



Original Article

The Role of Ultrasound in Defining Remission in Rheumatoid Arthritis

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Abstract

Objective: This review evaluates the role of Ultrasound in defining Rheumatoid arthritis (RA) remission, compares its sensitivity with traditional scores, and explores its integration into routine assessments, while identifying study limitations and future research directions.

Methods: A systematic literature search (2006–2023) was conducted in PubMed, Embase, and Cochrane, following PRISMA guidelines. Studies comparing ultrasound (especially PDUS) with clinical remission scores (DAS28, SDAI, CDAI) in RA were included. Three reviewers independently screened articles, with data extracted using a structured form and assessed for bias. Narrative synthesis was used due to study heterogeneity; descriptive statistics summarized ultrasound's sensitivity in detecting subclinical synovitis.

Results: Ultrasound detected subclinical synovitis in 28–95% of RA patients in clinical remission, with PD signals especially common in wrists. Ultrasound remission aligned best with SDAI <3.3, while DAS28 often underestimated residual disease. GS and PD synovitis were also found in asymptomatic joints, highlighting limitations of clinical scores alone. Some studies showed no clinical benefit from ultrasound-guided treatment, though PD negativity predicted sustained remission in others.

Conclusion: Ultrasound, particularly PDUS, was superior to clinical composite scores like DAS28 and CDAI in detecting subclinical synovitis. Many patients classified as in remission by DAS28 or CDAI still exhibit active disease when assessed by ultrasound. Incorporating PDUS into routine RA evaluations is critical for identifying subclinical synovitis and improving disease management. Standardized protocols and additional research are necessary to fully integrate ultrasound into clinical practice and enhance patient outcome.

Keywords: Rheumatoid Arthritis, Remission Induction, Ultrasonography, Synovitis, Imaging, Disease Activity

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder primarily affecting joints, leading to inflammation, pain, and potential disability. The main treatment goal in RA is achieving and maintaining remission to prevent long-term joint damage and preserve quality of life.^{1,2,3,4,12,13,14} Clinical composite scores such as DAS28, SDAI, and CDAI are commonly used to evaluate disease activity, but these methods have limitations, relying on patient-reported symptoms, physical exams, and biomarkers like CRP and ESR.^{1-7,8-14} These traditional measures may overlook subclinical inflammation, which can still

lead to disease progression.

Musculoskeletal ultrasound (MSUS), particularly power visualizing Doppler ultrasound (PDUS), offers a more accurate assessment of inflammation by synovial activity and detecting subclinical disease.^{1-7,14} PDUS can identify active synovitis even in joints that appear normal on clinical examination. This capability is crucial for identifying residual inflammation and preventing disease flares or joint damage. Emerging evidence supports the use of ultrasound as a more precise tool for assessing true remission in RA compared to traditional clinical scores.

Aim of the Review

This review evaluates the role of Ultrasound especially PDUS in defining RA remission, compares its sensitivity with traditional scores, and explores its integration into routine assessments, while identifying study limitations and future research directions.

Methods

This systematic review evaluates the role of ultrasound, particularly PDUS, in defining remission in RA, comparing it with clinical scores like DAS28, SDAI, and CDAI. Following PRISMA guidelines, the review ensures a comprehensive and transparent methodology.

Search Strategy

A literature search was conducted in PubMed, Embase, and the Cochrane Library for studies published from January 2006 to December 2023 comparing ultrasound findings with clinical remission definitions in RA.

Key Search Terms included; (1) Rheumatoid Arthritis, (2) Ultrasonography" OR "Ultrasound, (3) Remission, (4) DAS28" OR "SDAI" OR "CDAI, (5) Power Doppler.

The search was refined using specific inclusion and exclusion criteria outlined in Table 1.

Study Selection: Three reviewers independently assessed the titles and abstracts of all retrieved articles to determine their relevance. Full-text articles were reviewed for those that met the inclusion criteria (Figure 2). Any disagreements among the reviewers were resolved through discussion or by involving a third reviewer. The PRISMA flow diagram (Table 2) provides a detailed overview of the study selection process.

Data Extraction

Data were gathered using a structured form, which included the following details:

Study Information: First author, publication year, country, and study design; Patient Data: Sample size, age, disease duration, and baseline clinical characteristics; Ultrasound Details: Type of ultrasound (grey-scale or power Doppler), joints examined, scoring system, and operator proficiency; Remission Assessment: Criteria used (DAS28, SDAI, CDAI), definition of remission, and follow-up duration; Outcomes: Detection of subclinical

Table 1: Inclusion and Exclusion Criteria

Search Inclusion Criteria	Search Exclusion Criteria
Studies published in English from 2006 to 2023	Non-English language studies and animal studies
Randomized controlled trials, observational studies, and cohort studies	Reviews, case reports, editorials, and letters
Studies involving individuals aged 18 years and above	Papers without clinical remission or low disease activity assessments.
Additional materials and guidelines manually retrieved from article references and textbooks (cited in the bibliography)	Articles lacking disease activity assessments.
Studies involving patients diagnosed with RA according to ACR/EULAR criteria.	Studies not utilizing PDUS or grey-scale ultrasound for synovitis detection.
Studies assessing remission using clinical composite scores (DAS28, SDAI, or CDAI) and comparing these with ultrasound findings (especially PDUS)	Studies without sufficient data on the correlation between remission and ultrasound findings.
Full-text, peer-reviewed studies published between 2006 and 2023.	Studies assessing disease activity using other radiological techniques (e.g., MRI) without mentioning ultrasound.
Studies using ultrasound to detect subclinical synovitis in patients classified as being in remission according to clinical scores.	Papers not aligning with the objectives of this review.
Articles manually selected from references of EULAR or OMERACT meetings.	
Only articles with full text included.	
CASP checklist questions were applied to assist with selection	

synovitis, correlation between ultrasound findings and clinical scores, and relapse rates.

Risk of Bias Assessment: Bias was evaluated using the Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. The assessment considered selection, performance, detection, and reporting biases. Studies identified as high risk were interpreted with caution.

Data Synthesis: The findings were summarized narratively, highlighting the comparison between clinical remission and synovitis detected by ultrasound. Quantitative data were aggregated to evaluate the sensitivity of ultrasound relative to clinical scores.

Statistical Analysis: Due to the variability among studies, a meta-analysis was not conducted. Instead, descriptive statistics were used to summarize the detection rates of subclinical synovitis and the influence of ultrasound findings on clinical decision-making.

Definition of Clinical Remission: Most studies diagnosed RA based on ACR criteria. Remission was defined using multiple criteria, including DAS, DAS28, SDAI, and ACR/EULAR. Some studies set stricter thresholds (e.g., DAS28 <1.17, SDAI <1.51) but found PD activity remained largely unaffected. Remission time varied, with some patients achieving it in under six months.¹⁻⁹

Ultrasound Remission and Scoring: Ultrasound, particularly Power Doppler (PD) and Grey Scale (GS), was used in most studies. Synovitis was scored on a 0-3 scale, following OMERACT 2005 definitions. Ultrasound remission was defined as no GS or PD synovitis (GS + PD = 0) or lenient criteria (GS ≤ 1, PD ≤ 1). Some studies defined active disease based on PD signals in at least two joints.^{8,11-20}

Number and Regions of Joints Assessed by Ultrasound: Joint counts ranged from five to 44, with common joints including MCP, wrist, MTP, and PIP. Some studies used reduced joint sets, while others included ankles, knees, elbows, and peri-articular structures like tendons and ligaments.^{1,6,9,16,19,23}

Correlation Between Large Joint Counts and Reduced Joint Counts; Reduced joint counts were correlated with comprehensive joint counts, with Balsa et al. reporting a 7% misclassification risk. Naredo et al. and Backhaus et al. showed high correlations in reduced joint count models.^{1,6,17}

Ultrasound Correlations with Clinical Measures of Remission: PDUS was more sensitive than clinical scores (DAS28, SDAI, CDAI) in detecting subclinical synovitis in RA patients in clinical remission. Synovitis was detected in 28.2% to 95% of patients, with PD synovitis rates ranging from 28.2% to 62%. Horton et al. found limited overlap between DAS28 remission and ultrasound remission (25% overlap).^{4,9,12,15,22,26}

Comparison of Ultrasound Findings and Remission Scores; Studies comparing ultrasound findings with various remission scores (Table 3) showed that ultrasound remission best aligned with SDAI <3.3, showing high sensitivity and specificity, while DAS28 underestimated disease activity. Saleem et al. found that PD activity remained substantial in 25% of patients at DAS28 <1.17. Spinella et al. also noted a mismatch between clinical

and ultrasound findings, with subclinical activity detected despite absent tender/swollen joints.^{1,8,11,19}

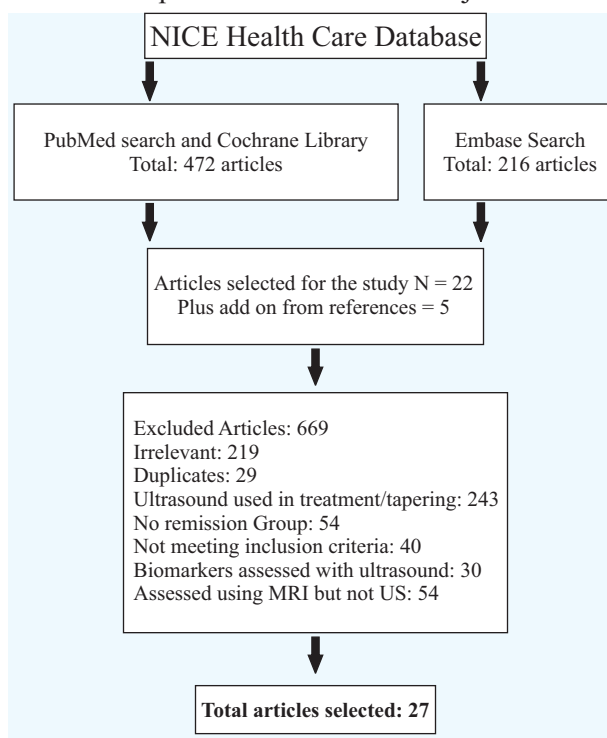


Figure 1: Flow Chart: Selection Strategy for Studies

Results

Ultrasound Findings in Clinical Remission: Spinella et al. found that a negative ultrasound scan was a strong predictor of clinical remission. In their study, 65% of patients in clinical remission had a positive ultrasound, while 35% had a negative scan¹⁹. Dale et al. (2014) conducted 369 ultrasound assessments in low-disease-activity patients. Of these, 25% indicated active disease by DAS28, while 24% of 271 DAS28-defined remissions still showed active disease. Notably, 67% of moderate-disease-activity assessments showed no synovitis. MCP2-5 and wrist joints were more predictive of recurrence, while foot joints (MTP2-5, Lisfranc) were better detected using SMI, which is not included in DAS28.^{15,22}

Table 2: Ultrasound correlations with clinical measures of remission

Patients in Clinical Remission	Absent PDA	Absent/Minimal
DAS28 Remission ^{3, 8, 15}	42%	62%
DAS44 Remission ^{3, 8, 15}	44%	66%
ACR/EULAR Remission ^{3, 8, 15}	40%	76%

In another study, 20 out of 31 clinical remission patients showed positive PD activity, with 17 having PD activity ≥ 2 , primarily in the wrist. PD activity occurred in 41.9% of wrist areas, with 16.1% showing ≥ 2 PD-positive signals. PD signals were less frequent in PIP (3.2%) and MCP joints (4.5%).²⁶ A discrepancy in tenosynovitis findings was noted: Brown et al. identified rare cases mostly in the wrist,² while Bellis et al. found GS tenosynovitis in 52.5% and PD tenosynovitis in 22.7% of clinical remission patients. Deeper remission correlated with minimal GS and PD activity.²³

Ultrasound Findings in Different Remission

Criteria: Balsa et al. reported ultrasound remission aligned best with SDAI < 3.3 , showing high sensitivity and specificity, while DAS28 underestimated disease activity.¹ Peluso et al. found lower PD activity in ACR remission compared to DAS remission.⁸ Saleem et al. observed stringent criteria (DAS28 < 1.17 , SDAI < 1.51) reduced joint counts but did not affect PD activity.¹¹ Spinella et al. noted mismatches between clinical and ultrasound

findings, with some tender/swollen joints not reflected on ultrasound.¹⁹

De Miguel et al. observed limited but significant correlations between composite indices and ultrasound counts over time. Another study found early reductions in ultrasound scores for ACPA-negative patients, though this effect waned later. Mortada et al. showed the U9 scale had good sensitivity and specificity in distinguishing disease activity, correlating strongly with CDAI and DAS28-ESR.²⁴

Two studies found no significant difference between ultrasound and composite scores. In these, ultrasound-guided treatment under tight control showed no imaging outcome differences after 18 months, though DAS44 improved significantly (control 43%, intervention 66%; $p=0.03$).^{7,21} Similarly, the ARCTIC study found no advantage of ultrasound-tight control over conventional treatment, with similar DAS28, SDAI, and ACR/EULAR remission rates at 12 and 24 months.⁷

Table 3: Characteristics of the study

Author	Patients	Disease Duration (Years)	Remission Criteria	Joints Assessed	US Mode	Scale	OMERAT Pathology Definition
Brown et al. (2006) ¹	124	7	PJ, DAS28, ACR	5 Joints: Wrist, 2-5 MCP	GS & PD	SQ	Y
Wakefield (2007) ²⁰	10	1.7	DAS28	42 Joints	GS & PD	SQ	NA
Ozgocmen et al. (2008) ¹⁰	52	9.3	DAS28, ACR	14 Joints: MCP, wrist, RCP, ulnar-carpal	PD	SQ	Y
Brown et al. (2008) ¹²	102	7	PJ, DAS28, ACR	5 Joints: Wrist, 2-5 MCP	GS & PD	SQ	Y
Saleem et al. (2009) ¹³	100	9	DAS28	6 Joints: Wrist & MCPs	GS & PD	SQ	Y
Backhaus et al. (2009)	91 (RA)	0.69-0.78	DAS28	7 Joints: Wrist, MCPs, PIPs, MTPs	GS & PD	SQ	Y
Scirè et al. (2009) ⁹	106	1.8	DAS	44 Joints	GS & PD	SQ	Y
Balsa et al. (2010)	97	5.9	PJ, DAS28, SDAI, ACR	42 Joints	GS & PD	SQ	Y
Saleem et al. (2010) ¹³	47	Early 1.58, Late 10	DAS28	6 Joints: Wrist & MCPs	GS & PD	SQ	Y
Saleem et al. (2011) ¹⁴	128	8	DAS28, SDAI, ACR	5 Joints: Wrist, 2-5 MCPs	GS & PD	SQ	Y
Peluso et al. (2011) ⁸	94 (48 early RA, 46 late RA)	Early RA=0.5, Late RA=9.8	DAS	10 Joints: Wrists, MCPs, PIPs	GS & PD	SQ	Y

Table 3: *Characteristics of the study*

Author	Patients	Disease Duration (Years)	Remission Criteria	Joints Assessed	US Mode	Scale	OMERAT Pathology Definition
Yoshimi et al. (2018)	31	NA	DAS28	22 Joints: Wrists, MCP, PIPs	GS & PD	SQ	NA
Foltz et al. (2012) ¹¹	85	2.9	DAS	14 Joints: Wrists, MCPs, MTPs	GS & PD	SQ	Y
Saleem et al. (2012)	93	7	PJ, DAS28, SDAI, ACR, ACR/EULAR	6 Joints: Wrist, MCPs	GS & PD	SQ	Y
Spinella et al. (2012)	54	NA	DAS28, ACR	22 Joints: Wrists, MCPs, PIPs	GS & PD	SQ	Y
Naredo et al. (2013)	67	7.5	PJ, DAS28, SDAI	44, 12, and 7 Joint Sets	GS & PD	SQ	Y
Yoshimi et al. (2018)	31 (4 dropped, 5 relapsed)	BR=7.25, Non-BR=5.8	DAS28	22 Joints: MCPs, PIPs, Wrists	GS & PD	SQ	NA
Dale et al. (2014) ²²	11	5.1	DAS28, SDAI	14 Joints: Radio-carpal, MCPs, MTPs	PD	SQ	NA
Dale et al. (2016)	111	<1	DAS28-ESR	14 Joints: Radio-carpal, MCPs, MTPs	PD	SQ	NA
Haavardsholm et al. (2016) ⁷	238	<2	DAS, ACR/EULAR, SDAI	32 Joints: MCPs, Radio-carpal, Elbow, Knee, MTPs	PD	SQ	NA
Horton et al. (2016) ²⁵	217	0.5	DAS28, DAS44, ACR/EULAR 2011	26 Joints: Wrists, MCPs, Knees, Ankle, MTPs	GS & PD	SQ	Y
Bellis et al. (2016) ²³	427	7	DAS28, CDAI, SDAI, ACR/EULAR	10 Joint Set: PIPs + Tendons, 14 Joint Set: MCPs, Ulnar & Radial Styloid	GS & PD	SQ	Y
De Miguel et al. (2017) ²⁴	319	7.5	DAS28, CDAI, SDAI, ACR/EULAR	12 Joints: Elbow, Wrist, MCPs, Knee, Ankle	PD, GS	SQ	NA
Ten Cate et al. (2018) ⁵	194	4.6	DAS28	12 Joints: Radiocarpal, MTP, MCPs	GS, PD	SQ	NA
Matsuo et al. (2020) ¹⁵	293	6.8 (Group 1), 9.8 (Group 2)	DAS28 <2.3, SDAI, CDAI	28 Joints: MCP, MTPs, Wrist, Ankle, Lisfranc	GS, SMI	SQ	Y
Mortada et al. (2021) ¹⁸	140	23.70 ± 14.60	CDAI, DAS28	8 Joints: Wrists, MCPs, Knees, Clinically Affected Joints	GS, PD	U9 Scale	Y
Fragoulis et al. (2022) ¹⁶	521	9.97 ± 8.75	DAS28-CRP	40 Joints: MCPs, PIPs, Wrist, Knee, Ankle, MTPs	GS, PD	SQ	Y

Table 4: Ultrasound disease activity in asymptomatic patients

Study	B-mode Synovitis	PD Synovitis	Outcome
Brown et al. 2008 ¹²	38%	15%	PD significantly associated with progressive structural damage over one year (OR 8.77 [95% CI 1.54, 49.89] $P = 0.014$).
Brown et al. 2006 ³	73.30%	43.30%	NA
Wakefield et al. 2007 ²⁰	48%	22%	8 weeks after infliximab infusion: GS = 35%, PD = 6.6%.
Saleem et al. 2009 ¹³	DMARD Group Remission: 82% TNF + DMARD Remission: 88%	43%	NA

PJ: Physicians judgment; DAS: Disease activity score; DAS28: Disease activity in 28 joints; ACR: American college of rheumatology; BR=Boolean remissionACR/EULAR: American college of rheumatology/European league against rheumatism; SDAI: Simplified disease activity index MTP:Metatarsophalangeal.MCP: Metacarpophalangeal joints; PIP: Proximal interphalangeal; GS: Grey Scale; Power Doppler: PD; SQ: Semi-quantitative scale; OMERACT: Outcome measures in rheumatology, SMI Superb microvascular imaging.

Ultrasound Disease Activity in Asymptomatic Joints of Patients in RA Remission

In five studies, ultrasound (US) assessment of asymptomatic joints in RA patients in remission revealed GS synovitis in 38% to 88% of cases^{2,3,10,13,20} and PD synovitis in 15% to 43% of cases^{2,3,10,13,20}

TNF: Tumor Necrosis Factor inhibitors, DMARD: Disease-Modifying Anti-Rheumatic Drugs,OR: Odds Ratio, PD: Power Doppler Ultrasound,GS: Grey Scale Ultrasound

Review of Ultrasound in Healthy Subjects: Two studies examined joints of healthy subjects, including patients from an osteoporosis clinic.⁸ Low-grade Power Doppler (PD) signals were identified at the wrist. Peluso et al.⁸ assessed 16 osteoporosis patients, finding synovial hypertrophy in 42% and 28% of joints, with PD activity in 12%. Across 672 joints, 11.3% displayed synovial hypertrophy, and 0.4% exhibited PD activity, mostly grade 1.

Predictors of Stable Remission: Three studies evaluated sustained remission in RA patients.^{9,4,16} Scirè et al.⁹ found negative PD signals predicted stable remission (>90%), defining remission as negative PD signals. Saleem et al.¹⁴ observed no link between PD signals and sustained remission after biologic discontinuation, with 35% of patients showing low PD activity. Another study suggested a

combined GS-SMI score as a remission predictor.¹⁵

Discussion

This review highlights the importance of PDUS in assessing RA remission. Ultrasound helps detect subclinical disease activity often missed by clinical scores, preventing premature treatment tapering and potential disease flare-ups. Early detection of inflammation allows for timely treatment adjustments, reducing the risk of joint damage.

Standardization of Ultrasound Protocols

Standardizing ultrasound protocols is essential for consistent RA management. Although some argue small joint sets (e.g., 7 joints) may miss inflammation compared to larger sets, studies show strong correlations between reduced joint counts and overall disease activity, with a reduced count being effective for RA assessments.⁶ The OMERACT-EULAR initiative supports using 7- and 12-joint sets, with MCP and wrist joints being prioritized for ultrasound assessments.⁶

Feasibility and Practicality of Ultrasound Assessments: Assessing a larger number of joints provides valuable insights but may not always be practical. Prioritizing MCP and wrist joints, along with previously inflamed joints, can improve remission assessments while reducing time and cost.

Ultrasound Modalities for Remission Assessment: PDUS is more sensitive than GS in detecting synovitis and predicting flares but requires expertise. GS findings, common in healthy joints, may be less relevant for RA remission.⁸

Correlation with Clinical Measures: Subclinical synovitis, especially PD signals, correlates with increased flare risk, unlike GS hypertrophy. Baseline PD activity predicts joint damage.^{4,8,9,15,23,27}

Treating Asymptomatic Synovitis: GS synovitis occurs in 38%-88% and PD in 15%-43% of asymptomatic joints.^{2,3,10,13,20} Since PD predicts joint

damage, early intervention may prevent flares, but guidelines are needed.

Limitations of the Reviewed Studies: The reviewed studies have limitations, including lack of standardized protocols, operator dependency, and varying sample sizes. Short-term outcomes were the focus, emphasizing the need for more extensive longitudinal studies to understand the long-term effects of routine ultrasound use.

Conclusion

Integrating ultrasound, especially PDUS, into routine RA assessments is vital for detecting subclinical synovitis and improving disease management. Although ultrasound offers promising benefits, standardizing protocols and further research are needed to optimize its clinical use. Collaborative efforts are essential to enhance the understanding and implementation of ultrasound in RA care.

Ethical Approval: The IRB/EC approved this study via letter no null dated December 21, 2023.

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Authors' Contribution

MA, NRR: Conception

MM, FAK: Design of the work

IK, MF: Data acquisition, analysis, or interpretation

MM, FAK, IK, MF: Draft the work

MA, NRR: Review critically for important intellectual content

All authors approve the version to be published

All authors agree to be accountable for all aspects of the work

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