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**The association of power Doppler signal with DAS 28  
in patients presenting arthritic symptoms**

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**The association of power Doppler signal with DAS 28  
in patients presenting arthritic symptoms**

**A Dissertation**

**Submitted to the Department of Medicine  
and the Graduate School of Yonsei University  
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for the degree of Master in Medicine.**

**Seoung Wan Nam**

**June 2016**

**This certifies that the Dissertation of  
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**June 2016**

## 감사의 글

이 학위논문의 앞장에 지금의 제가 있을 수 있도록 도움을 주신 많은 분들께 감사의 인사를 드립니다. 우선 저를 류마티스라는 학문의 길로 이끌어 주시고 애정 어린 마음으로 지도해 주신 강태영 교수님께 깊이 감사 드립니다. 원주에서의 전공의 생활 동안 보아온 교수님의 열정적인 모습을 늘 마음에 깊이 새기고 본받을 수 있도록 정진하겠습니다. 아울러 본 학위논문을 위해 지도편달 해주신 신경외과 허철 교수님과 심장내과 김장영 교수님, 논문의 통계적 부분에 많은 도움을 주신 최은희 교수님, 전공의 기간 동안 많은 가르침을 주신 이향선 교수님께도 깊이 감사 드립니다.

류마티스 선배로서 밝고 성실한 모습으로 모범을 보여준 박정은 선생님, 힘든 전공의 시절 늘 함께 하였던 벗 한용재 선생에게도 감사를 전합니다. 타지에서 근무하고 있는 저를 위해 귀찮은 서류 작업 들을 대신 처리해 준 박상욱 선생에게도 깊이 감사 합니다. 바쁜 류마티스 전임의 스케줄 속에서도 끝까지 논문을 마무리 지을 수 있도록 배려해 주시고 늘 많은 가르침을 주시는 한양대학교 류마티스내과 유대현 교수님, 배상철 교수님, 전재범 교수님, 김태환 교수님, 성윤경 교수님, 최찬범 교수님, 조수경 교수님과

선배 이성원 선생님, 든든한 동기 권혁희 선생에게도 깊은 감사와 존경의 마음을 전해 드립니다.

언제나 나에게 큰 힘이 되어 주는 사랑하는 아내와 나의 아버지, 어머니, 장인어른, 장모님, 사랑하는 동생 승아에게도 말로 다 표현 못할 사랑과 감사의 마음을 전합니다. 힘든 순간이 있었지만 나를 응원해주는 소중한 분들이 계셨기에, 그리고 사랑하는 가족이 있었기에 학위과정을 무사히 마칠 수 있었습니다. 그 밖에도 저를 아껴 주셨던 모든 선배, 후배, 동료 여러분들께 깊이 감사 드립니다. 아직은 익힐 것도 많고 가야 할 길도 멀지만 감사 드려야 할 모든 분들의 따뜻한 마음을 기억하며 류마티스 내과 의사로서 열정적인 삶을 살아 가도록 노력하겠습니다.

2016년 6월 27일

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## ABSTRACT

### **The association of power Doppler signal with DAS 28 in patients presenting arthritic symptoms**

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**Objective:** To examine the relationship between power Doppler ultrasonography (PDUS) parameters with the disease activity grade reflected by the 28 joint Disease Activity Score (DAS 28) in patients presenting arthritic symptoms.

**Methods:** Thirty-three patients with inflammatory arthritis features were consequently enrolled in the study. The PDUS exam of target joints, measurements of DAS 28 and its components (tender joint count, swollen joint count, ESR, CRP, and Patient Global Visual Analogue Scale) were conducted on every 4 week interval visits, until the initially detected Doppler signal disappeared in target joints. Total 80 visit data was gathered and analyzed accordingly in this study. Pearson's correlation coefficients were represented to

reveal the relationship between the PDUS parameters and DAS 28. Then, the total study population was divided into two groups, rheumatoid arthritis (RA) group and non-RA group. The same statistical analysis process was performed in each group, and the results were evaluated and compared each other.

**Results:** The correlation between the sum of power Doppler semi-quantitative grade of target joints (sum of PD grade) and DAS 28 assessed at each follow up visit was 0.59 by the Pearson correlation coefficient ( $P < 0.0001$ ). The Pearson correlation coefficient between the sum of power Doppler quantitative analysis area (sum of PD area) and DAS 28 was 0.61 ( $P < 0.0001$ ). In the RA group, the Pearson correlation coefficients became higher between the PDUS parameters and DAS 28 ( $r = 0.60$ ,  $P < 0.0001$  for PDUS grade.  $r = 0.63$ ,  $P < 0.0001$  for PDUS area.). On the contrary, the correlation became weaker between PDUS parameters and DAS 28 in non-RA group. Pearson correlation coefficients between the sum of PD grade and DAS 28 was 0.56 ( $P = 0.0031$ ), and Pearson correlation coefficient between the sum of PD area and DAS 28 was 0.57 ( $P = 0.0038$ ) in non-RA group.

**Conclusions:** Our study data showed significantly high correlation between PDUS parameters and DAS 28. These results support that the PDUS technique is reliable tool for determining the activity of synovitis in daily clinical practice.

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**Key words:** Power Doppler ultrasonography; Arthritis; Disease activity

# 1. Introduction

Activity of arthritis has traditionally been measured indirectly by subjective or objective clinical data, laboratory parameters, and imaging finding. Among imaging techniques, musculoskeletal ultrasound (US) is increasingly widely used at various clinical settings in evaluating and monitoring patients with inflammatory arthritis [1]. US is more cost effective and less time consuming than other imaging modalities such as MRI. Moreover, it can offer real time bedside imaging, which helps clinicians to apply more precise interventional procedures such as joint fluid aspiration or intraarticular injection.

Power Doppler US (PDUS) techniques detect synovial flow, which is a sign of increased synovial vascularization [2]. It has been proven that the presence of intraarticular power Doppler signal differentiates active synovitis from inactive intraarticular thickening [3-9]. Previous studies on the application of PDUS finding on rheumatoid arthritis (RA) patients revealed its usefulness on detecting early RA from undifferentiated arthritis, and also on determining the degree of treatment efficacy [9-11]. Wakefield et al introduced PDUS techniques as a promising tool to improve disease activity assessment in inflammatory arthritis in 2003 [12]. However, there has been only few clinical study data on supporting the usefulness of PDUS on predicting RA disease activity [1].

The purpose of this study was to demonstrate the relationship between cumulative PDUS parameters with the disease activity grade reflected by the 28-joint Disease Activity Score (DAS 28) in patients presenting inflammatory arthritis features.

## 2. Material and Methods

The study prospectively included 33 consecutive patients (22 women, age range 19-81 years) with arthritic symptoms of less than 24 week duration from the outpatient clinic at Department of Rheumatology of Wonju Severance Christian Hospital, Wonju, South Korea, from 2014 to 2015. Arthritis patients were limited to those with at least one tender or swollen joint count among hand, wrist, elbows, shoulder, foot, ankle, knee, and hip. All of them underwent US evaluation at the baseline and those without positive PDUS signal at the interesting joints were not enrolled in this study. All these patients gave their informed consent to be enrolled in this study according to the Declaration of Helsinki and the study was approved by the hospital ethics committee. During the study period, patients received routine medical care at the discretion of their rheumatologist. Doppler ultrasound exam of target joints, measurement of DAS 28 and its components (tender joint count, swollen joint count, ESR, CRP, Patient Global Visual Analogue Scale, Doctor's Global Visual Analogue Scale) were performed on every 4 week interval visits, until the initially detected intraarticular Doppler signal disappeared completely in the target joints. Also we repeatedly assessed if patients met the RA classification criteria (either the 1987 American College of Rheumatology (ACR) classification criteria or the 2010 ACR/European League against Rheumatism (EULAR) classification criteria) on every visit.

Accordingly, total 80 visit data was gathered and analyzed in this study. Ultrasound examination was repeated by the same EULAR musculoskeletal ultrasound level 2 expert. Scanning was performed using a General Electric Logiq e. The same preset was used in all US examinations. Power Doppler semi-quantitative grade was classified from 0 to 3 according to the one proposed by EULAR ultrasound working group (0 =absence, no intraarticular flow; 1 = mild, single-vessel signal or isolated signals; 2 = moderate, confluent vessels; 3 = marked, vessel signals in more than half of the intraarticular area) [14]. And, quantitative Doppler signal intensity analysis was performed using manufacturer add-on software (GE Healthcare, Logiq e). In detail, free hand Region of Interest (ROI) was drawn for quantification of ROI, and the area of ROI, ratio of positive power Doppler pixels within the ROI were calculated with the GE Q Analysis software. When there was Doppler signal positivity in more than two joints, the sum of all the positive joint value was used for the analysis.

For statistics, data were expressed according to the properties of the variable. Continuous variables were presented as mean and standard deviation. Categorical variables were presented as frequency and percentage. In order to compare two groups, we conducted the two-sample t-test or chi-square test as appropriate. We represented the linear correlation between Power Doppler and DAS 28 using Pearson's correlation coefficients and scatter plot with linear regression line. P-value less than 0.05 was considered statistically significant and all statistical analysis were performed using SAS 9.2 version (SAS Inc., Cary, NC, USA). The total study population was then divided into

rheumatoid arthritis (RA) group and non-rheumatoid arthritis (Non-RA) group for further analysis. Patients were classified as RA group if they were ever diagnosed as rheumatoid arthritis according to the 1987' ACR classification criteria or the 2010' ACR/EULAR classification criteria during the study follow up period. The same statistical analyses were performed in each group and the results were evaluated and compared each other.



### 3. Results

Complete follow up data was obtained from 30 patients of the 33 patients included in the study. Three patients attended only the baseline visit and did not complete the study follow up schedule. Available data from those three patients was also analyzed. At the baseline analysis, there were 16 patients who met the RA classification criteria (either the 1987' ACR classification criteria or 2010' ACR/EULAR classification criteria). One patient who was initially classified as Non-RA at the baseline was reclassified as RA on his fourth visit (3 months after the baseline assessment). There were 6 patients (35.29%) neither with rheumatoid factor (RF) positivity nor anti-CCP antibody positivity at the baseline in RA group (seronegative RA patients). And, there were 7 patients (43.75%) either with RF positivity or anti-CCP antibody positivity at the baseline in non-RA group. And, four of them were both positive in RF and anti-CCP antibody. Baseline characteristics for the included study population are shown in Table 1. There were no significant differences between RA and non-RA group in the following: gender, age, number of visits, tender joint count, VAS-GH-Patient, VAS-GH-Physician, CRP, ESR, sum of PDUS semi-quantitative grade, sum of PDUS quantitative scale, positive RF, anti-CCP. The DAS 28 and swollen joint count were significantly higher in RA group.

The correlation between the sum of power Doppler semi-quantitative grade of every target joint (sum of PD grade) and DAS 28 assessed at each follow up visit was 0.59 in total study population by Pearson correlation coefficient ( $P < 0.0001$ ) (Figure 1a). And,

the correlation between the sum of power Doppler quantitative analysis area of every target joint (sum of PD area) and DAS 28 was 0.61 (Pearson's correlation coefficient  $r = 0.61$ ,  $P < 0.0001$ ) (Figure 1b). In the RA group, Pearson correlation coefficient between the sum of PD grade and DAS 28 was 0.60 ( $P < 0.0001$ ) (Figure 2a) and Pearson correlation coefficient between the sum of PD area and DAS 28 was 0.63 ( $P < 0.0001$ ) (Figure 2b). On the contrary, the correlation became weaker between PDUS parameters and DAS 28 in non-RA group. Pearson correlation coefficients between the sum of PD grade and DAS 28 was 0.56 ( $P=0.0031$ ), and Pearson correlation coefficient between the sum of PD area and DAS 28 was 0.57 ( $P = 0.0038$ ) in non-RA group (Table 2). Though all the results on the correlation between PDUS intensity parameters and DAS 28 showed significantly high correlation, the correlation intensity differed depending on the different PD intensity measurement methods and arthritis classification.

**Table 1. Baseline characteristics.**

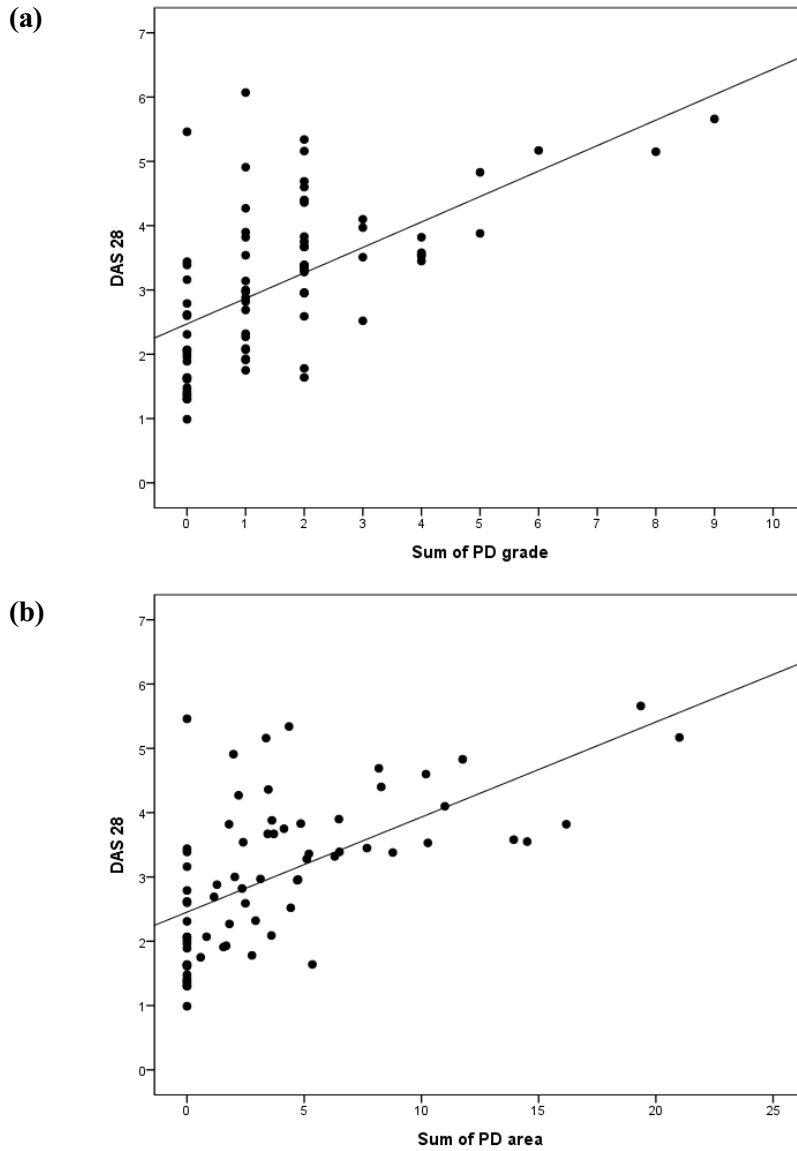
Characteristic	Total patients (n=33)	RA group (n=17)	Non-RA group(n=16)	P-value
Gender-Female	22 (68.75%)	10 (62.50%)	12 (75%)	0.4456
Age (years)	56.75 ± 14.03	54.50 ± 15.35	59.00 ± 12.66	0.3728
Number of visits	2.42 ± 1.80	2.81 ± 1.97	2.06 ± 1.60	0.2360
Swollen joint count	2.72 ± 1.68	3.56 ± 1.79	1.94 ± 1.14	0.0039
Tender joint count	2.06 ± 2.19	2.69 ± 2.68	1.47 ± 1.46	0.1218
VAS-GH-Patient	72.88 ± 18.07	76.25 ± 17.46	69.71 ± 18.58	0.3059
VAS-GH-Physician	70.76 ± 16.40	75.00 ± 15.49	66.76 ± 16.67	0.1523
CRP (mg/ml)	2.68 ± 3.70	2.61 ± 3.34	2.74 ± 4.11	0.9215
ESR (mm/h)	43.12 ± 27.47	50.56 ± 30.27	36.12 ± 23.30	0.1333
DAS28	4.06 ± 0.99	4.43 ± 0.85	3.72 ± 1.00	0.0366
Sum of PDUS semi-quantitative grade	2.36 ± 2.21	2.75 ± 2.52	2.00 ± 1.87	0.3368
Sum of PDUS quantitative scale	5.87 ± 5.57	6.65 ± 5.23	5.14 ± 5.96	0.4759
IgM-RF positive	17 (51.52%)	10 (62.50%)	7 (41.18%)	0.2206
Anti-CCP positive	11 (33.33%)	7 (43.75%)	4 (23.53%)	0.2181

Continuous variables were presented as mean and standard deviation (mean ± SD). Categorical variables were presented as frequency and percentage. In order to compare two groups, we conducted the two-sample t-test or chi-square test as appropriate. RA: Rheumatoid arthritis; VAS-GH: Visual analog scale-global health; DAS 28: Disease activity score 28; PDUS: Power Doppler ultrasonography.

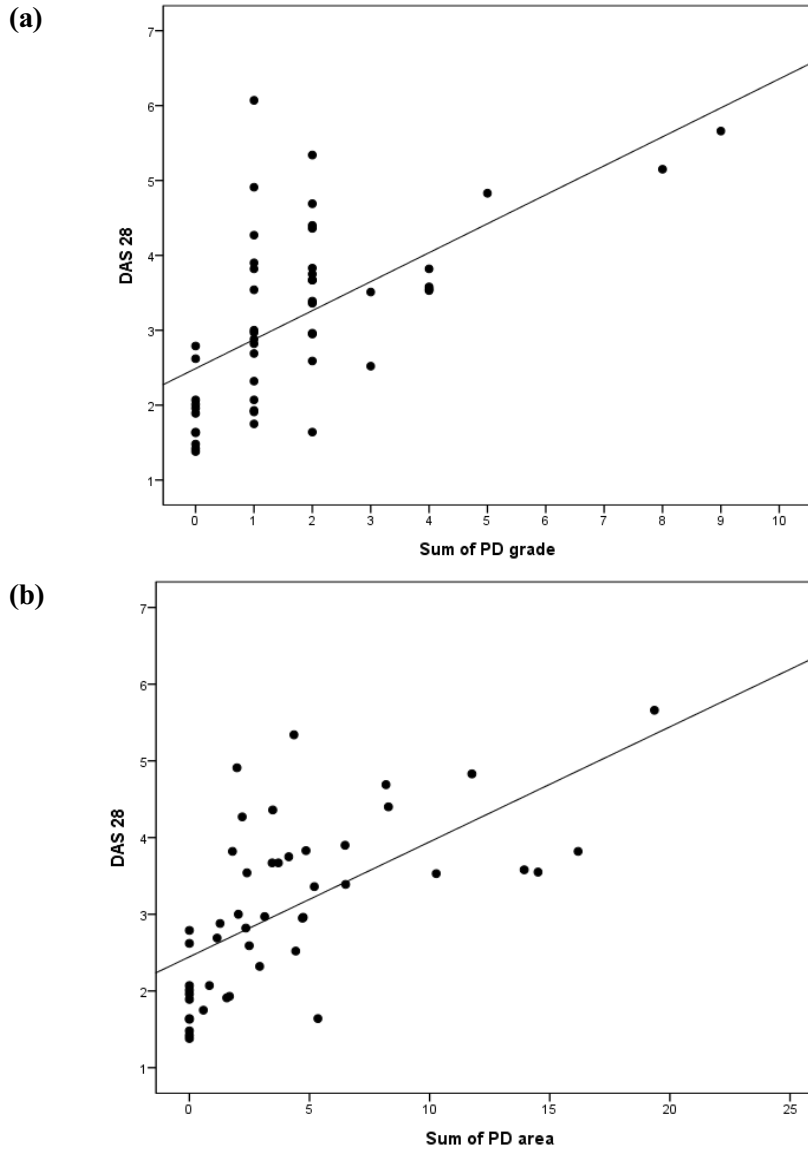
**Table 2. Comparison of the Pearson correlation coefficients between power Doppler signal intensity parameters and DAS 28 in each group.**

	<b>Sum of PD grade</b>	<b>Sum of PD area</b>
Total patients	0.59 (P < 0.0001)	0.61 (P < 0.0001)
RA group	0.61 (P < 0.0001)	0.63 (P < 0.0001)
Non-RA group	0.56 (P = 0.0031)	0.57 (P = 0.0031)

Pearson's correlation coefficients (r) are presented. RA: Rheumatoid arthritis; PD grade: the sum of power Doppler semi-quantitative grade of every target joint; PD area: the sum of power Doppler quantitative analysis area of every target joint



**Figure 1. (a) Correlation between the sum of power Doppler semi-quantitative grade of every target joint (sum of PD grade) and DAS 28 (Pearson's correlation coefficient  $r = 0.59$ ,  $P < 0.0001$ ). (b) Correlation between the sum of power Doppler quantitative analysis area of every target joint (sum of PD area) and DAS 28 (Pearson's correlation coefficient  $r = 0.61$ ,  $P < 0.0001$ ).**



**Figure 2. (a) Correlation between the sum of power Doppler semi-quantitative grade of every target joint (sum of PD grade) and DAS 28 in RA group (Pearson's correlation coefficient  $r = 0.60$ ,  $P < 0.0001$ ). (b) Correlation between the sum of power Doppler quantitative analysis area of every target joint (sum of PD area) and DAS 28 in RA group (Pearson's correlation coefficient  $r = 0.63$ ,  $P < 0.0001$ )**

## 4. Discussion

Previous studies on evaluating RA patients using ultrasound used routine assessment of 60 joints or 28 joints [15, 16]. However it is not easy to perform the routine US examination of over 20 joints in daily clinical practice, especially if physicians are asked to examine many patients in a given time. It might be feasible to further examine only clinically suspicious joints with pain, tenderness, or swelling using PDUS to determine the presence or the intensity of its positive signal. We conducted PDUS exam only on the joints with arthritic symptoms (pain, tenderness, or swelling). If there was Doppler signal positivity in more than two joints, the sum of all the positive joint value was used for the analysis. We assumed that the sum of PDUS intensity parameters from all target joints will reflect the disease activity mores precisely than the parameter from the one representative joint. PDUS measurement parameters were then analyzed with DAS 28 assessed at each patient visit. The DAS28 was calculated from four components: tender joint count, swollen joint count, visual analogue scale (VAS) score of the patient's global health and the laboratory parameter erythrocyte sedimentation rate (ESR). It was developed as a tool to evaluate the disease activity of RA patients and has been most widely used for this purpose [17]. We conducted regular PDUS exam only if patients showed positive PDUS finding at the baseline exam. PDUS positivity signify active synovitis status of the examining joints and the synovitis is considered to be the primary pathogenic mechanism responsible for the characteristic behavior of RA and other

inflammatory arthritis [2-9, 18-20]. Hence, comparing the PDUS intensity parameters of arthritic joints and DAS 28 has clinical implication of predicting disease activity using PDUS in daily clinical practice.

Overall our results showed significantly high positive correlation between PDUS grade parameters and DAS 28. Comparing the intensity of correlation between the sum of PDUS semi-quantitative grade (sum of PD grade) with DAS 28 and the sum of PDUS positive quantitative analysis area (sum of PD area) with DAS 28, sum of PD area showed slightly stronger correlation with DAS 28 in all the groups (Total study population, RA group, Non-RA group) as shown in the Table 2. When dividing the total study population into RA and Non-RA groups, RA group showed higher positive correlation with DAS 28 compared to other groups both in the cases of Sum of PD grades and Sum of PD area (Table 2). All these results support the reliability of the PDUS signal intensity parameters in predicting the activity of the inflammatory arthritis especially in the RA patients.

This study was single center, prospective cohort study evaluating the relationship between the cumulative PDUS parameters in patients presenting inflammatory arthritic features with the disease activity reflected by DAS 28. We tried to simulate the daily clinical practice setting by targeting joints with clinically positive finding. However, this study has limitation of having small sample size. And, there was no evidence that DAS 28 reflects disease activity in non-RA patients. But, all of our study population had inflammatory arthritis features having proven by positive PDUS signal at the baseline.



Though we did not perform extended survey to confirm the final diagnoses in the non-RA group, we assumed that non-RA group patients could have undifferentiated arthritis with potential to develop as RA, inflammatory osteoarthritis, or all other forms of inflammatory arthritis. As all of these inflammatory arthritis share the common pathophysiology of having synovitis that can also accompany systemic clinical features such as elevated ESR or CRP level [21]. Thus, their disease activity might also affect the DAS 28 level. And, our study results showed positive correlation between PDUS grade parameters and DAS 28 also in non-RA group, though the intensity of correlation was lower than RA group.

## **5. Conclusion**

Our results showed significantly high positive correlation between PDUS intensity parameters and DAS 28. PDUS technique is a reliable measure of inflammatory arthritis activity especially in RA patients. PDUS technique is less time consuming, convenient, and reliable tool for determining the activity of synovitis in daily clinical practice.

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## 국문요약

### 관절염 증상을 가진 환자에서 파워 도플러와 DAS 28의 관계

**연구 목적:** 관절염 증상을 가진 환자에서 파워 도플러 초음파의 결과 값과 질병 활성도의 측정에 쓰이는 DAS 28의 관계를 규명한다.

**연구 방법:** 염증성 관절염 소견을 보이는 33명의 환자들이 본 연구에 참여하게 되었다. 이들을 대상으로 파워 도플러 초음파 측정과 더불어 DAS 28의 구성 요소인 압통 관절의 수, 종창 관절의 수, ESR, CRP, 환자의 global VAS의 확인 및 DAS 28의 산출을 매 4주 간격의 추적 관찰 때에 시행 하였다. 추적 관찰은 환자의 대상 관절의 파워 도플러 양성 소견이 완전히 사라질 때까지 이루어 졌으며 총 80회 추적관찰 방문에 대한 자료가 모아져 이를 분석 하였다. 파워 도플러 측정값과 DAS 28의 관계는 피어슨 상관분석을 통하여 분석 하였다. 또한 총 연구군을 류마티스 환자군과 비(非)류마티스 환자군으로 나누어 같은 분석을 시행하고 그 결과를 비교하였다.

**연구 결과:** 각 추적 방문 시에 대상관절들의 파워 도플러 반정량 측정 결과의 합과 DAS 28의 피어슨 상관계수는 0.59 ( $P < 0.0001$ )이었고 파워 도플러 정량적 측정 결과의 합과 DAS 28 사이의 피어슨 상관계수는 0.61 ( $P < 0.0001$ ) 이었다. 류마티스 관절염 환자 그룹에서는 반정량 측정 결과의 합과 DAS 28의

피어슨 상관계수가 0.60 ( $P < 0.0001$ ), 정량 측정 결과의 합은 DAS 28과의 피어슨 상관계수가 0.63 ( $P < 0.0001$ )으로 전체 환자군에 비해 파워 도플러 결과 값이 DAS 28과 더 강한 양의 상관 관계를 보였다. 반면 비류마티스 관절염 군에서는 DAS 28과의 피어슨 상관계수가 비정량 측정법의 경우에는 0.56 ( $P = 0.0031$ ), 정량 측정법의 경우에는 0.57 ( $P = 0.0038$ )로 더 약한 양의 상관 관계를 보였다.

**결론:** 본 연구의 결과는 파워 도플러 측정값의 크기와 DAS 28 과의 사이에 통계적으로 유의한 양의 상관 관계를 보여 주었으며, 이 결과를 통해 파워 도플러 초음파가 일상적 진료 현장에서 활막염 활성화도 평가의 신뢰성 있는 도구로 사용될 수 있음을 뒷받침 해준다.

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**핵심되는 말:** 파워 도플러, DAS 28, 관절염, 질병 활성화도