

**STATE OF THE ART: CLINICAL, LAB AND
IMAGING IN THE TREATMENT OF PATIENTS
WITH RHEUMATOID ARTHRITIS**

**HOW DO WE ASSESS AND FOLLOW DISEASE
ACTIVITY IN RA?**

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DISCLOSURES

- None

TREATING RHEUMATOID ARTHRITIS

- Significant changes in the past decade
- Treat-to-target strategies have improved outcomes
- Clinicians are striving to utilize precise measurements to track disease activity in hopes of achieving the best possible clinical outcome

BEST PRACTICES IN THE TREATMENT OF EARLY RA

**Establish the diagnosis of RA
early in the course of the disease**

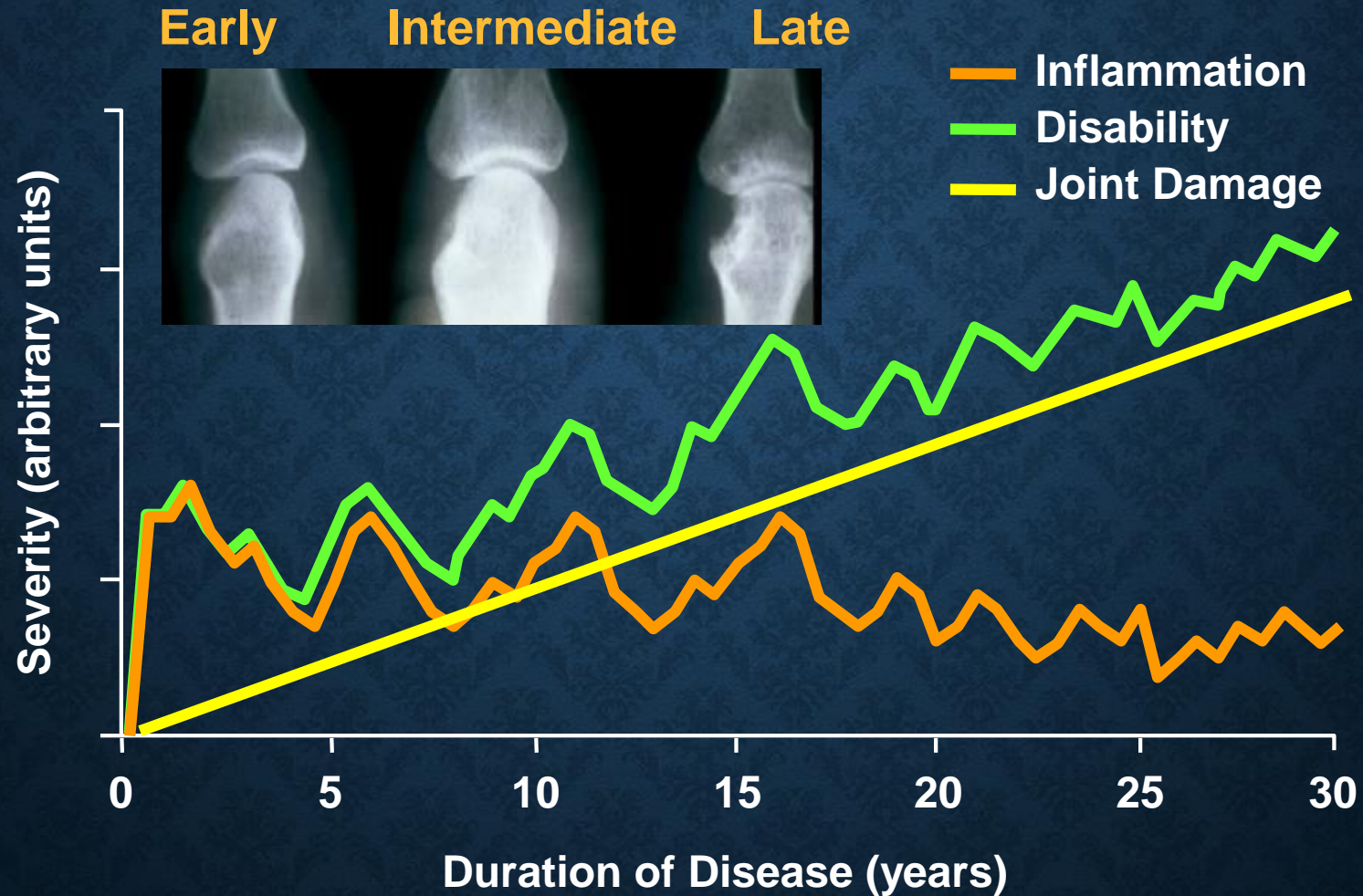
- RA is a persistent and progressive disease that can lead to functional decline, disability, deformity, poor quality of life, and shortened life expectancy
- Profile the patient to “stratify” the disease and establish a prognosis
 - Mild, moderate, or severe disease
 - Aggressive/progressive vs indolent disease

BEST PRACTICES IN THE TREATMENT OF EARLY RA

Treat RA early and vigorously

- Define a new target for therapy
 - Use the most optimal therapy first to maintain low or no disease activity – “zero tolerance for synovitis”
 - Institute tight disease control with the most effective combination of therapeutic agents
 - Prevent or postpone development of the hallmarks of established disease, disability, and comorbidities that reduce life span

THE PROGRESSION OF RA



Graph: Adapted from Kirwan JR. *J Rheumatol.* 2001;28:881–886.
Photo: Copyright © American College of Rheumatology.

OPTIMAL “WINDOW OF OPPORTUNITY” FOR TREATING RA

- **Radiographic progression occurs early and continues over the lifetime of a patient¹⁻³**
- **Erosions can be detected by MRI within 4 months of RA onset**
- **70% of patients have radiographic damage within the first 3 years after onset of symptoms¹**
- **The rate of progression is significantly more rapid in the first year than in the second and third years**

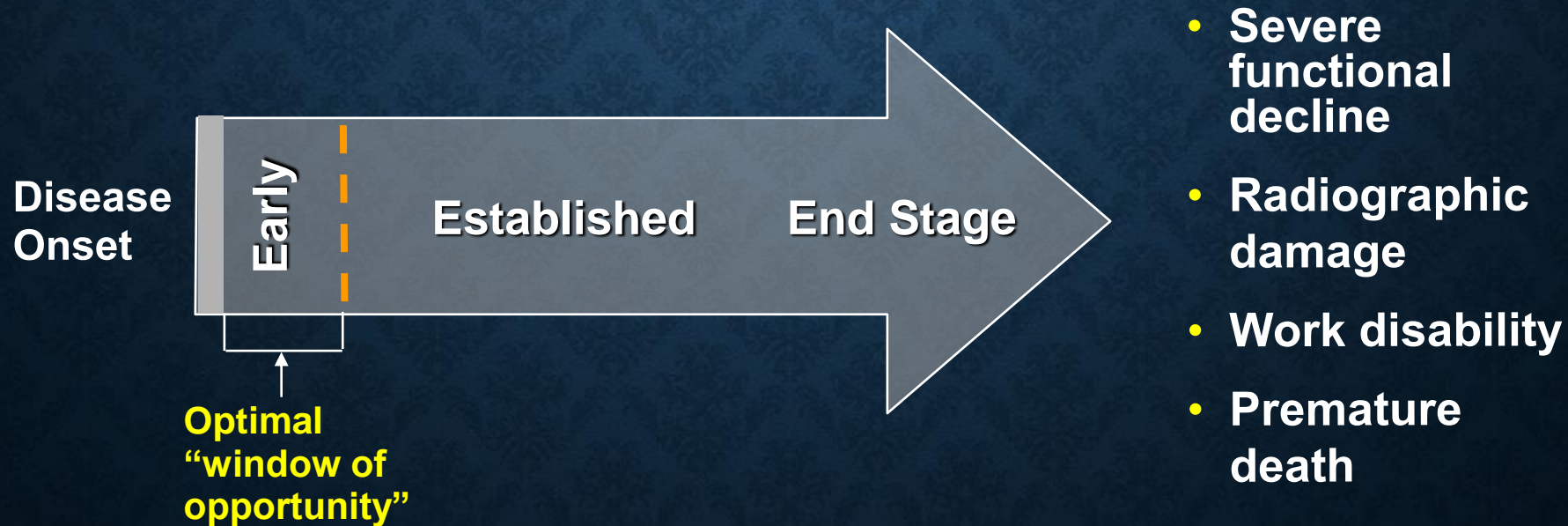
1. van der Heijde DM, et al. *J Rheumatol*. 1995;22:1792–1796.

2. O’Dell JR. *Arthritis Rheum*. 2002;46:283–285. Editorial.

3. Landewe RBM, et al. *Arthritis Rheum*. 2002;46:347–356.

“WINDOW OF OPPORTUNITY”

- Therapeutic “window of opportunity” during the first year after the onset of RA, offers the greatest opportunity for achieving optimal short- and long-term outcomes
- Aggressive treatment and tight control (ie, frequent monitoring, and goal-oriented changes in treatment strategies) need to be applied during the “window of opportunity”



TREAT TO TARGET STRATEGY

Rheumatoid Arthritis

TREAT TO TARGET

- Based on a shared decision between patient and physician
- The primary goal is to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, normalization of function, and social participation
- Eradication of inflammation is the most important way to achieve these goals
- Measuring disease activity and adjusting therapy accordingly optimizes outcomes

TREAT TO TARGET

- The primary target should be a state of clinical remission.
 - low disease activity is an acceptable alternative goal (particularly in long-standing disease)
- Until target is reached, therapy should be adjusted at least every 3 to 6 months
- **Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity**
 - Use validated composite measures of disease activity
- The desired treatment target should be maintained throughout the remaining course of the disease

ASSESSMENT OF DISEASE ACTIVITY IN RA

- How do we determine if we have tight disease control in RA?
 - Clinical
 - Laboratory
 - Imaging

CLINICAL

- Physical exam
- Disease activity measures
 - Physician and/or patient reported

PHYSICAL EXAM IN RA

- Careful palpation of joints
- Symmetric joint swelling
- Early disease – can be asymmetric and should not preclude the diagnosis of RA



American College of Rheumatology (ACR) Clinical Slide Collection 1997

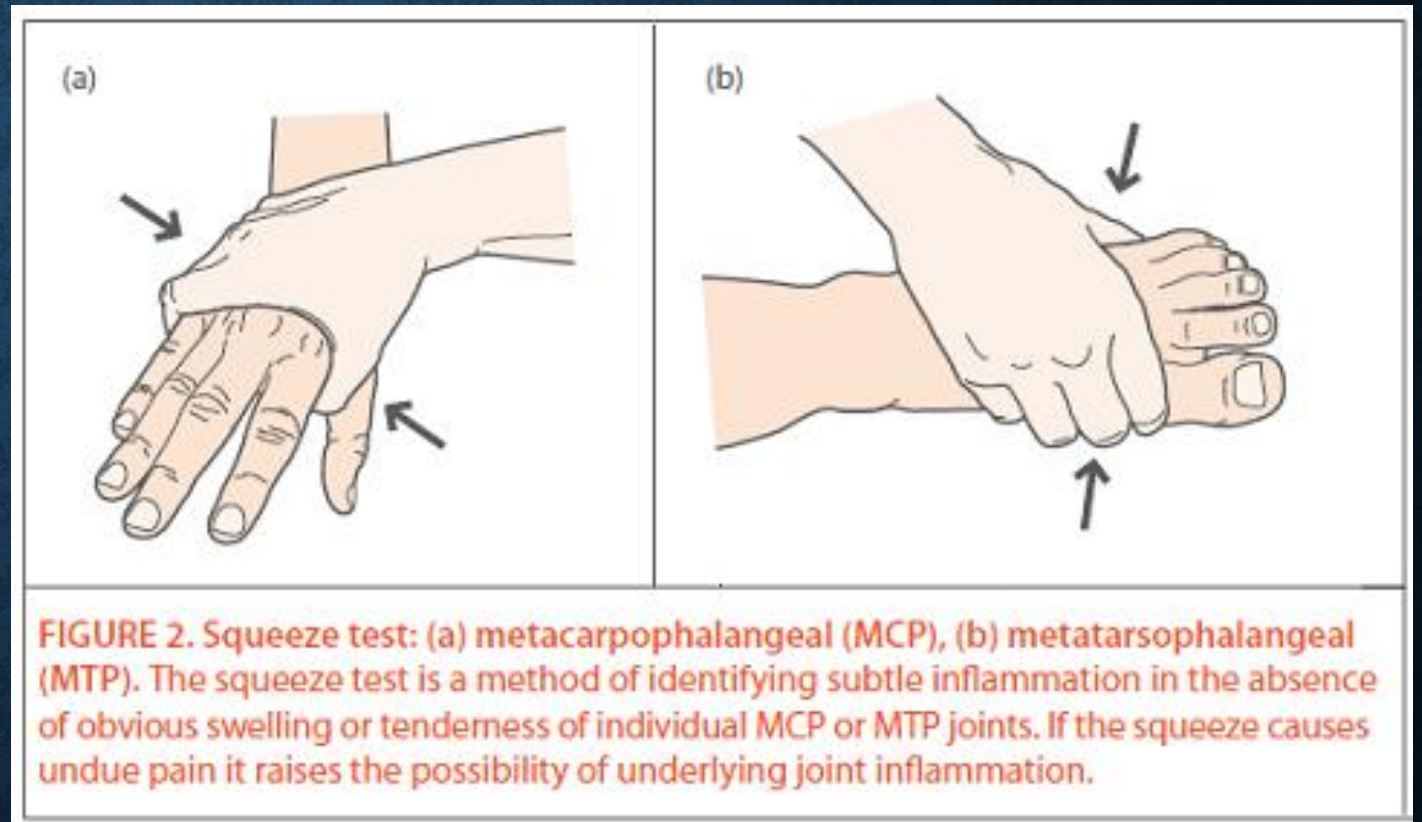
PHYSICAL EXAM IN RA

- Swelling/synovitis - doughy or spongy in RA in contrast to firm knobby enlargement in OA



PHYSICAL EXAM IN RA

- Pain on passive motion indicating joint inflammation
- Squeezing across the MCPs and MTPs
- Joints may feel warm to the touch



DISEASE ACTIVITY MEASURES IN RA

- 2012 ACR recommendations
 - Patient Activity Scale (PAS)
 - Patient Activity Scale-II (PAS-II)
 - Routine Assessment of Patient Index DATA (RAPID-3)
 - Clinical Disease Activity Index (CDAI)
 - Simplified Disease Activity Index (SDAI)
 - Disease Activity Score with 28-joint count (DAS28)

DISEASE ACTIVITY MEASURES IN RA

- Patient-reported assessments
 - PAS, PAS-II, RAPID-3
- Composite physician and patient assessment
 - CDAI
- Composite measures with laboratory acute-phase reactants
 - SDAI, DAS28

DISEASE ACTIVITY MEASURES IN RA

- Other measures are often used:
 - Health Assessment Questionnaire (HAQ): assesses functional measures/limitations
 - Short-Form 36 (SF 36): measures quality of life are often used
- Patient reported measures have limitations, however patients perspective is critical in overall assessment
- Use of these measures varies widely among rheumatologists
 - Physician preference/experience, ease of completion for physician/patient, and need for labs

Joint Scores

Tender:

Swollen:

To enter joint scores, I prefer to:

Use Mannequin

Type totals

Additional Measures

ESR: mm/hr

CRP: mg/l

Patient Global Health: mm



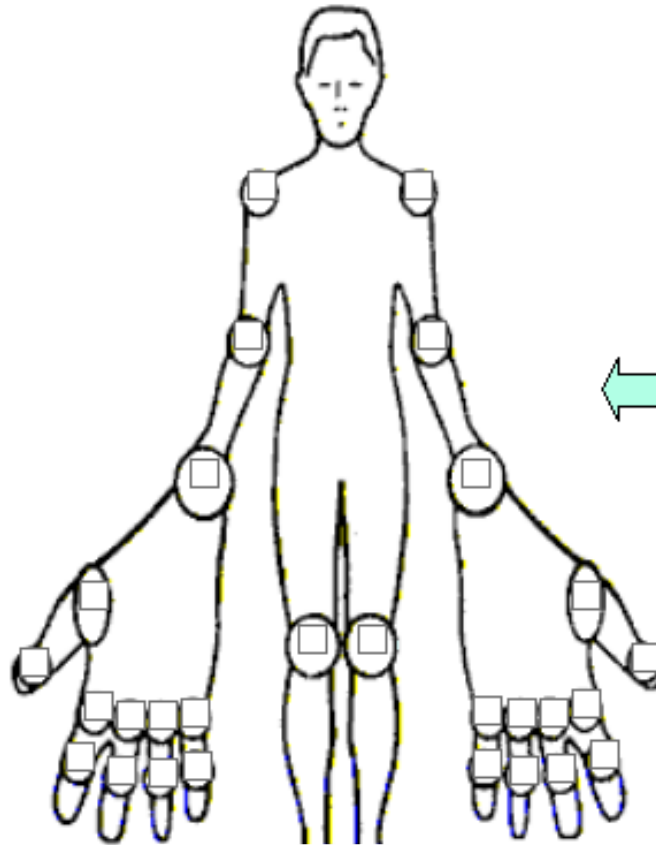
0 - Best

Worst - 100

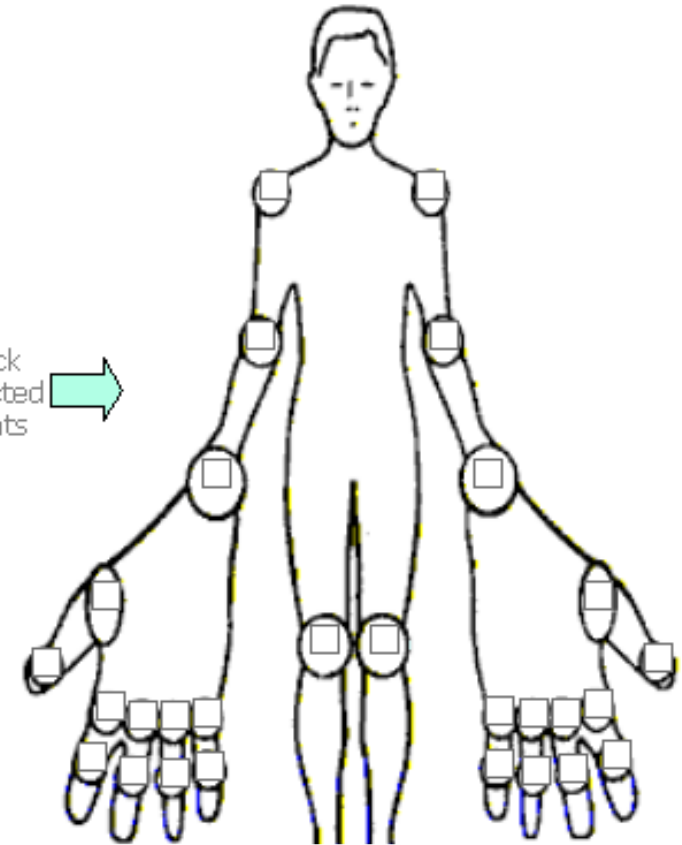
DAS28

Calculate

Tender Joints



Swollen Joints



Click affected joints

DAS28	DISEASE ACTIVITY
>5.1	HIGH
<3.2	LOW
<2.6	REMISSION

COMPOSITE MEASUR

- SDAI
 - 28 tender and swollen joint count
 - Patient and physician global assessments
 - CRP
 - Resembles CDAI but adds CRP

Simple Disease Activity Index (SDAI)

Joint	Left		Right	
	Tender	Swollen	Tender	Swollen
Shoulder				
Elbow				
Wrist				
MCP 1				
MCP 2				
MCP 3				
MCP 4				
MCP 5				
PIP 1				
PIP 2				
PIP 3				
PIP 4				
PIP 5				
Knee				
Total	Tender:		Swollen:	



Patient Global Assessment of Disease Activity

Considering all the ways your arthritis affects you, rate how well you are doing on the following scale:

Very Well 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 Poor

Your Name _____ Date of Birth _____ Today's Date _____

Provider Global Assessment of Disease Activity

Very Well 0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10 Poor

How to Score the SDAI

Variable	Range	Value
Tender joint score	(0-28)	
Swollen joint score	(0-28)	
Patient global score	(0-10)	
Provider global score	(0-10)	
C-reactive protein (mg/dL)	(0-10)	
Add the above values to calculate the SDAI score	(0-86)	

SDAI Score Interpretation	
0.0 - 3.3	Remission
3.4 - 11.0	Low Activity
11.1 - 26.0	Moderate Activity
26.1 - 86.0	High Activity

LABORATORY

- **Serum Biomarkers**

- Important to know RF/CCP status at baseline
 - Prognostic indicator, can predict more severe/erosive disease
 - Not routinely followed as measure of disease activity
- 14-3-3n (eta) protein
 - Like RF and CCP, prognostic indicator for erosive disease (also erosive PsA)
 - No role in monitoring disease activity

LABORATORY

- **Acute phase reactants (ESR and CRP)**
 - Varying opinions as to which is best in monitoring inflammatory arthritis
 - CRP falls more quickly, normalizing 3-7 days after resolution of tissue injury
 - ESR can take weeks to normalize
 - Many factors can falsely elevate both, particularly ESR
 - CRP changes minimally with age whereas ESR rises

LABORATORY

- **Multiple Biomarkers of Disease Activity (MBDA)**

- Commercial test (VECTRA-DA)
- Measure of 12 serum biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, YKL-40, MMP-1, MMP-3, leptin, resistin, SAA, CRP)
 - Algorithm generates a score measuring disease activity from 1-100
- Marker of disease activity and may predict erosive disease and risk of flare after stopping remittive therapy

VECTRA DA SCORE	LEVEL OF DISEASE ACTIVITY
45-100	HIGH
30-44	MODERATE
1-29	LOW

LABORATORY

- **Multiple Biomarkers of Disease Activity (MBDA) - (VECTRA-DA)**
 - Studies suggest correlation with DAS28-CRP as well as other disease activity measures
 - May be an important marker of disease activity in conjunction with physical exam and other biomarkers of disease activity
 - Limitations:
 - ? Discordance between test results and exam findings (high score and lack of clinical synovitis)
 - Cost
- Not a perfect test but ongoing research identifying its strengths and weaknesses

ROLE OF IMAGING IN ASSESSING RA ACTIVITY

- Diagnosing disease
- Assessing disease severity
- Predicting rate of progression
- Monitoring disease progression
- Monitoring treatment response

IMAGING MODALITIES

- X-ray
- MRI
- Ultrasound
- CT

THE USE AND VALUE OF IMAGING TECHNOLOGIES IN RA

	Plain Radiographs	Ultrasound	Power Doppler Ultrasound	MRI	Computed Tomography
Diagnosis	+ / +++	+++	+	+++	+
Level of Inflammation	+	+++	+++	++	++
Presence and extent of synovitis	+ / -	+++	+	+++	+
Presence of tenosynovitis	-	+++	+	+++	+ / -
Presence and extent of erosions	+ / +++	+++	+	+++	++

1) Hoving JL, et al. *J Rheumatol*. 2004;31:663–675; 2) Backhaus M, et al. *Arthritis Rheum*. 1999;42:1232–1245; 3) Wakefield RJ, et al. *Arthritis Rheum*. 2003;48:285–288; 4) Terslev L, et al. *Arthritis Rheum*. 2003;48:2434–2441; 5) Ostergaard M, et al. *Best Pract Res Clin Rheum*. 2005;19:91–116.

X-RAY

- Conventional X-rays can be useful in the diagnosis of RA if erosions or periarticular osteopenia are present
- Little value for detecting synovitis, tenosynovitis, or subtle soft tissue inflammation.
- Primarily detect the later signs of disease activity in patients with RA



Modified Sharp Scores

Erosion scores

- 16 joints in each hand/wrist
- 6 joints in each forefoot
- Scale: 0–5
- Total score: 0–220

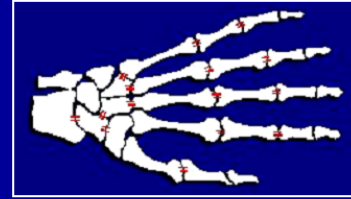
Joint space narrowing (JSN) scores

- 15 joints in each hand/wrist
- 5 joints in each forefoot
- Scale: 0–4
- Total score: 0–160

Modified total Sharp score

- Sum of erosion and JSN scores
- Total score: 0–380

Modified Sharp Scoring Method



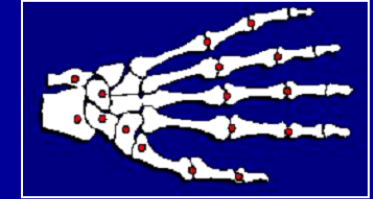
= Joint space narrowing (JSN)



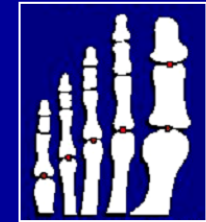
Joints evaluated

JSN Scores

- 0 = normal
- 1 = focal or doubtful
- 2 = > 50% of original space remaining
- 3 = < 50% of joint space remaining or subluxation
- 4 = bony ankylosis or luxation



• Erosions



Joints evaluated

Erosion Scores

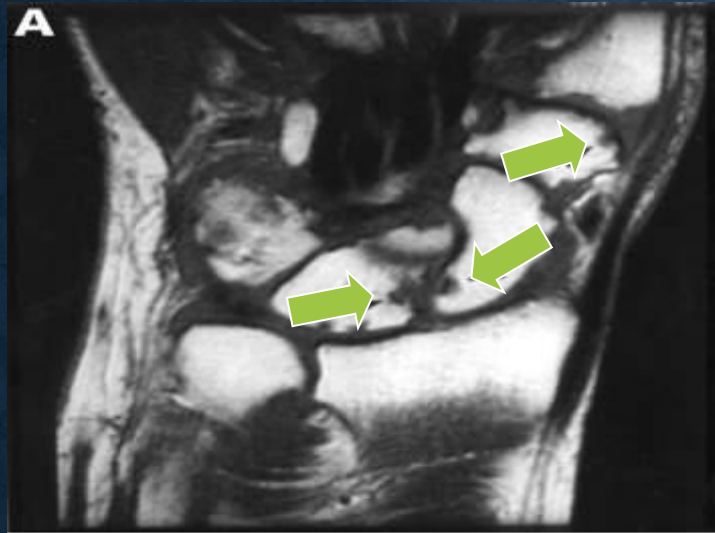
- 0 = normal
- 1 = discrete
- 2–4 = depending on surface area involved
- 5 = complete collapse

MRI AND ULTRASOUND

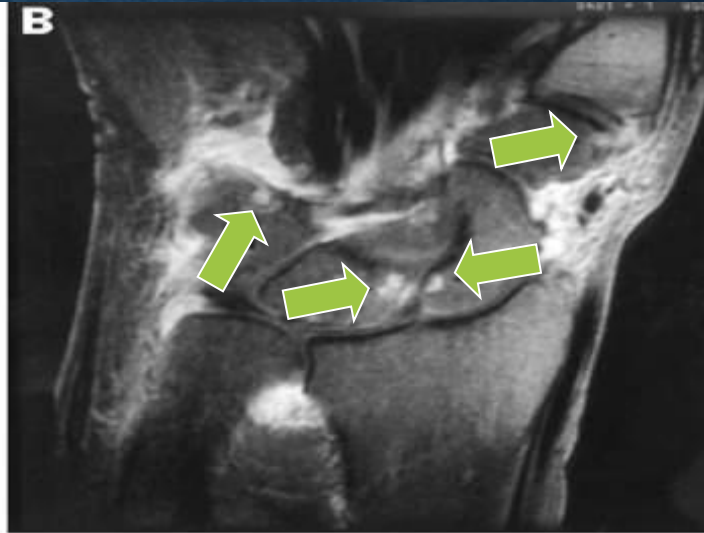
- Powerful tools for detecting erosive disease, joint and tendon sheath effusions, synovitis, and tenosynovitis.
- Highly sensitive for detecting early inflammatory and destructive changes in joints when X-ray may be normal.
- MRI is particularly sensitive to changes in inflammatory activity over time
 - Value in predicting the future rate of radiographic progression.

RA: Disconnect Between Plain Radiographs and MRI

T1-weighted
MRI
showing
erosions



T1-weighted
FS, PG MRI
showing
erosions
containing
enhancing
synovium



T1-weighted
PG MRI
showing
synovial
hypertrophy



Plain
radiograph
showing
focal
lucencies
but no
erosions



FS = fat suppressed; PG = post-gadolinium.
McQueen FM, et al. *Ann Rheum Dis*.1998;57:350–356.

MRI IS SUPERIOR TO X-RAY FOR DETECTING EROSIONS

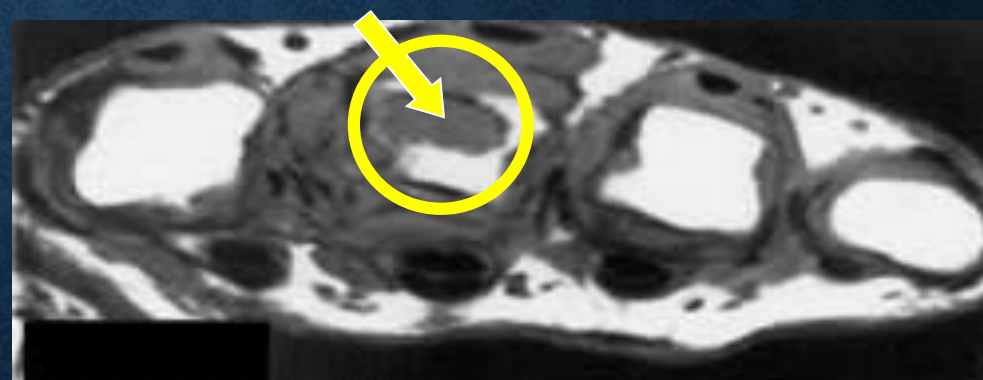
X-ray: No clear signs of erosions



MRI: Erosion detected



Coronal View

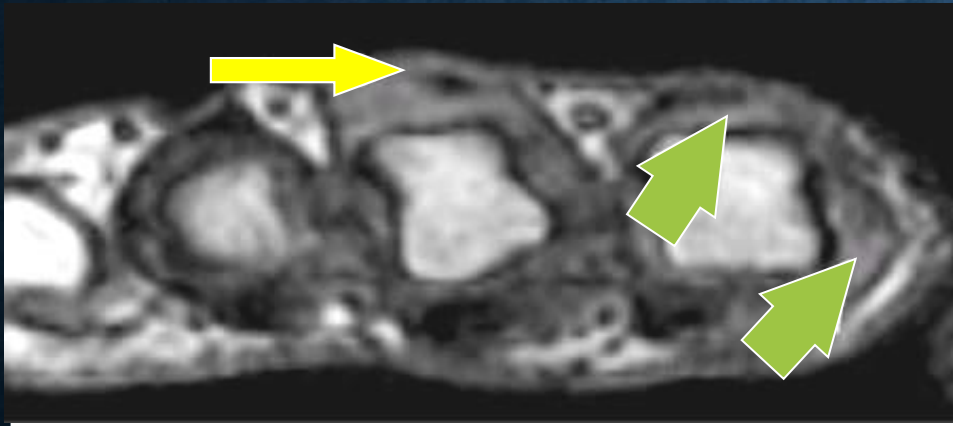


Axial View

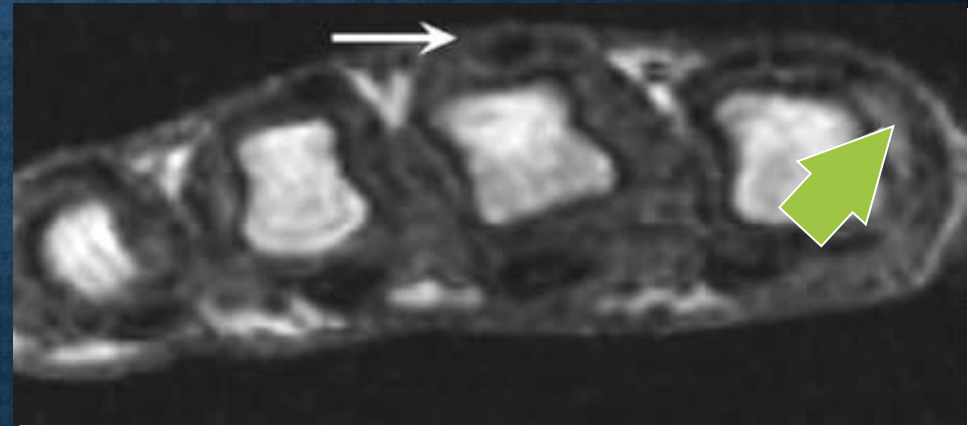
Views are of the second to fifth dominant-hand MCP joints.
Bird P, et al. *Arthritis Rheum.* 2004;50:1383–1389.

MRI WITH CONTRAST CAN TRACK DISEASE ACTIVITY IN PATIENTS WITH EARLY RA

Baseline



After 6 months of therapy with a
TNF antagonist



Synovitis indicated by green arrows. Tenosynovitis indicated by yellow arrow.
Images are axial T1-weighted gadolinium contrast-enhanced MRIs of the second to fifth MCP joints.
Ostergaard M, et al. *Best Pract Res Clin Rheum.* 2005;19:91–116.

MUSCULOSKELETAL ULTRASOUND

- A promising tool for the assessment of joint damage and disease activity in patients with RA.
- The sensitivity of PDUS for detecting synovial inflammatory activity is comparable to that of postcontrast MRI
 - May be a more cost effective way of monitoring disease activity
- ACR has issued recommendations for reasonable use of ultrasound in clinical practice
 - Reasonable to use MSKUS to monitor disease activity in RA and other inflammatory arthritides

MUSCULOSKELETAL ULTRASOUND

- Some studies suggest that US, particularly with power doppler (PDUS) has greater sensitivity at detecting synovitis compared with physical exam
 - However US is viewed as a complimentary procedure, not alternative to physical exam
- Significance of subclinical synovitis detected on US still being debated
 - Several studies suggest that synovitis detected in patients in remission may confer up to 12-fold risk of relapse
 - No clear benefit with Ultrasound remission vs clinical remission
 - RA being identified in its earliest phases (“preclinical RA”), US may be important prognostic indicator if subclinical synovitis is detected

MUSCULOSKELETAL ULTRASOUND

- **Limitations**

- Mostly small studies of US in monitoring disease activity, lack of long-term outcome data
- No clear standard for type and number of joints monitored
- Some disagreement on relevance of synovitis, particularly in early disease and remission
- Highly operator dependent and some variability among interpretation and grading of synovitis
- Variability among quality of US equipment

MUSCULOSKELETAL ULTRASOUND

- A number of protocols have been developed to monitor disease activity as well as to assess for remission
- They vary by joints examined (US7 vs US10 vs 28 joints, etc) and method for detecting and grading synovitis (grey-scale vs power doppler)
- PDUS correlates well with most disease activity measures (DAS28-CRP), clinical assessment of synovitis, laboratory markers of inflammation, MRI, and even histopathology

MUSCULOSKELETAL ULTRASOUND

- Grey scale US (GSUS)
 - Imaging of anatomical structures
 - Visualization of synovial hypertrophy and effusion
- Power Doppler US (PDUS)
 - Detects blood flow
 - Can detect increased microvascular blood flow as seen in active synovitis

ULTRASOUND GRADING OF SYNOVITIS

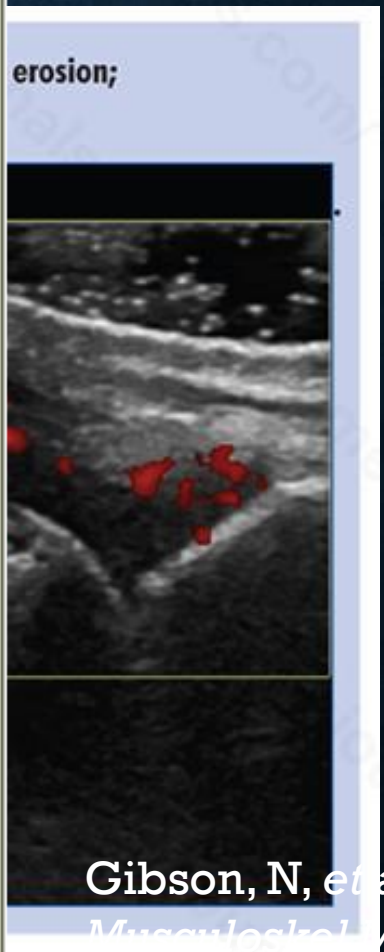
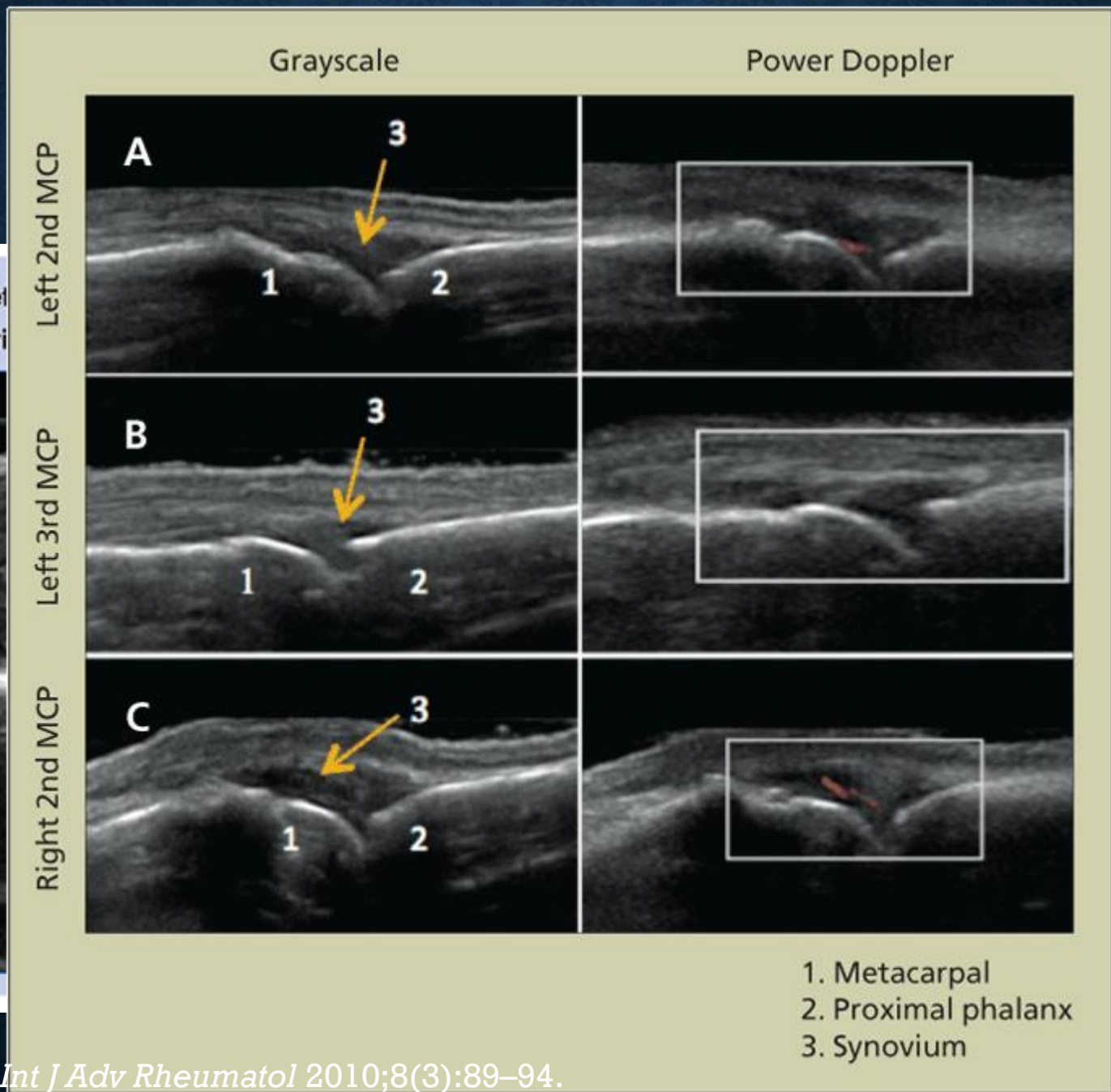
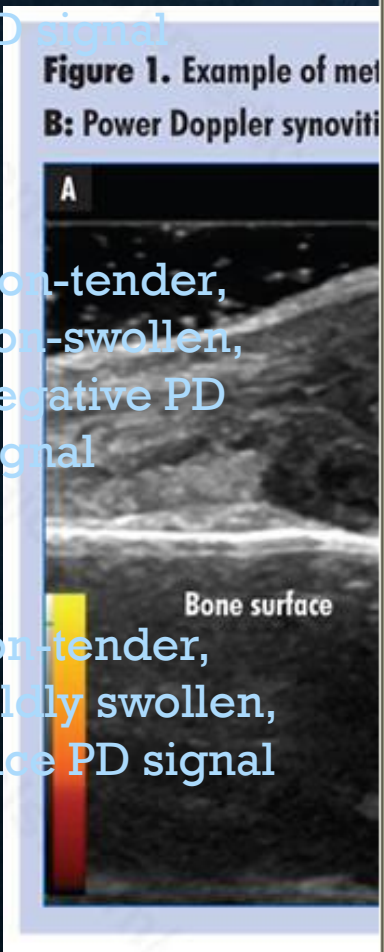
Table 1 Definitions of severity grades (0–3) for each elementary component and for the EULAR-OMERACT combined score

Synovitis	SH (greyscale)	Doppler (PD)	Combined score* (greyscale SH + PD)
Grade 0 (normal)	No SH independently of the presence of effusion	No Doppler signal	No SH and no PD signal
Grade 1 (minimal)	Minimal hypoechoic SH* up to the level of the horizontal line connecting bone surfaces between the metacarpal head and the proximal phalanx	Up to three single Doppler spots OR up to one confluent spot and two single spots OR up to two confluent spots	Grade 1 hypoechoic SH and ≤ grade 1 PD signal
Grade 2 (moderate)	Moderate hypoechoic SH [†] extending beyond joint line but with the upper surface concave (curved downwards) or hypertrophy extending beyond the joint line but with the upper surface flat	>Grade 1 but ≤50% Doppler signals in the total greyscale background	Grade 2 hypoechoic SH and ≤ grade 2 PD signal; or grade 1 SH and a grade 2 PD signal
Grade 3 (severe)	Severe hypoechoic SH [†] with or without effusion extending beyond the joint line but with the upper surface convex (curved upwards)	>Grade 2 (>50% of the total greyscale background)	Grade 3 hypoechoic SH and ≤ grade 3 PD signal; or grade 1 or 2 SH <u>and</u> a grade 3 PD signal

Tender, mildly swollen, trace PD signal

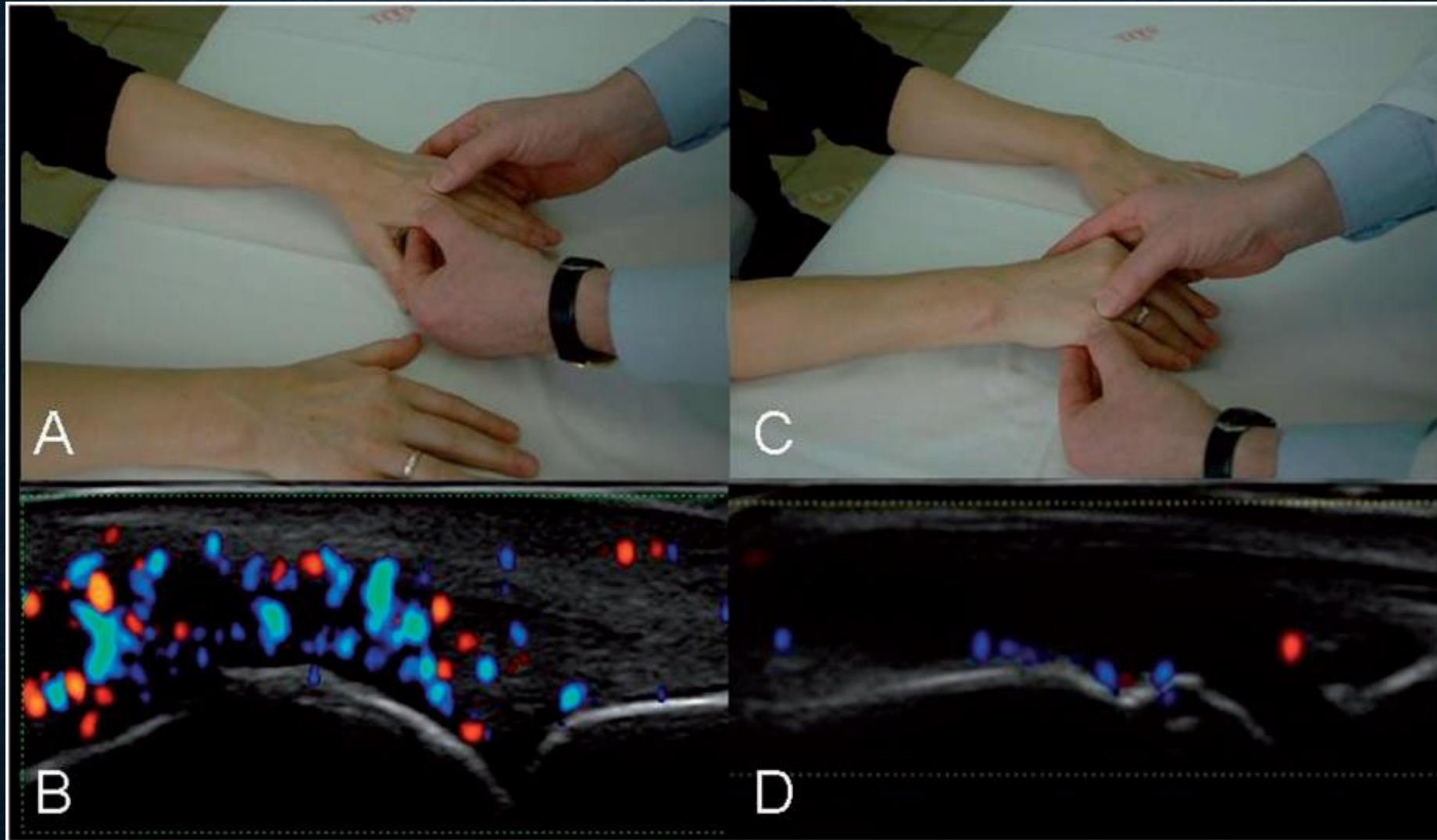
Non-tender, non-swollen, negative PD signal

Non-tender, mildly swollen, trace PD signal



erosion;

(A and B)
US of
clinically
swollen
MCP joint
(PDUS
grade 3
synovitis)



(C and D)
US of
clinically
non-
swollen
and non-
tender
MCP joint
(grade 2
synovitis)

ULTRASOUND OF MCP JOINTS IN THE SAME PATIENT WITH EARLY RA



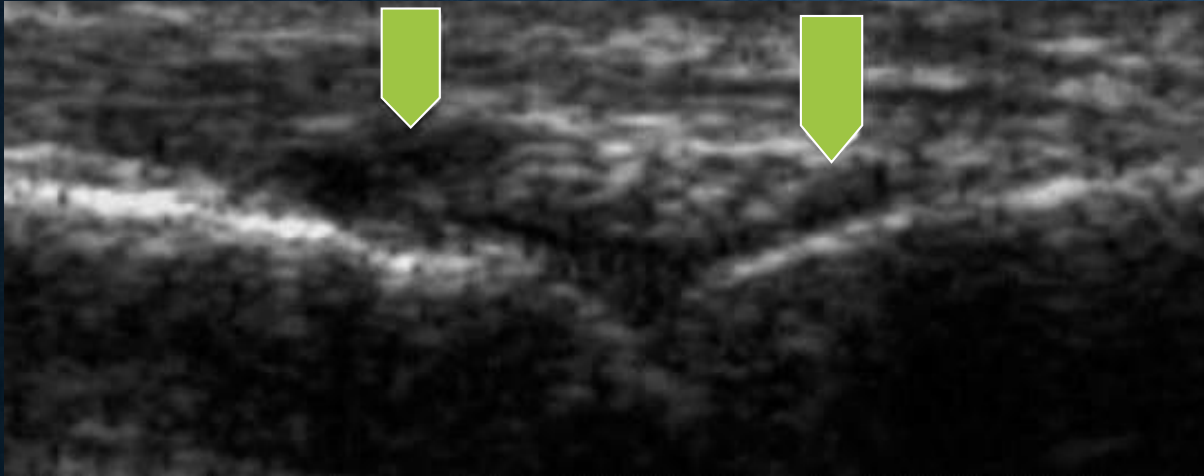
Longitudinal Plane

Transverse Plane



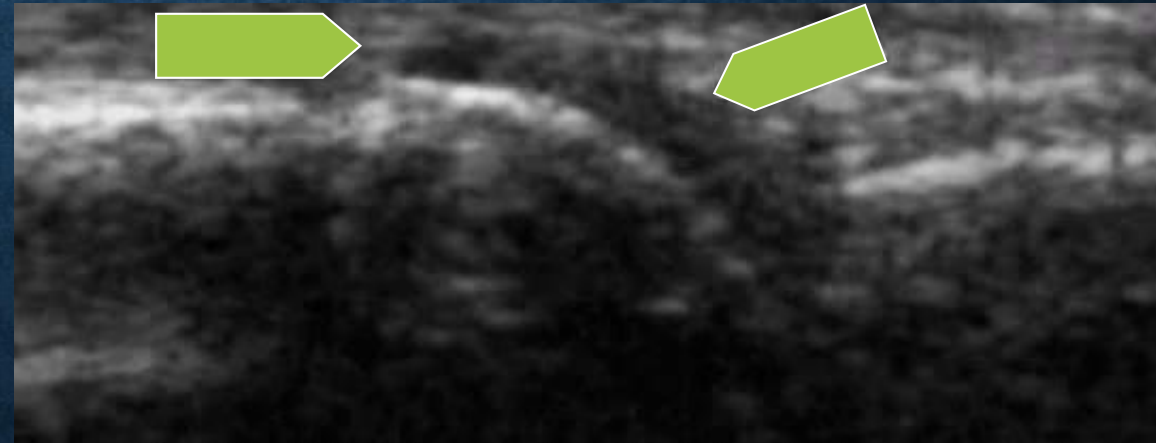
Erosions indicated by green arrows. Views are of the radial aspect of the second metacarpal head.
Ostergaard M, et al. *Best Pract Res Clin Rheum.* 2005;19:91–116.

ULTRASOUND CAN TRACK DISEASE ACTIVITY IN PATIENTS WITH EARLY RA



Baseline – intra-articular hypoechoogenic thickening of the synovium, indicating high-grade synovitis

After 6 months of therapy with a TNF antagonist – thickening is less pronounced, indicating mild synovitis



The patient was treated for 6 months with a TNF antagonist; images are of the second MCP joint in the longitudinal plane.

Ostergaard M, et al. *Best Pract Res Clin Rheum.* 2005;19:91–116.

MUSCULOSKELETAL ULTRASOUND

- In the hands of an experienced operator US can be an effective tool in monitoring disease activity and assessing for clinical and subclinical synovitis
- Also useful in distinguishing inflammatory from non-inflammatory arthritis when diagnosis is in question (i.e. RA with coexisting fibromyalgia)
- Live test, can quickly and easily examine multiple joints
 - Visualizing joints/inflammation helps to increase patients understanding of there diagnosis which enables them to participate more fully in their treatment plan

ASSESSMENT OF DISEASE ACTIVITY IN RA

- Currently we rely on composite measures of patient and physicians global assessment, and assessment of tender/swollen joints
- Laboratory testing (acute phase reactants and MBDA) are often used in conjunction
- Imaging, particularly musculoskeletal ultrasound is becoming more widely utilized to monitor disease activity
- Continued need for better and more reliable biomarkers to predict the onset of RA, make the diagnosis at an earlier stage, and determine those patients at highest risk for rapidly progressive and erosive disease
- Need for biomarkers that will help predict who will respond to certain drugs

ASSESSMENT OF DISEASE ACTIVITY IN RA

- A treat-to-target approach in the management of RA leads to better outcomes
- Important to define a treatment target up front
- Collecting data to assess and monitor disease activity is essential to this strategy
- Additionally moving forward physicians will be obligated to track such outcome Measures

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