

Power Doppler Ultrasonography is an Important Technique in Rheumatoid Arthritis, Ankylosing Spondylitis and Osteoarthritis Arthritis among Egyptians

Die Power-Doppler-Sonografie ist ein bei Ägyptern mit rheumatoider Arthritis, Spondylitis ancylosans und Arthrose wichtiges Untersuchungsverfahren

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Key words

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Bibliography

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ABSTRACT

Angiogenesis is controlled by a variety of angiogenesis modulators of which VEGF is one of the most important. The increased power Doppler (PD) signals determined by ultrasonography are an indirect marker of synovial vascularity in arthritis. The aim of this study was to identify the importance of the

power Doppler technique in different form of arthritis, by finding relationships of the power Doppler sonography (PDS) score with synovial VEGF and US findings (effusion, thickness). 20 rheumatoid arthritis (RA), 20 ankylosing spondylitis (AS), and 20 osteoarthritis (OA) patients with active knee arthritis were included. Synovial effusion, synovial hypertrophy, and PD signal scores were calculated in arthritic joints. Synovial vascular endothelial growth factor (VEGF) fluid samples were studied. Comparisons between the groups were made; the synovial hypertrophy score and effusion score were significantly higher in RA and spondylarthritis than in OA. PD scores were significantly different between the groups. Synovial VEGF levels were significantly higher in patients with RA and AS than in OA. Synovial effusion score and synovial hypertrophy score were positively correlated with VEGF levels. Also a significant correlation was found between PD score and VEGF, synovial effusion and thickness. In large joints like the knee, detecting PD signals alone was sufficient to assess the angiogenesis, and there were significant positive correlations with VEGF, effusion and thickness score. Therefore, when investigating knee arthritis, the PD technique should be employed.

ZUSAMMENFASSUNG

Die Angiogenese wird durch zahlreiche Modulatoren, von denen VEGF der wichtigste ist, kontrolliert. Bei Arthrose ist das verstärkte Power-Doppler-Signal ein indirekter Marker für die Vaskularisierung der Synovialis. In der vorliegenden Studie sollte die Bedeutung der Power-Doppler-Sonografie bei verschiedenen Formen der Arthrose ermittelt werden. Dazu wurde der Zusammenhang zwischen dem Score der Power-Doppler-Sonografie (PDS), dem VEGF-Spiegel der Synovia und dem Ultraschallbefund der Synovialis (Erguss, Hypertrophie) bestimmt. Die Studieerfolgte an jeweils 20 Patienten mit rheumatoider Arthritis (RA), Spondylitis ankylosans (AS) und Arthrose (OA) mit aktiver Gonarthrose. Ermittelt wurden der Ausmaß des Gelenkergusses und der Hypertrophie der Synovialis sowie die PD-Signal-Scores. Außerdem wurde in Synoviaprobe die Konzentration von Vascular Endothelial Growth Factor (VEGF)

bestimmt. Anschließend wurden Gruppenvergleiche durchgeführt. Der Hypertrophie-Score der Synovialis und der Gelenkerguss-Score waren bei rheumatoider Arthritis und Spondylitis signifikant höher als bei Arthrose. Auch die PD-Scores unterschieden sich signifikant zwischen den Gruppen. Die Konzentrationen von VEGF in der Synovia waren bei Patienten mit rheumatoider Arthritis und Spondylitis signifikant höher als bei Arthrose. Der Gelenkerguss-Score und der Hypertrophie-Score der Synovialis korrelierten positiv mit den VEGF-

Spiegeln. Außerdem bestand ein signifikanter Zusammenhang zwischen dem PD-Score und VEGF, sowie dem Gelenkerguss und der Dicke. In großen Gelenken, wie dem Knie, reichte der Nachweis von PD-Signalen alleine schon aus, um die Angiogenese zu beurteilen und bestand ein signifikanter positiver Zusammenhang mit dem VEGF-Spiegel, dem Gelenkerguss-Score und dem Hypertrophie-Score. Daher sollte bei der Untersuchung der Gonarthrose eine PD-Sonografie durchgeführt werden.

Introduction

Angiogenesis is the growth of new blood vessels from preexisting vasculature requiring a precise balance between angiogenic and angiostatic factors in order to maintain tissue homeostasis. Angiogenesis is essential to chronic inflammation and seems to be the critical pathogenetic mechanism in both the establishment and persistence of rheumatoid arthritis (RA) [1]. There is also increasing evidence that angiogenesis plays a crucial role in the pathogenesis of osteoarthritis (OA) [2]. Ultrasonography using high-frequency linear probes can visualize synovial membrane thickening, joint effusions, and bone erosions [3]. Consequently, power Doppler ultrasonography (PDUS) has been shown to be effective in detecting small vessels or slow blood flows and can be used to identify the increased blood flow of soft tissue. It has been demonstrated that the increased signals obtained by using PDUS correspond to increased local blood flows; therefore, this technique can be used for evaluating the degree of inflammation [4]. There are studies reporting its capability in diagnosing inflammatory states in joints [5]. Vascular endothelial growth factor (VEGF) is a crucial mediator of angiogenesis. It has been implicated in neovascularization associated with cancer metastasis, as well as arthritis. Hypoxia present in the inflamed joints, as well as hypoxia-inducible factors, mediate VEGF production that leads to endothelial cell proliferation and angiogenesis [6].

The aim of this study was to identify the importance of the power Doppler technique in different forms of arthritis, by finding the relations of the power Doppler sonography score with synovial VEGF and US findings (effusion, thickness).

Patients and Methods

20 patients presenting with RA from the attendance of the outpatient clinic and inpatients at the rheumatology department of Benha university hospitals were included in this study. Their mean age was 41.3 ± 13.3 years, 16 patients were females and 4 patients were males and the mean duration of illness was 5.67 ± 4.74 years. Another 20 patients with OA and 20 with ankylosing spondylitis (AS) were enrolled. All patients were fulfilling the recommended classification criteria for each disease [7–9].

All groups were subjected to the following: (i) Clinical assessment of the knee by clinical examination on the same day as radiography and power Doppler ultrasonography. Activity of knee inflammation was classified according to a modified index of synovitis activity [10]. (ii) Synovial levels of VEGF were estimated to evaluate angiogenesis by using a Komabiotec product, human

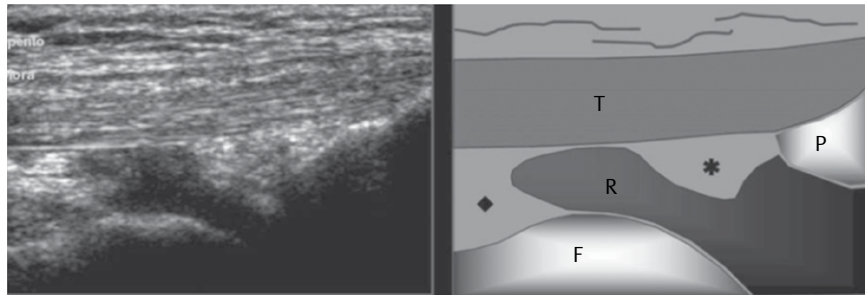
VEGF enzyme linked immunosorbent assay (ELISA) kit, catalog number K0331132. (iii) Musculoskeletal ultrasonography and power Doppler examination: US was performed by 2 sonographers (rheumatologist and radiologist) with experience in musculoskeletal US (► Fig. 1). Examinations included measurement of synovial thickness, effusion (length of suprapatellar bursa) and power Doppler grading. Sonography of the knee joints was done using a Logiq e system with a linear array transducer with 8–13 MHz frequency band, made by the Logiq e machine, according to the guidelines for musculoskeletal ultrasound in rheumatology [11].

Knee ultrasound is obtained by sets of sagittal images of both knees with the patient in the recombinant position with the knee in 30° flexion. The US transducer is positioned longitudinally above the patella, and the synovial membrane thickness was measured when the probe touches the middle portion of the basis patellae. Measurement of total synovial thickness was performed by applying firm compression with the transducer to express the suprapatellar fluid into the joint recesses. The synovial thickening appears as a succession of irregularly proliferating branches, mildly echoic, jutting out from the synovia into the articular cavity; the assessment of the synovial pannus is considerably easier when associated with a fluid collection because it works as a contrast agent. The thickness was graded from 0 to 3 using this scale [12]: 0, if the thickness was <2 mm; grade 1, for a thickness between 2 and 5 mm; grade 2, for 6–8 mm and grade 3 for thickness >8 mm. (iv) Assessment of intraarticular fluid was performed by measuring the length of the suprapatellar bursa. Longitudinal images were obtained with manual compression of lateral synovial recesses to express intraarticular fluid into the suprapatellar bursa.

Power Doppler settings were standardized with a pulse repetition frequency of between 700 and 1 000 Hz, and the gain was set as suggested by [13]. The PDS signal was scored or graded from 0 to 3 according to: score 0 absence of PD signal, score 1 single vessel dots – mild hyperemia, score 2 confluent vessel dots over less than half the area of the synovium (► Fig. 2) – moderate hyperemia, score 3 confluent vessel dots over greater than half the area of the synovium – marked hyperemia.

Statistical analysis

Statistical analysis was done by using SPSS, statistical package of social science program version 10, 1999. Statistical methods of the results were carried out according to the following formula [14]. The data were parametric by using Kolmogorov-Smirnov test, the qualitative data were presented in the form of number and percentages. The quantitative data were presented in the form of



► **Fig. 1** Longitudinal view of quadriceps tendon and suprapatellar recess. T = quadriceps tendon; ◆ = prefemoral fat pad; * = suprapatellar fat pad; R = suprapatellar recess; F = femur P = patella.



► **Fig. 2** Power Doppler of the left knee (grade 2).

mean and standard deviation. One way ANOVA (f-test) was used for comparison of quantitative data of more than 2 groups. Student (t-test) was used for comparison of quantitative data of 2 groups. The Kendal (Spearman) correlation coefficient was done to study a relation between 2 variables; significance was considered when the P-value was less than 0.05. High significance was considered when the P-value was less than 0.001.

Results

This study included 3 groups: Group (I) included 20 patients with rheumatoid arthritis, 16 patients were females and 4 patients were males whose ages ranged between 19–72 years (mean \pm SD 41.3 \pm 13.3 years) and their disease duration ranged between 1–23 years (mean \pm SD 5.67 \pm 4.74 years). Group (II) included 20 patients with AS, 16 patients were males and 4 patients were females. Group (III) included 20 patients with OA fulfilling the ACR criteria for the diagnosis of knee OA (Altman et al., 1986), 16 patients were females and 4 patients were males (► **Table 1**).

Synovial VEGF levels in all groups

The mean synovial VEGF in RA patients was 796.43 pg/mL (SD \pm 301.3), with a highly significant increase ($P < 0.001$) as compared to AS, 656.6 pg/mL (SD \pm 266.7), and OA groups 455.7 \pm 217.7 (► **Table 2**).

► **Table 1** Demographic characteristics among all studied groups.

Variable	Age	Number	Disease duration	Sex f/m
RA	41.3 \pm 13.3 years	20	5.67 \pm 4.74 years	16/4
AS	35.3 \pm 10.3	20	6.66 \pm 4.74	4/16
OA	47.0 \pm 5.7	20	5 \pm 4.11	16/4

► **Table 2** Synovial VEGF levels among all groups.

	OA	AS	RA
Mean	455.7	656.6	796.43
Standard deviation	217.7	266.7	301.3
F	3.23		
P-value	<0.001 (highly significant)		

Musculoskeletal ultrasound examination

The mean synovial thickness in RA patients was 11.72 mm (SD \pm 2.63), with a highly significant increase ($P < 0.001$) as compared to AS patients, 7.4 mm (SD \pm 2.6), and OA group, 3.4 \pm 0.56 (► **Table 3**). VEGF synovial levels showed a more highly significant difference ($p < 0.01$) in RA versus AS patients than in OA according to their synovial thickness $P < 0.001$ (► **Table 4**).

The mean synovial effusion (mm) in RA patients was 15 \pm 5.58 with a highly significant increase ($P < 0.001$) as compared to AS patients, 10.8 \pm 6.88 and OA patients, 2.83 \pm 1.66. There was a statistically significant difference ($p < 0.05$) with regard to VEGF synovial levels in different forms of arthritis according to their effusion. In OA it was 465.3 \pm 120.3, in AS VEGF was 782.2 \pm 223 and in RA 804.3 \pm 349.9 (► **Table 5**).

Power Doppler

There was a significant difference ($p < 0.05$) in the mean of power Doppler grading in different forms of arthritis. In OA the mean

► **Table 3** Synovial thickness among all groups.

	OA	AS	RA
Mean	3.4 ± 0.56	7.42 ± 2.9	11.72 ± 2.63
F	3.3		
P-value	<0.001 (highly significant)		

► **Table 4** VEGF synovial levels in patients according to synovial thickness.

Synovial thickness	VEGF synovial		r	F	P
	N	Mean ± SD			
OA	11	477.5 ± 88.4	0.841	5.83	<0.001
AS	13	652 ± 78.6	0.951		
RA	19	915.4 ± 309.5	0.911		

► **Table 5** VEGF synovial levels in patients in relation to their effusion (suprapatellar bursa diameter).

Synovial thickness	VEGF synovial		r	F	P
	N	Mean ± SD			
OA	15	655.5	0.850	0.14	<0.05
AS	15	782.2 ± 223	0.920		
RS	20	804.3 ± 349.9	0.990		

Significant (P<0.05)

► **Table 6** VEGF synovial levels in RA patients in relation to their power Doppler grades.

	VEGF synovial		r	F	P
	N	Mean ± SD			
OA	15	462.8 ± 130.2	0.421	3.83	<0.05
AS	15	648.9 ± 204.2	0.512		
RA	20	1045.2 ± 303	0.613		

Significant (P<0.05)

grade was 0.93 ± 0.432 . In AS the mean was 1.54 ± 0.42 and in RA the mean was 2.195 ± 0.52 .

There was a statistically significant difference ($p < 0.05$) with regard to VEGF synovial levels in patients in relation to their power Doppler grades. In OA the mean synovial VEGF was 462.8 ± 130.2 ,

in AS the mean synovial VEGF was 648.9 ± 204.2 and in RA the mean synovial VEGF was 1045 ± 303 (► **Table 6**).

Discussion

Angiogenesis is essential to chronic inflammation and seems to be a critical pathogenic mechanism in both the establishment and persistence of RA. There is also increasing evidence that angiogenesis plays a crucial role in the pathogenesis of OA [15]; the study of angiogenesis led to the identification of several endothelial growth factors, VEGF being the most specific one induced by hypoxia [5, 6]. In our study, the VEGF synovial fluid level was estimated in all patients, it was 796.43 ± 301.3 pg/mL in RA and thus significantly higher than in AS and OA. These findings coincided with those of many studies, which reported higher concentrations of VEGF for RA patients than for healthy controls or patients with osteoarthritis [12, 15].

Our results are consistent with the findings of many authors who demonstrated that the levels of VEGF were also elevated in other forms of inflammatory arthritis, this suggests that it is not unique for only RA [16].

Several investigators have described local VEGF expression in the joints of RA patients, where it is synthesized and released by different cell types, such as subsynovial macrophages, fibroblasts surrounding micro vessels, vascular smooth muscle cells and synovial lining cells [17, 18]. Also many researchers concluded that human neutrophils secrete VEGF and levels of neutrophil-associated VEGF in RA synovial fluids correlate well with free VEGF in joint effusions and with the patient's disease activity. However, there is no correlation between VEGF concentrations measured in matched serum and synovial fluid samples from RA patients [19].

In our study, the mean synovial thickness in RA patients was 11.72 mm (SD ± 2.63), with a highly significant increase ($P < 0.001$) as compared to AS patients, 7.42 mm (SD ± 2.9), and the OA group, 3.40 ± 0.56 .

These findings coincided with those of many investigators who reported that the mean synovial thickness and effusion of the knee were significantly higher in inflammatory arthritis than in OA [20]. Also, this agreed with other researchers who detected the mean synovial thickness to be 6.85 mm [21]. In our study, we found a significant correlation between VEGF and ultrasonographic findings (synovial thickness and effusion), also between VEGF and PDUS grading. These agreed with the findings of many researchers [18–20].

Power Doppler ultrasonography (PDUS) is a new technique with the capability of detecting low velocity flow signals using an angle independent method. Previous studies have shown that PDUS is a suitable method to detect synovial hyperemia in the inflamed rheumatoid joints [22]. PDUS has been used for the purpose of assessing synovial membrane inflammation since the middle 1990s [23]. Several studies have confirmed that PDUS is a reliable method for assessing synovitis [24]. The validity of PDUS was demonstrated by several studies, which showed significant correlations between qualitative power Doppler and quantitative histopathological analysis in hip and knee synovitis [25]. In addition, the sensitivity and specificity of PDUS in detecting synovial inflammation has been validated (88.8% and 97.9%, respectively) by many studies in com-

parison to dynamic magnetic resonance imaging as a reference. Decreases in synovial membrane thickness and power Doppler signals are an extremely sensitive means of evaluating treatment responses, as shown after local glucocorticoid injection or systemic administration of methotrexate or TNF- α antagonists [26, 27]. Power Doppler imaging may also have the potential to predict those patients most at risk of accelerated joint destruction. However, much work has yet to be done to standardize the use of these imaging technologies [19]. Thus, the ability of power Doppler US to demonstrate active inflammation, suggests that this imaging modality may become an extremely important tool in assessing the amount of inflammation and the response to therapy in patients with inflammatory joint disease [23]. In our study, the mean power Doppler US grade in rheumatoid knees was grade III, AS knees were scored as grade II and OA were scored as grade I, other studies gave similar power Doppler findings in RA patients and different forms of arthritis [28, 29]. Since US and PDUS have clearly demonstrated inflammation and blood flow, we analyzed whether there was a correlation between VEGF and ultrasonographic findings. There were positive significant relations between synovial VEGF, synovial thickness and effusion. This can be explained as VEGF-mediated endothelial proliferation and angiogenesis which is necessary for synovial tissue proliferation [30]. VEGF is highly 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. Also, we found a highly significant relation between VEGF and power Doppler scoring since RA had higher synovial levels of VEGF than AS and OA, respectively [31]. This can be explained as VEGF causes angiogenesis in the synovium and so increases the intensity of power Doppler signals. Many researchers explained this contrast by the suggestion that VEGF production occurs in both early stages as well as during the course of RA [32].

The current results support the use of power Doppler ultrasound for detection of different grades and forms of knee arthritis. In conclusion, power Doppler is a simple and rapid technique and should be done routinely in the diagnosis of different form of knee arthritis.

Conflict of interest

None.

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