

류마티스 관절염의 진단과 질병활성도의 측정

서울대학교 의과대학
이 은봉

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- Rheumatoid arthritis
 - Clinical features
 - Diagnosis
 - Disease activity score
- Summary



Clinical features

Rheumatoid arthritis

- Definition

- Chronic systemic inflammatory disease predominantly affecting diarthroidal joints and frequently a variety of organs

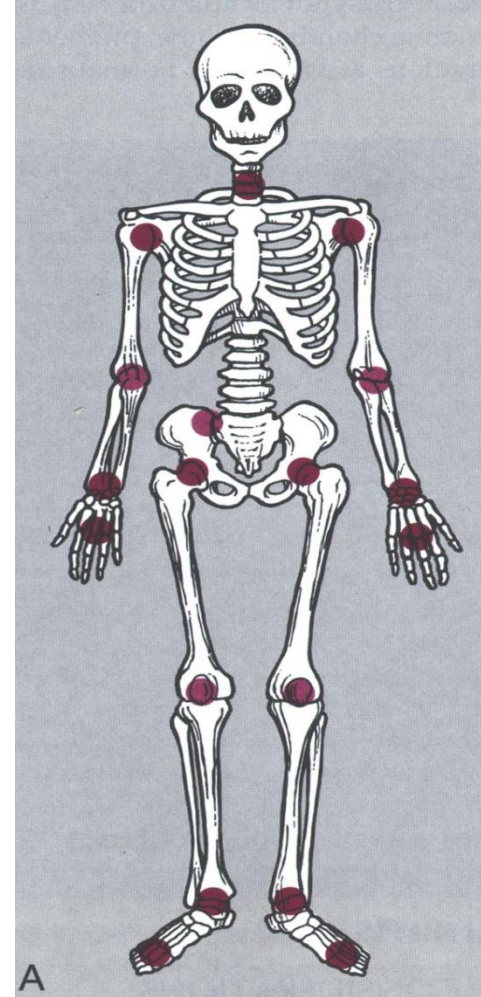
- Epidemiology

- Prevalence 0.5–1.0 %
- Peak incidence 4th–6th decades
- Women: men 2–3:1

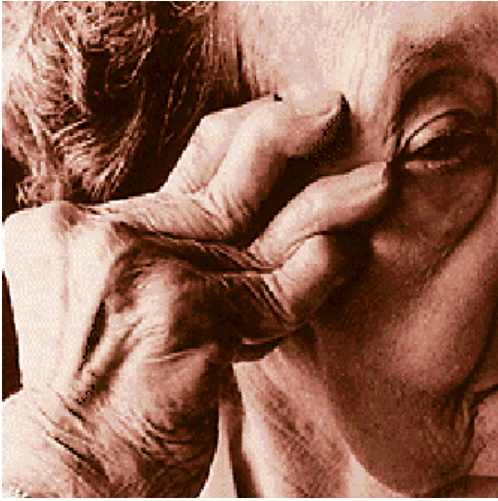


Articular manifestations

- Symmetric polyarthritis
 - PIP, MCP, wrist, elbow, shoulder, knee, ankle, MTP joints, TM joints
- Deformity
 - Swan neck deformities
 - Buttonhole deformities
 - Z-deformity
 - Piano-key deformity



Articular deformities



Swan-neck deformity



Boutonniere deformity

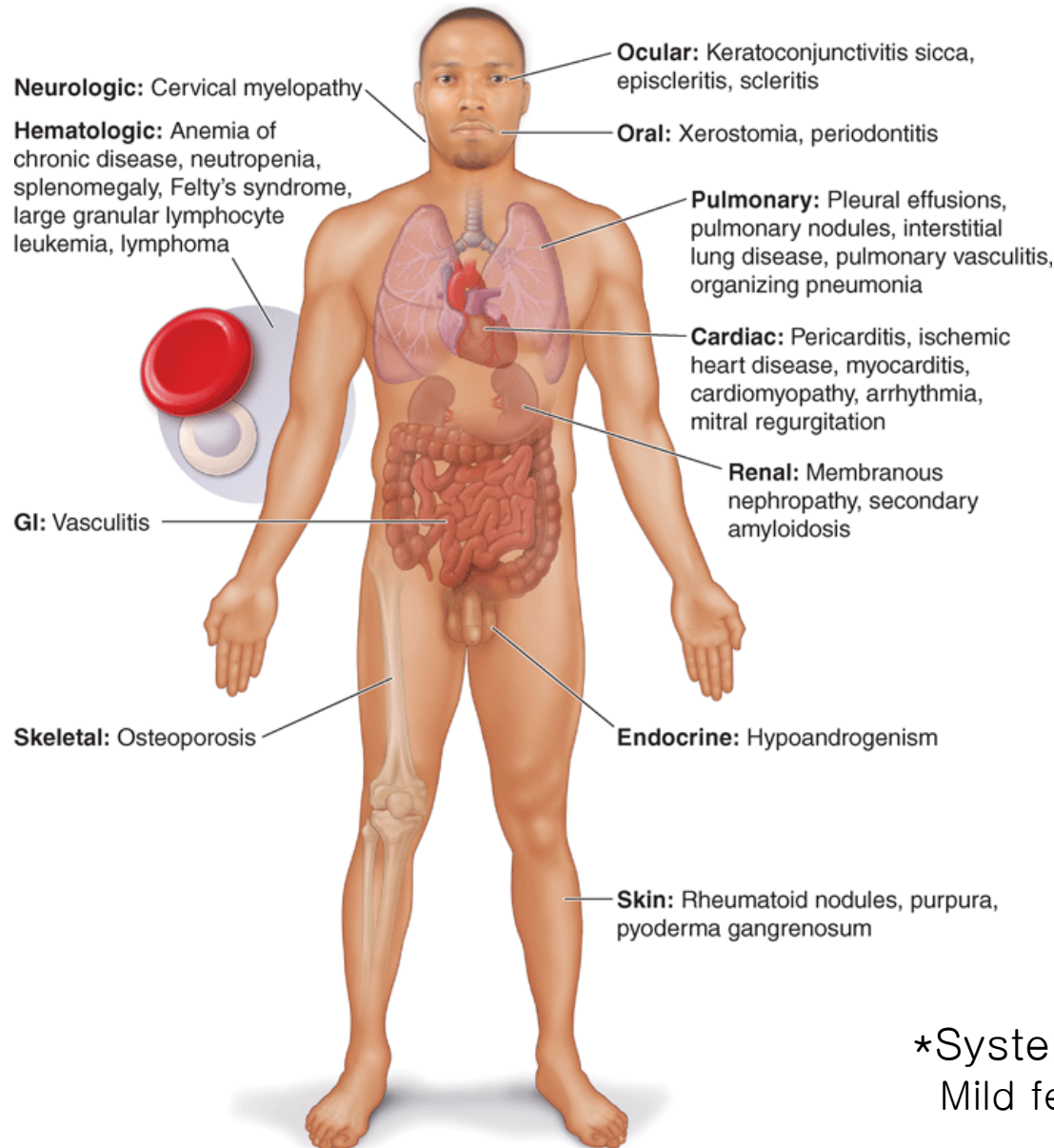


Piano-key sign



z-deformity

Extraarticular manifestations



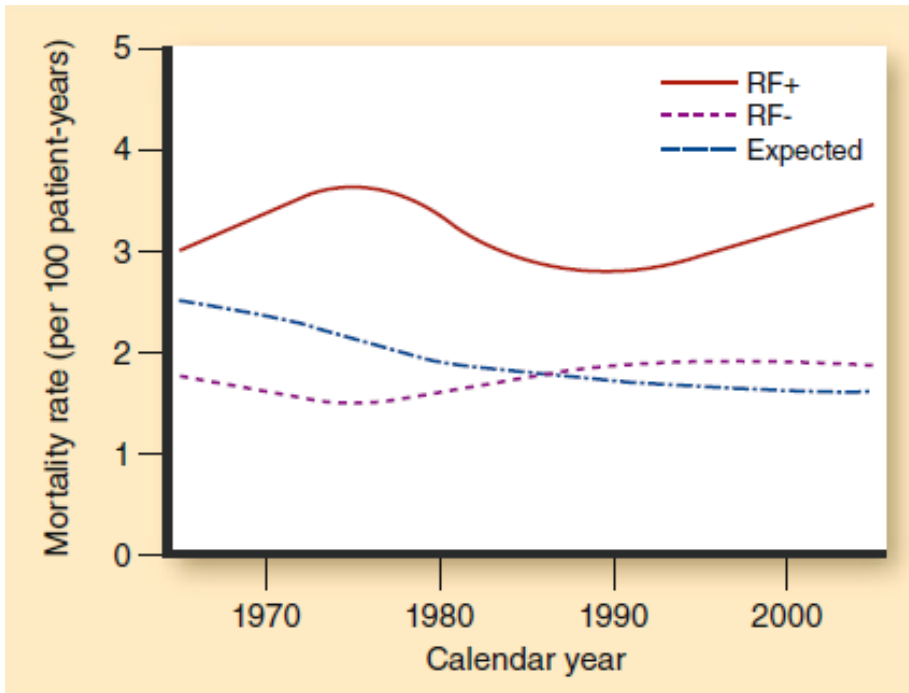
*Systemic manifestations
Mild fever, anorexia, weight loss

Laboratory features

- Blood
 - Rheumatoid factor, anti-CCP antibodies
- Joint imaging
 - Plain radiograph
 - Soft tissue swelling
 - Erosion
 - Joint space narrowing
 - Subluxation
 - Ankylosis
 - MRI
 - Bone marrow edema
 - Ultrasound

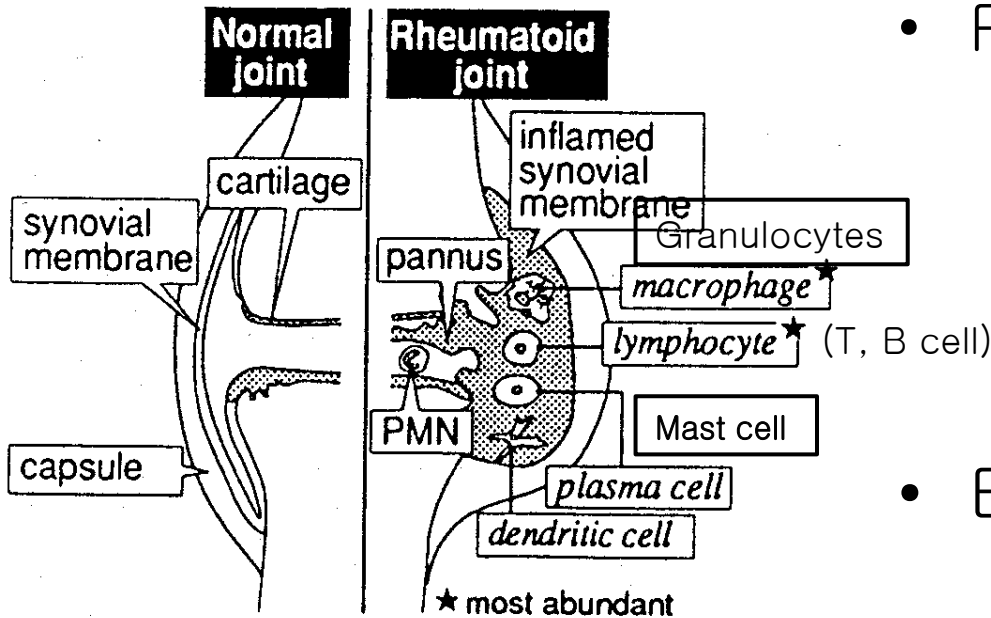


Clinical course



- Shortening of median life expectancy
 - 7 years in Men
 - 3 years in Women
- Risk factors for short survival
 - Systemic extraarticular involvement
 - Low functional capacity
 - Low socioeconomic status
 - Low education
 - Chronic prednisone use

Pathology



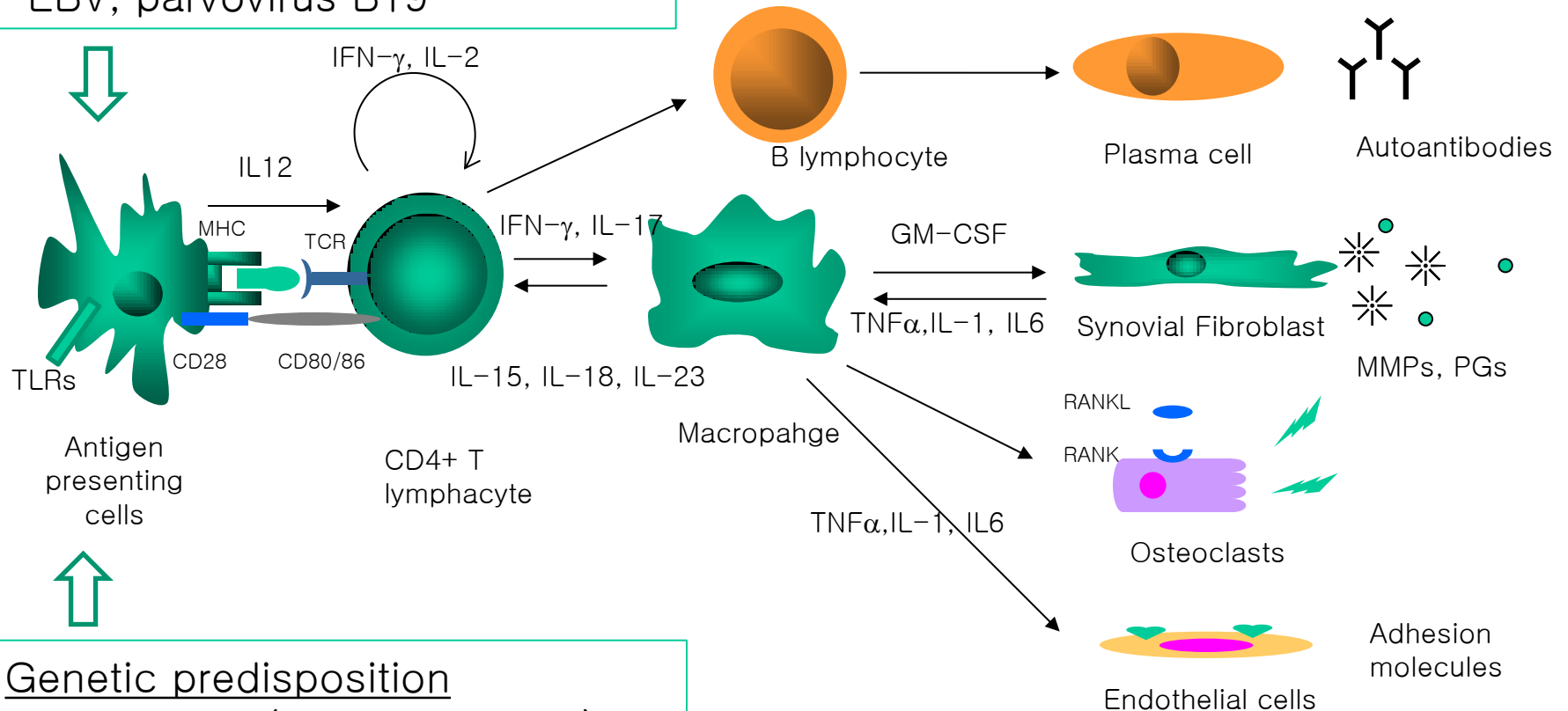
Pannus : A thickened cellular membrane of granulation-reactive fibrovascular tissue

- Pathology
 - Synovial inflammation
 - Synovial proliferation
 - Focal bone erosion
 - Thinning of articular cartilage (loss of proteoglycans)
- Bone loss in RA
 - Marginal erosion (osteoclast)
 - Periarticular osteopenia (Inflammation of the BM cavity)
 - Generalized osteoporosis

Pathogenesis

Environmental factors

- Smoking
- EBV, parvovirus B19



Genetic predisposition

- HLA-DRB1 (Shared epitope)
- PTPN22, PADI4

Diagnosis

ACR 1987 criteria

Criterion ($\geq 4/7$)	Definition
Morning stiffness	At least 1 hr
Arthritis of 3 or more joint area	PIP, MCP, wrist, elbow, knee, ankle, MTP joints
Arthritis of hand joints	Wrist, MCP, or PIP joints
Symmetric arthritis	PIP, MCP, MTP joints are acceptable without absolute symmetry
Rheumatoid nodules	Subcutaneous nodules observed by the physician
Serum rheumatoid factor	Detection by any method that is positive in $<5\%$ of normal controls
Radiologic changes	Erosions or unequivocal periarticular osteopenia

Revised criteria, 2010

Classification ($\geq 6/10$)	Score
A. Joint involvement 1 large joint* 2–10 large joints 1–3 small joints** 4–10 small joints >10 joints (at least 1 small joint)	0 1 2 3 5
B. Serology (at least 1 test) Negative RF and negative ACPA Low-positive RF or low-positive*** ACPA High-positive RF or high-positive ACPA	0 2 3
C. Acute-phase reactants (at least 1 test) Normal CRP and normal ESR Abnormal CRP or ESR	0 1
D. Duration of symptoms < 6 weeks ≥ 6 weeks	0 1

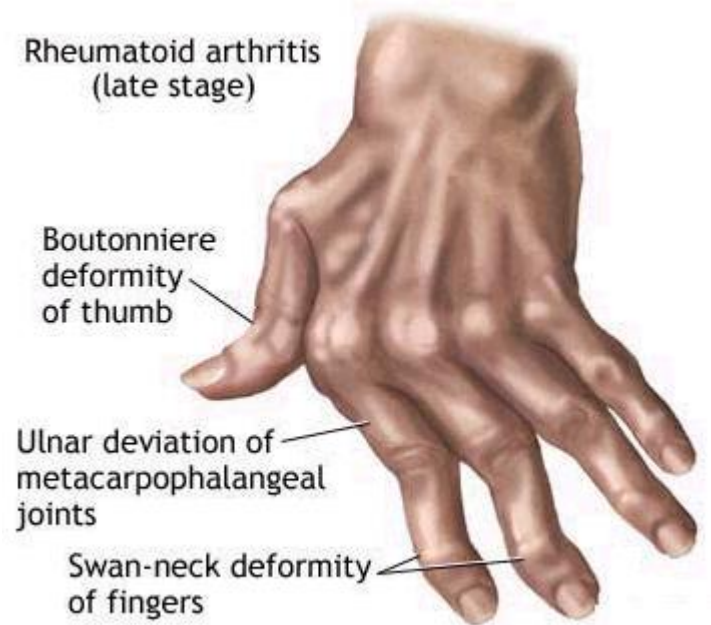
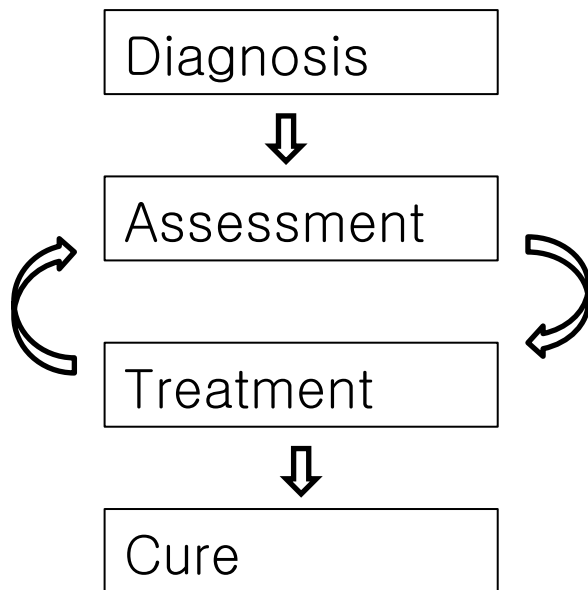
*Large joint (shoulders, elbows, hips, knees, and ankles)

** Small joint (MCP, PIP, 2–5MTP, thumb IP, wrists)

***Low positive: higher than ULN but less than 3 times of ULN

Disease activity

Clinical practice



Complexities of assessment

- There is no single “gold standard”
- Laboratory tests are limited
 - ESR is normal in >40% of patients with RA
- Formal joint counts have poor reliability
- Radiographs are rarely read quantitatively

Measurement tools

	Activity	Damage	Function
Joint count	Swelling Tenderness	Deformity	Pain on motion Limited motion
Laboratory data	ESR CRP		
Global measures			Physical assessment of global status Patient assessment of global status
Functional measures			Functional disability (HAQ) Short-form 36 Pain score
Radiographic measures		Joint space narrowing Erosion Malalignment	

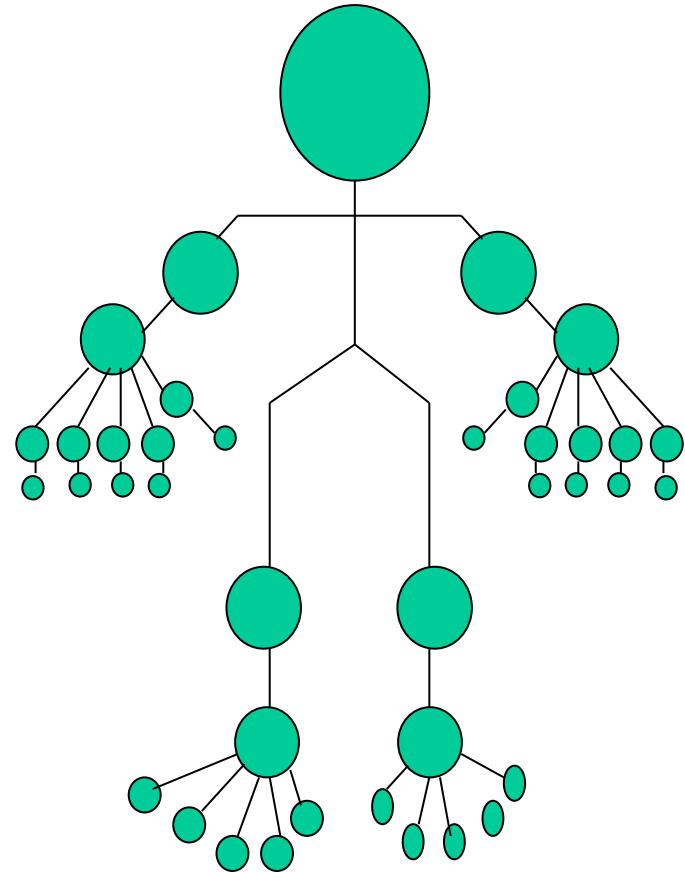
OMERACT core data set

(Outcome measures in Rheumatology)

- Number of swollen joints
- Number of tender joints
- Pain assessed by the patient
- Patient's global assessment of disease activity
- Physician's global assessment of disease activity
- Laboratory evaluation (ESR, CRP)
- Radiographic assessment for joint damage
- Self-administered functional assessment (e.g. Health assessment questionnaire)

Joint swelling and tenderness

- Joint swelling
0=no swelling
1=swelling
- Joint tenderness
0=no tenderness
1=tenderness



Articular index

	Joint counts
Ritchie index	53
ACR tender joint count	68
ACR swollen joint count	66
Thompson and Kirwan index	38
44 joint count	44
36 joint count	36
28 joint count	28

Pain



An unpleasant sensory and emotional experience associated with actual and potential tissue damage, or described in terms of such damage

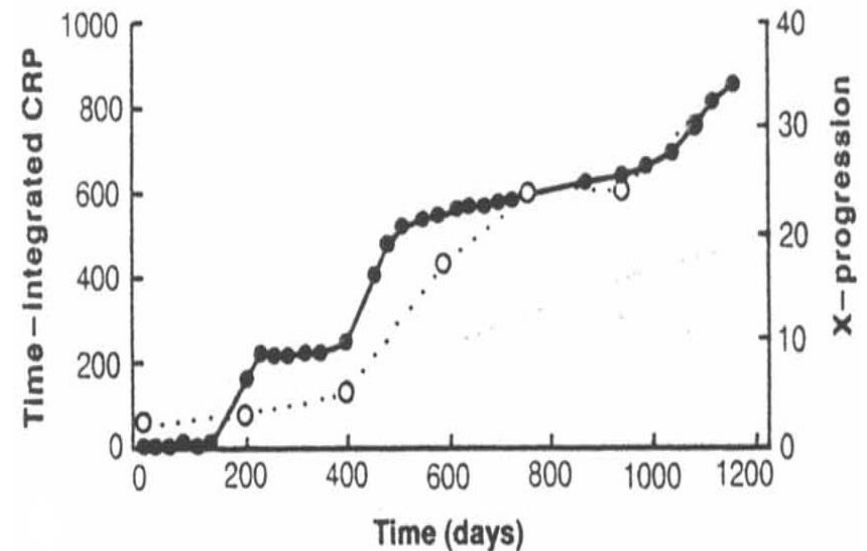
Global disease activity by the patient or physician

Considering all the ways your arthritis affects you,
mark “X” on the scale for how well you are doing.



Acute phase reactants

- Acute phase reactants
 - ESR, CRP
- Correlation with clinical disease activity
- Time integrated values
 - Correlation with radiologic progression



Health assessment questionnaire (HAQ)

- The first PRO (patient reported outcome)
- Dimensions
 - Disability, pain, medication effects, costs of care, mortality
- Classification
 - Short HAQ (HAQ-DI)
 - Disability, pain VAS, patient global VAS
 - Full HAQ

Example

HEALTH ASSESSMENT QUESTIONNAIRE-DI

Name_____ Date_____

Please check the response which best describes your usual abilities over the past week:

	<u>Without ANY</u> <u>Difficulty</u>	<u>With SOME</u> <u>Difficulty</u>	<u>With MUCH</u> <u>Difficulty</u>	<u>UNABLE</u> <u>To Do</u>	
Dressing & Grooming					
Are you able to:					
-Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____	Dressing_____
-Shampoo your hair?	_____	_____	_____	_____	
Arising					
Are you able to:					
-Stand up from a straight chair?	_____	_____	_____	_____	Rise _____
-Get in and out of bed?	_____	_____	_____	_____	
Eating					
Are you able to:					
-Cut your meat?	_____	_____	_____	_____	Eating_____
-Lift a full cup or glass to your mouth?	_____	_____	_____	_____	
-Open a new milk carton?	_____	_____	_____	_____	
Walking					
Are you able to:					
-Walk outdoors on flat ground?	_____	_____	_____	_____	Walking_____
-Climb up five steps?					

Please check any AIDS OR Devices that you usually use for any of these activities:

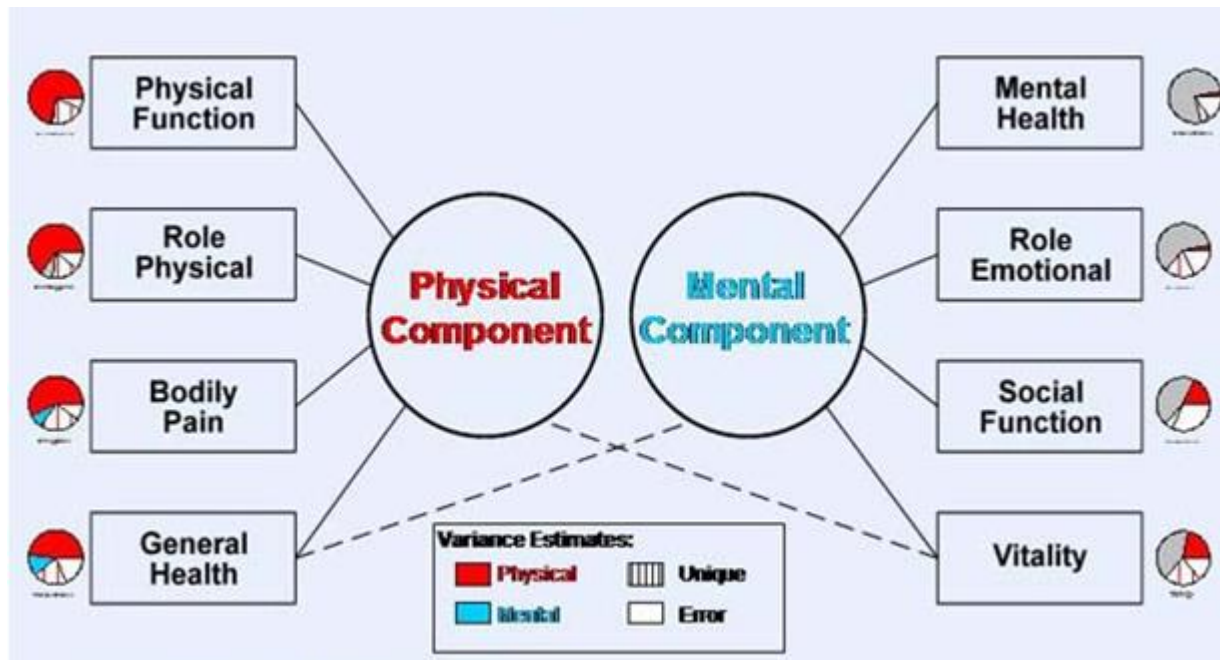
- | | |
|-------------------------------------|--|
| <input type="checkbox"/> Cane | <input type="checkbox"/> Devices used for dressing (button hook, |
| <input type="checkbox"/> Walker | zipper pull, long-handled shoe horn, etc.) |
| <input type="checkbox"/> Crutches | <input type="checkbox"/> Built up or special utensils |
| <input type="checkbox"/> Wheelchair | <input type="checkbox"/> Special or built up chair |
| | <input type="checkbox"/> Other (Specify: _____) |

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

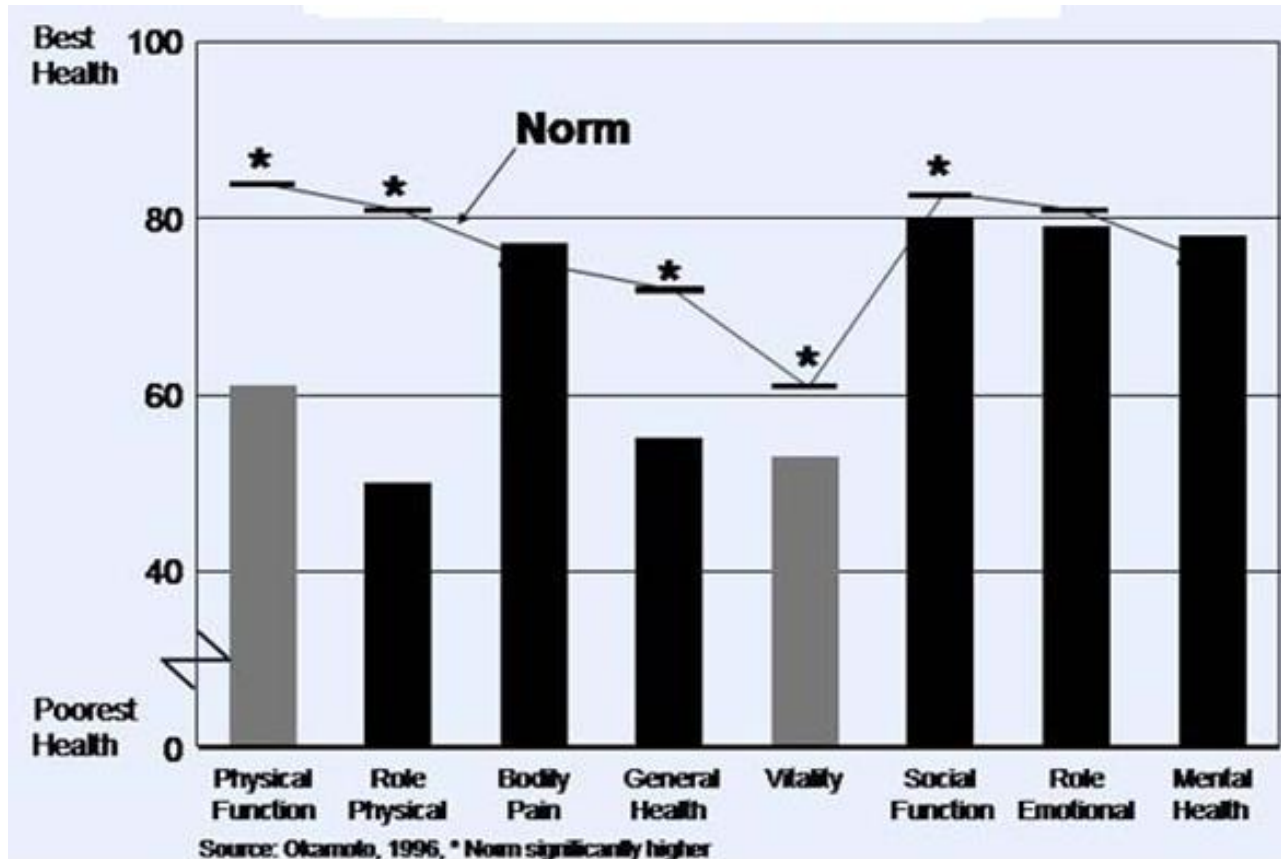
- | | |
|--|----------------------------------|
| <input type="checkbox"/> Dressing and Grooming | <input type="checkbox"/> Eating |
| <input type="checkbox"/> Arising | <input type="checkbox"/> Walking |

Short form 36 (SF-36)

- Patient reported outcome
- Assessment of overall health status (Quality of Life)



Interpretation of SF-36



Example

Short form 36

SF-36(tm) Health Survey

Instructions for completing the questionnaire: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

Patient Name: _____

SSN#: _____ Date: _____

Person helping to complete this form: _____

1. In general, would you say your health is:

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

2. Compared to one year ago, how would you rate your health in general now?

- ☐ Much better now than a year ago
- ☐ Somewhat better now than a year ago
- ☐ About the same as one year ago
- ☐ Somewhat worse now than one year ago
- ☐ Much worse now than one year ago

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

- ☐ Yes, limited a lot.
- ☐ Yes, limited a little.
- ☐ No, not limited at all.

b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?

- ☐ Yes, limited a lot.
- ☐ Yes, limited a little.
- ☐ No, not limited at all.

c. Lifting or carrying groceries.

- ☐ Yes, limited a lot.
- ☐ Yes, limited a little.
- ☐ No, not limited at all.

Composite index for
disease activity

American College of Rheumatology preliminary definition of improvement of rheumatoid arthritis

ACR20

- 20% improvement in tender joint count
- 20% improvement in swollen joint count
- 20% improvement in 3 of following 5
 - Patient assessed global disease activity
 - Physician assessed global disease activity
 - Patient pain assessment
 - Functional disability
 - Acute phase reactant (ESR or CRP)

*ACR20, 50, 70 response

Felson, Arthritis Rheum, 1995

Disease Activity Score (DAS)

- **Components**

- Ritchie articular index (26 articular index)
- Swollen joints (44 joints)
- ESR
- General health

- **DAS 4 (0–9.4)**

$$\begin{aligned} &= 0.53938 \times \sqrt{\text{Ritchie score}} \\ &+ 0.06465 \times (\text{number of swollen joints}) \\ &+ 0.330 \times \ln(\text{ESR}) \\ &+ 0.00722 \times (\text{general health}) \end{aligned}$$

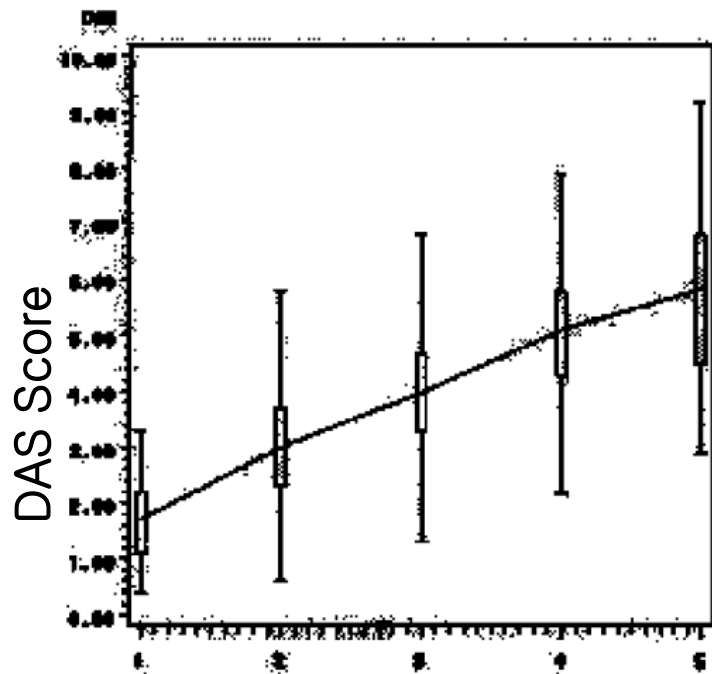
*DAS 3 is composed of Ritchie index, swollen joints, and ESR

Disease activity score

- More valid than single measures
- Continuous scale with Gaussian distribution
- Clinically interpretable
- Sensitive to small change

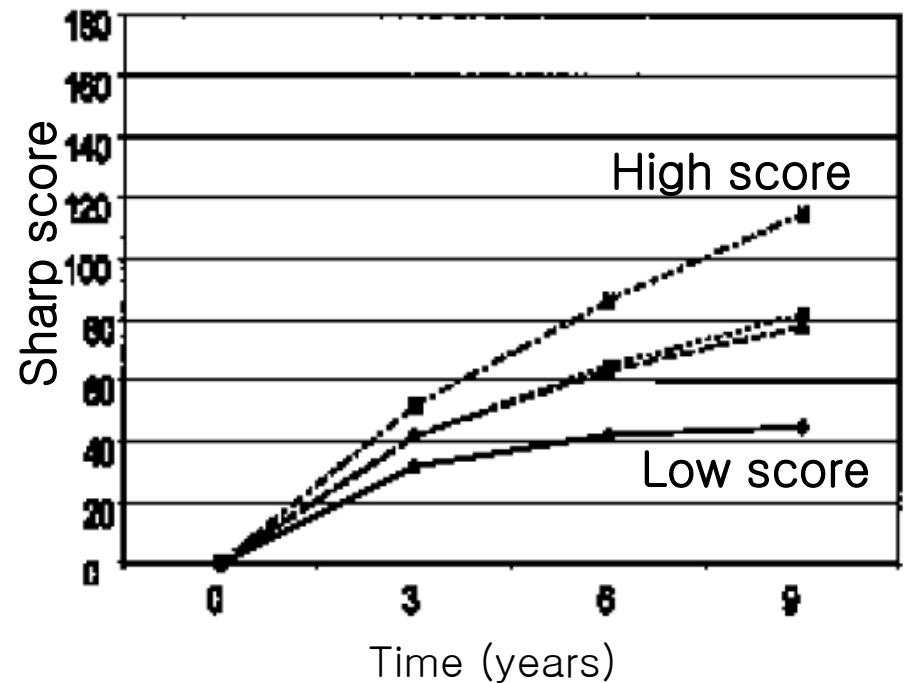
Advantage of DAS

Patient's assessment



Patient's global assessment

Radiographic progression



Van Ede Ae et al, Arthritis Rheum 2001
Welsing PMJ et al, Arthritis Rheum 2004

Modified DAS (DAS 28)

- **Components**

- Tender joint counts (28 TJC)
- Swollen joint counts (28 SJC)
- ESR (mm/h)**
- General health (0–100 mm)

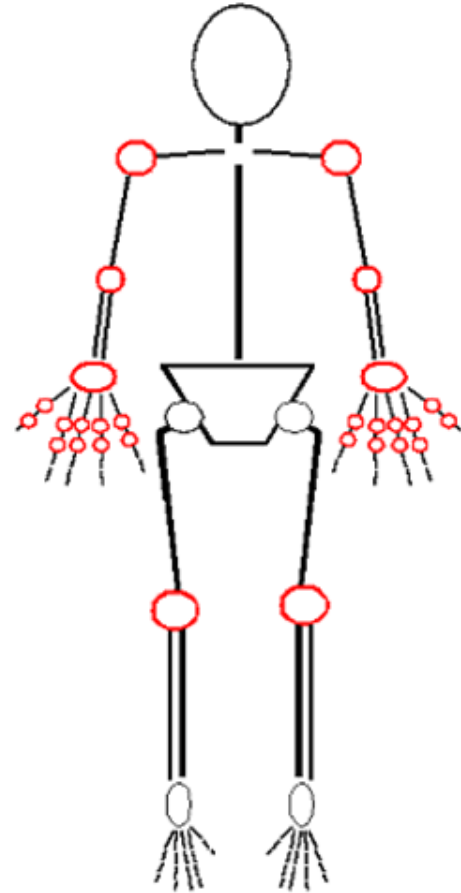
- **DAS 28-4 (0–9.4)**

$$= 0.56 \times \sqrt{\text{TJC28}}$$

$$+ 0.28 \times \sqrt{\text{SJC28}}$$

$$+ 0.70 \times \ln(\text{ESR})$$

$$+ 0.014 \times (\text{General Health})$$



$$* \text{DAS28-3} = 0.56 \times \sqrt{\text{TJC28}} + 0.28 \times \sqrt{\text{SJC28}} + 0.70 \times \ln(\text{ESR}) + 0.16$$

**CRP (mg/L) can be used with different formula.

Interpretation of DAS28

- Disease activity

DAS score	Disease activity
≤ 3.2	Low
3.2–5.1	Moderate
>5.1	High

* <2.6 : Remission

* $\Delta 1.2$: Significant change

*Correlation between DAS and DAS28 is 0.97

Simplified disease activity index (SDAI)

Clinical disease activity index (CDAI)

Elements	SDAI	CDAI	DAS28
Swollen joints	Simple count (0–28)	Simple count (0–28)	Simple count* (0–1.48)
Tender joints	Simple count (0–28)	Simple count (0–28)	Simple count* (0–2.96)
Acute phase reactants	CRP in g/l/dL (0.1–10)	–	ESR* (0.49–3.22)
Patient global health	–	–	VAS in mm* (0–1.40)
Patient global disease activity	VAS in cm (0–10)	VAS in cm (0–10)	
Evaluator global disease activity	VAS in cm (0–10)	VAS in cm (0–10)	
Total index	0.1–86.0	0–76.0	0.49–9.07

*Modification **Immediate scoring

Alehata, Clin Exp Rheumatol, 2005

Response/remission

American College of Rheumatology preliminary definition of improvement of rheumatoid arthritis

ACR20

- 20% improvement in tender joint count
- 20% improvement in swollen joint count
- 20% improvement in 3 of following 5
 - Patient assessed global disease activity
 - Physician assessed global disease activity
 - Patient pain assessment
 - Functional disability
 - Acute phase reactant (ESR or CRP)

*ACR20, 50, 70 response

Felson, Arthritis Rheum, 1995

EULAR response criteria

		DAS improvement		
DAS at endpoint	DAS 28 at endpoint	>1.2	0.6-1.2	0.6
2.4	3.2 Low disease activity	Good response	Moderate response	No response
2.4-3.7	3.2-5.1 Medium disease activity	Moderate response	Moderate response	No response
>3.7	>5.1 High disease activity	Moderate response	No response	No response

SDAI and CDAI response criteria

	Moderate response	Major response
CDAI	≥ 6 points	≥ 14 points
SDAI	≥ 7 points	≥ 17 points

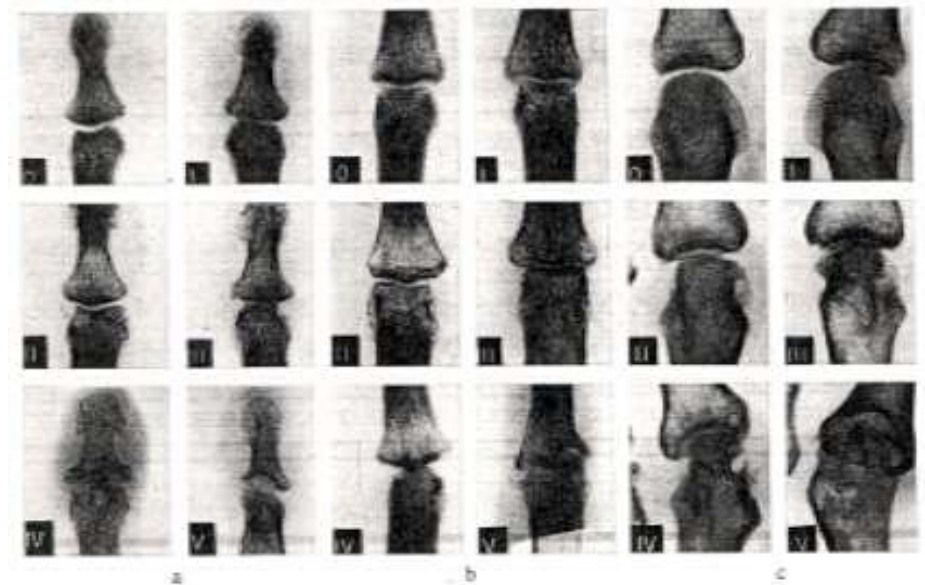
Remission

	Score	Clinical criteria
Das-28 remission	< 2.6	Joint count ESR/CRP Patient global assessment
CDAI remission	< 2.8	Joint count (/28) ≤ 1 Patient global assessment ≤ 1
SDAI remission	< 3.3	Joint count (/28) ≤ 1 Patient global assessment ≤ 1 CRP (mg/dL) ≤ 1
ACR/EULAR remission	SDAI < 3.0	Joint count ≤ 1 CRP (mg/dL) ≤ 1 Patient global assessment ≤ 1

Structural damage

Larson score

- Degree of radiographic progression
- Comparison with standard reference films (grade 0–5)
- PIP, MCP, wrist joints



DIP

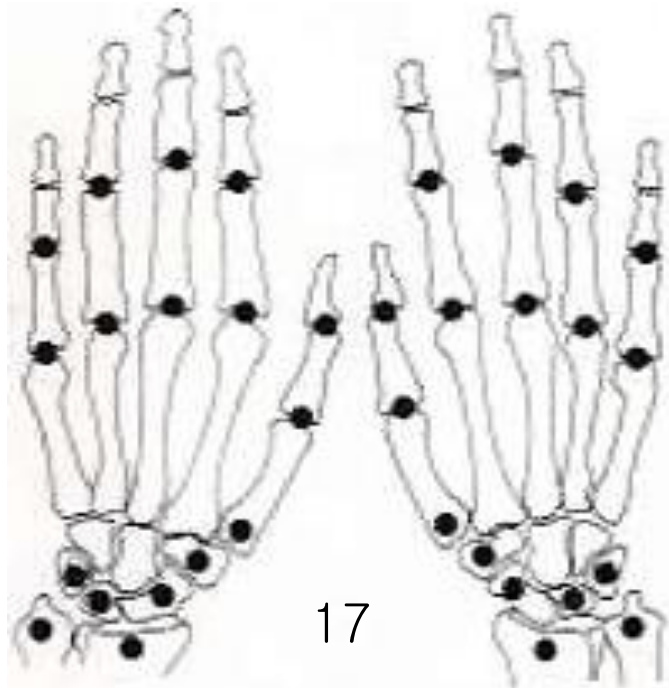
PIP

MCP

Sharp score

- Radiographic progression
- Erosions (grade 0–5) for 34 joints
- Joint space narrowing (grade 0–4) for 36 joints
- Hand and wrist joints
 - * modification by van der Heijde : feet added

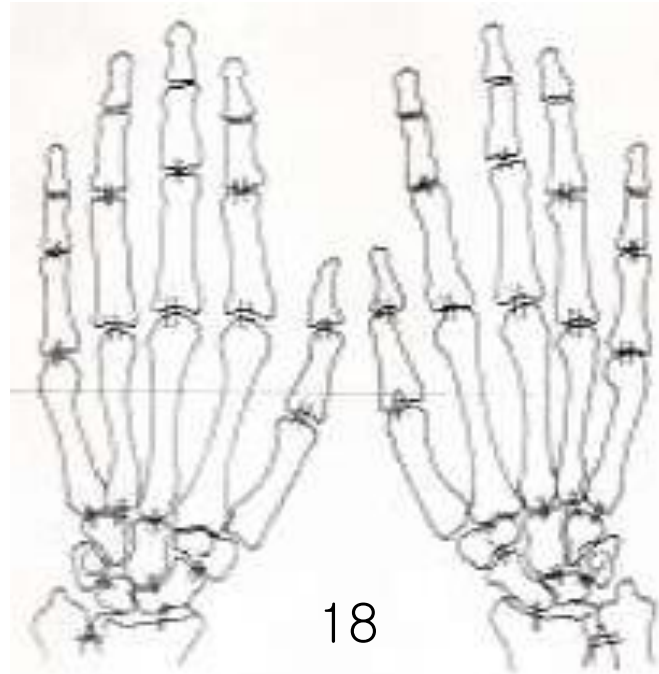
Sharp method (original)



17

Joint erosion

- 0: normal
- 1: discrete erosions
- 2-3: Larger erosions (surface area)
- 4: erosions over middle of the bone
- 5: complete collapse



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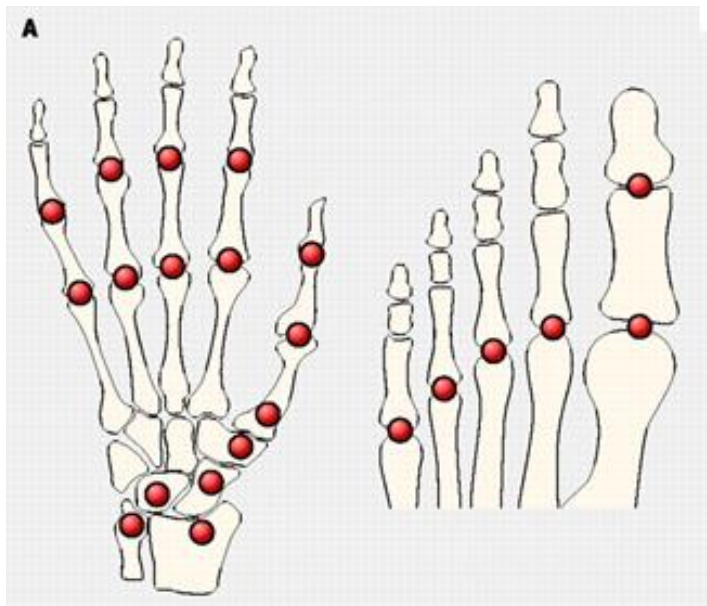
Joint space narrowing

- 0: no narrowing
- 1: focal or minimal narrowing
- 2: less than 50% loss of joint space
- 3: greater than 50% loss of joint space
- 4: ankylosis

Total score 0-314

Van der Heijde/Sharp method

Erosion



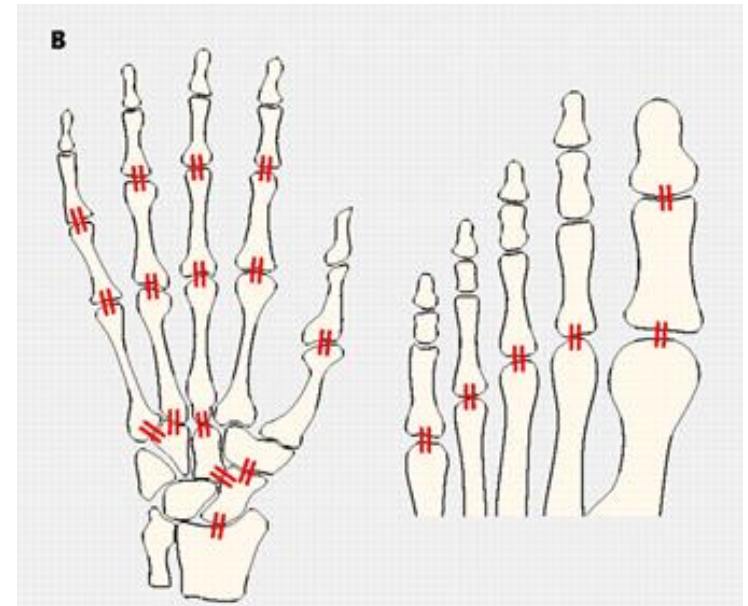
Hand

Foot

Erosion Sites 16
Range 0–5

6
0–10

Joint space narrowing



Hand

Foot

JSN Sites 15
Range 0–4

6
0–4

Total score 0–448

Summary

- Clinical disease activity score
 - ACR20 response
 - DAS-28
- Patient reported outcome (functional score)
 - HAQ-DI
 - Short form 36
- Structural damage
 - Van der Heijde modified Sharp score