0.214-0.364	0.517
Knee OA severity degree	0.235	0.17-0.453	0.035*

*Dependent variable: Synovial inflammation, *Significant ($p < 0.05$), VEGF: Vascular Endothelial Growth Factor, OA: Osteoarthritis, DM: Diabetes mellitus CI: Confidence interval; B: Constant*

associated ($p = 0.031$) with synovial inflammation, in the other hand it also showed the association of overweight and degree of knee OA variables ($p < 0.05$) in high plasma VEGF levels with the occurrence of synovial inflammation. In contrast, the consumption of OA therapy drugs, the presence of OA outside the knee joint, hyperuricemia, and DM as confounding variables have not been shown to be associated with synovial inflammation in knee OA ($p > 0.05$).

Overweight is incorporated into confounding variables because it is related to VEGF level and knee OA, hence it is important knowing its influence to the association of VEGF levels with the occurrence of synovial inflammation in knee OA. Overweight is known correlated with VEGF levels in circulation, in which adipose tissue also produces VEGF in a considerable number.[21] Overweight is also a risk factor in knee OA due to increased mechanical load, while pathogenesis of knee OA itself is associated with synovial inflammatory involvement. Dysfunctional fat cells in high BMI patients produce an excess of proinflammatory adipokines. This adipokine interacts with osteoblasts, synovium and chondrocytes by inducing proinflammatory mediators and cartilage degradation factors. Synovial fibroblast activation occurs and leads to various inflammatory changes in the synovium.[13] In this study, it was evident that overweight along with high VEGF levels were also significantly associated with synovium inflammation in knee OA.

The degree of knee OA severity in this study was proven to affect the association between plasma VEGF levels and the occurrence of synovial inflammation in knee OA ($p = 0.035$), as shown in Table 5. In several studies, OA degree of severity was found associated with either VEGF levels in synovial fluid[14] or plasma,[15] thus its effect on the associations between VEGF levels and synovial inflammation in knee OA was analyzed. VEGF triggers the occurrence of angiogenesis, and in OA angiogenesis is assumed related to bone remodeling process (i.e., osteophyte formation) and cartilage degradation through the induction of proteolysis enzymes production (matrix metalloproteinase/MMP).[22] The magnitude of osteophytes and cartilage damage caused by osteolytic enzyme activity is the basis of severity classification of knee OA.

Hyperuricemia and DM are associated with VEGF levels through induction of vascular endothelial cell dysfunction.[23,24] The presence of endothelial dysfunction will trigger an angiogenesis process involving VEGF and other proangiogenic factors.[25] Hence hyperuricemia and DM are included in the confounding variables to determine their effect on plasma VEGF and synovial inflammation association in knee OA. However, multiple regression analysis showed no significant correlation of hyperuricemia and DM with inflamed synovium in knee OA ($p > 0.05$).

This study was subject to some limitations. Synovial VEGF is hardly measured through direct evaluation, as it relates to the ethical feasibility aspect in which the subject of this study is not undergoing surgery, so a synovial biopsy cannot be performed without any strong indication. There are a lot of various features of other molecular biochemical reaction, which is involved in synovial inflammation process in knee OA. Further research on the molecular level involvement of synovial inflammation needs to be conducted for therapeutic aspects as well as decreasing morbidity.

CONCLUSION

Higher plasma VEGF levels in knee OA with synovial inflammation were found compared to knee OA without synovial inflammation. There was an association between high plasma VEGF levels with

the occurrence of synovial inflammation in knee OA, along with overweight and degree of knee OA involvement.

DISCLOSURE

The content of this manuscript had been presented in the Congress of Indonesian Radiology Society on November 20th-22nd, 2014, Makassar. Some revisions had been made from its original layout for publication purpose.

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