



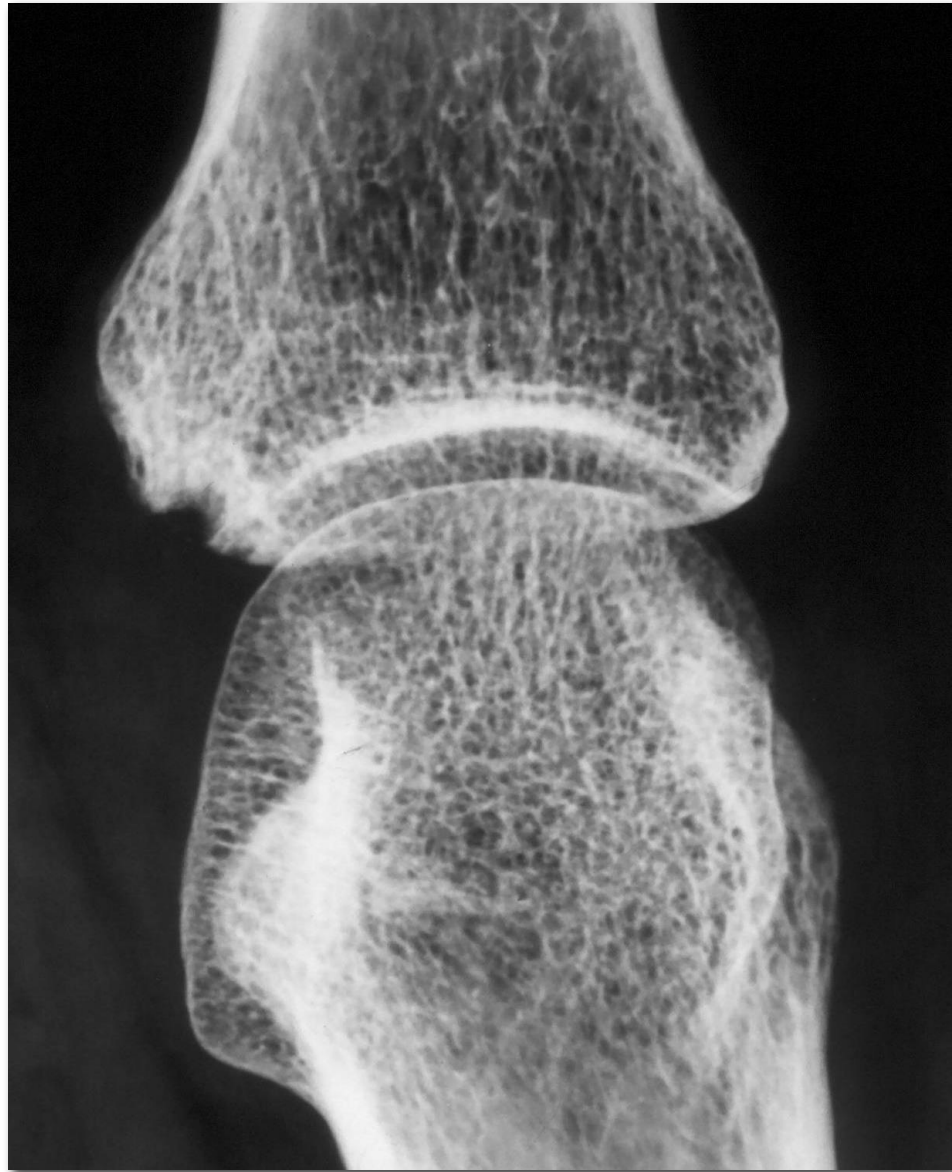
# L'erosione ossea nell'AR dalla fisiopatologia all'immagine

Carlomaurizio Montecucco

Unità di Reumatologia  
Università di Pavia  
IRCCS Policlinico S. Matteo



## erosion in rheumatoid arthritis

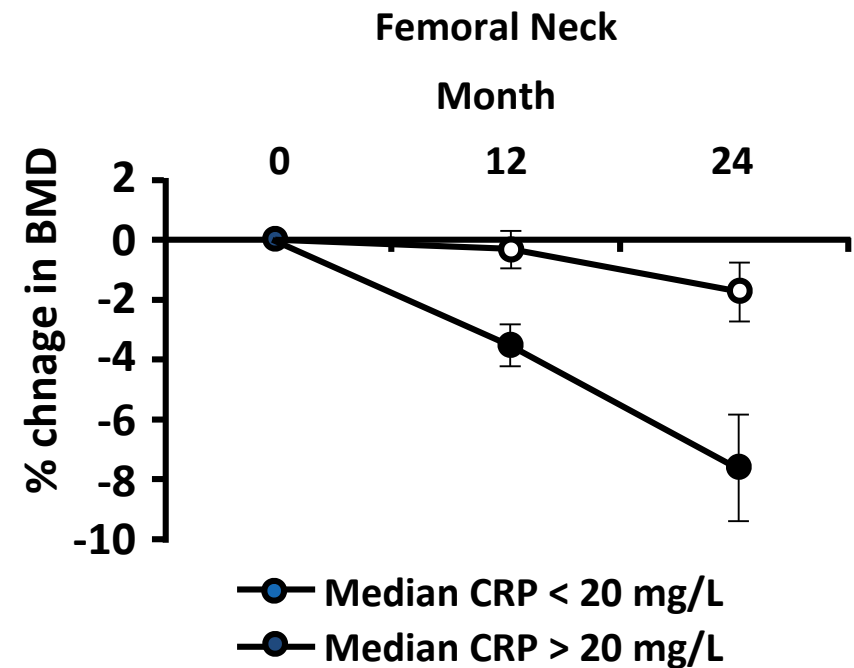
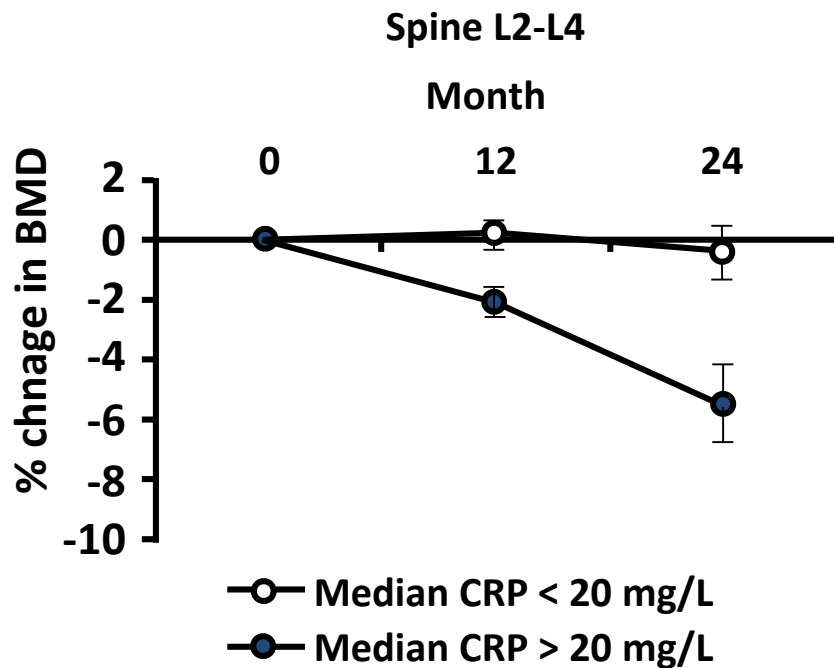


# Generalized osteopenia in RA

## Determinants in longitudinal studies

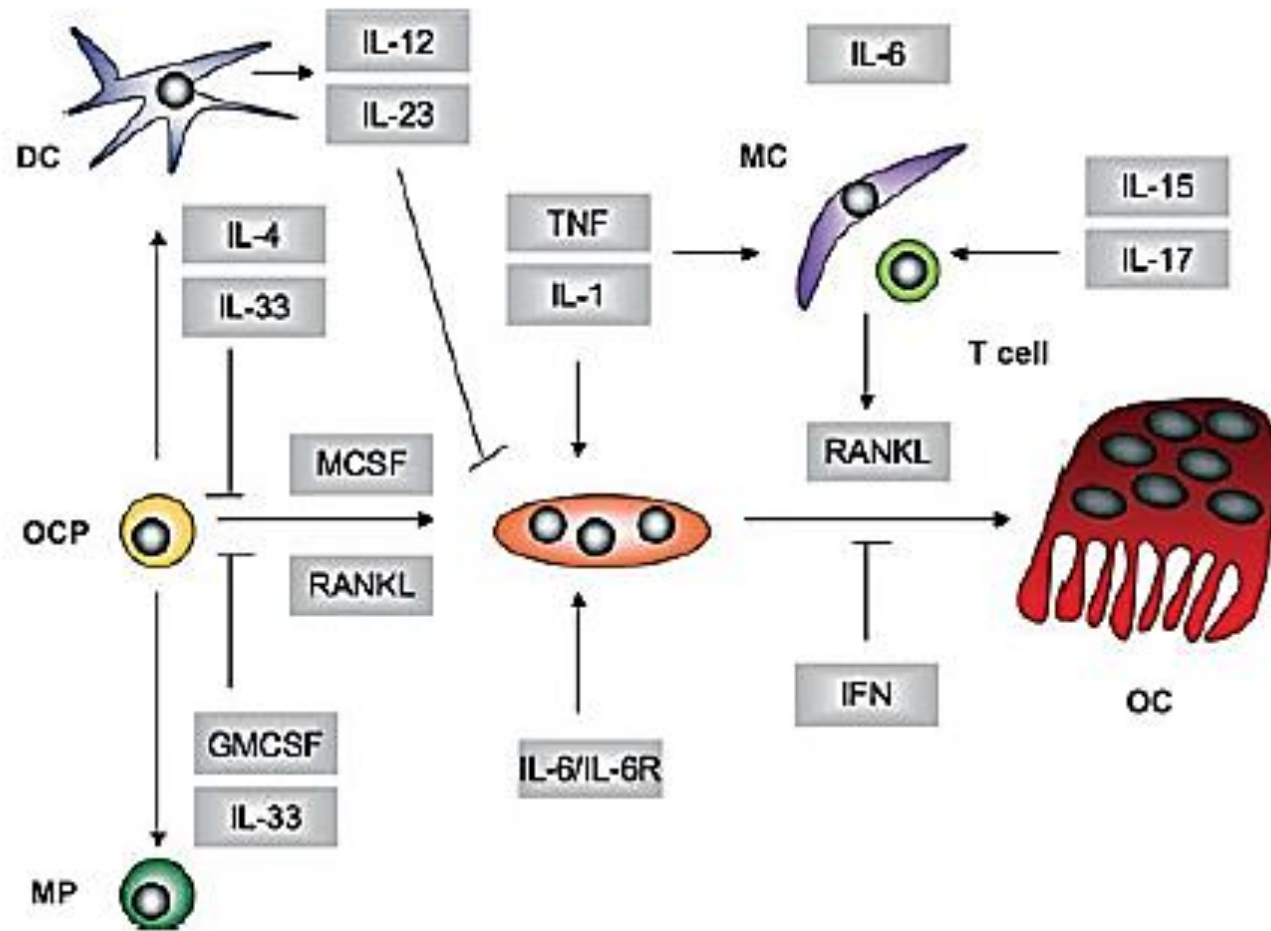
Prospective 2 year study in early RA (n=154)

Median CRP levels is the best single predictor of bone loss in early RA

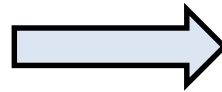


Modified from Gough Lancet 1994

# Effects of cytokines on the bone



# INFLAMMATION



# BONE LOSS

## 10.475 participants

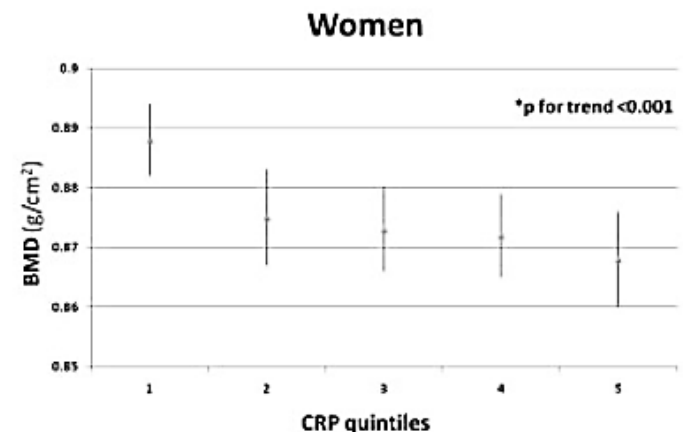
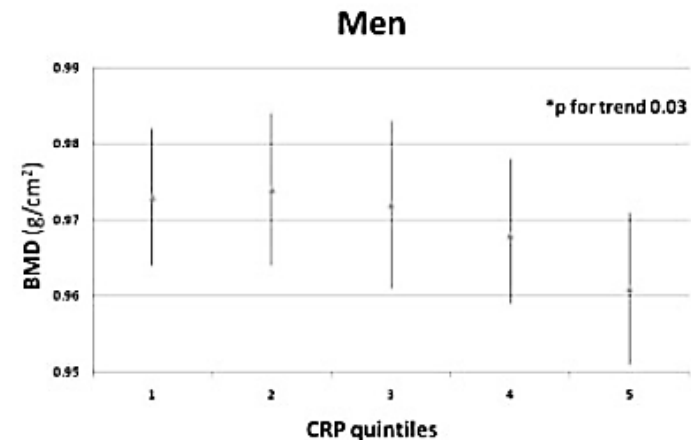
(53% Caucasian, 22% Mexican American, 18% African American, 7% other races)

total body BMD, subtotal BMD, BMD of the extremities, wrists and trunk subregions

*inversely associated with*  
quintiles of CRP concentration

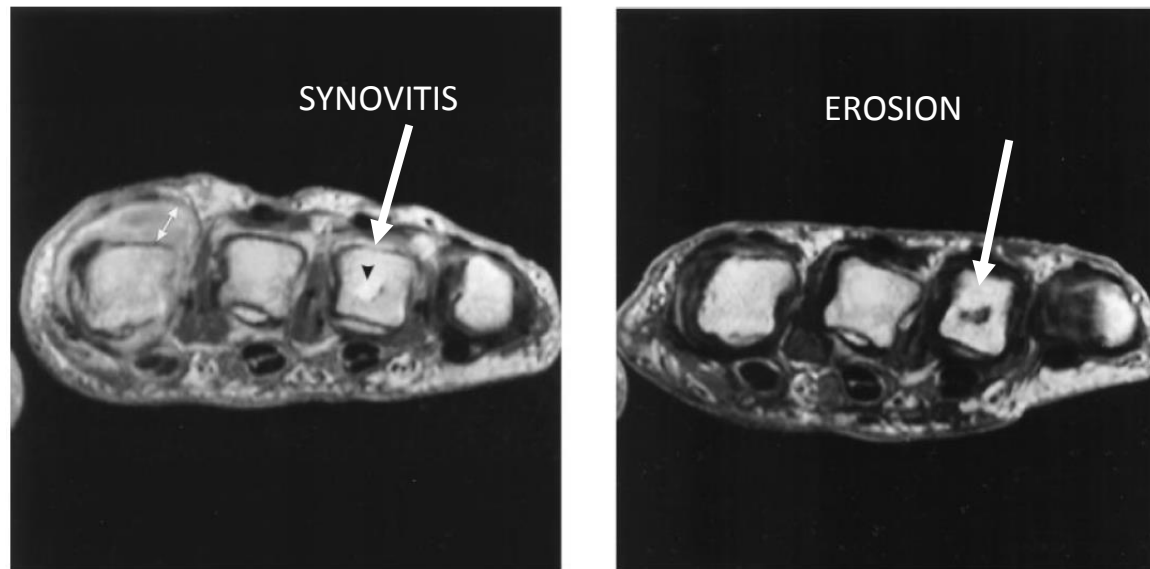
Covariates:

age, sex, race/ethnicity, level of education, poverty index, smoking status, alcohol intake, BMI, physical activity, comorbidities, medications



# Relationship between inflammation/synovitis and joint damage

- † Magnetic resonance imaging studies have revealed that, at least in early RA, **synovitis** appears to be the primary abnormality, and **bone damage** occurs in proportion to the level of synovitis but not in its absence (Conaghan PG, et al. *Arthritis Rheum* 2003;48:64-71).



Axial T1-weighted post-gadolinium sequences of the second through fifth metacarpophalangeal joints.

# INFLAMMATION



# BONE LOSS

SYSTEMIC INFLAMMATION  
(rheumatic diseases, inflammatory  
bowel diseases, ..)

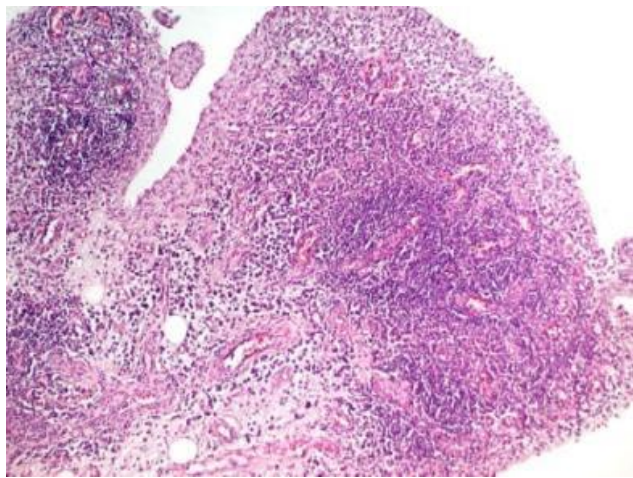


GENERALIZED OSTEOPOROSIS

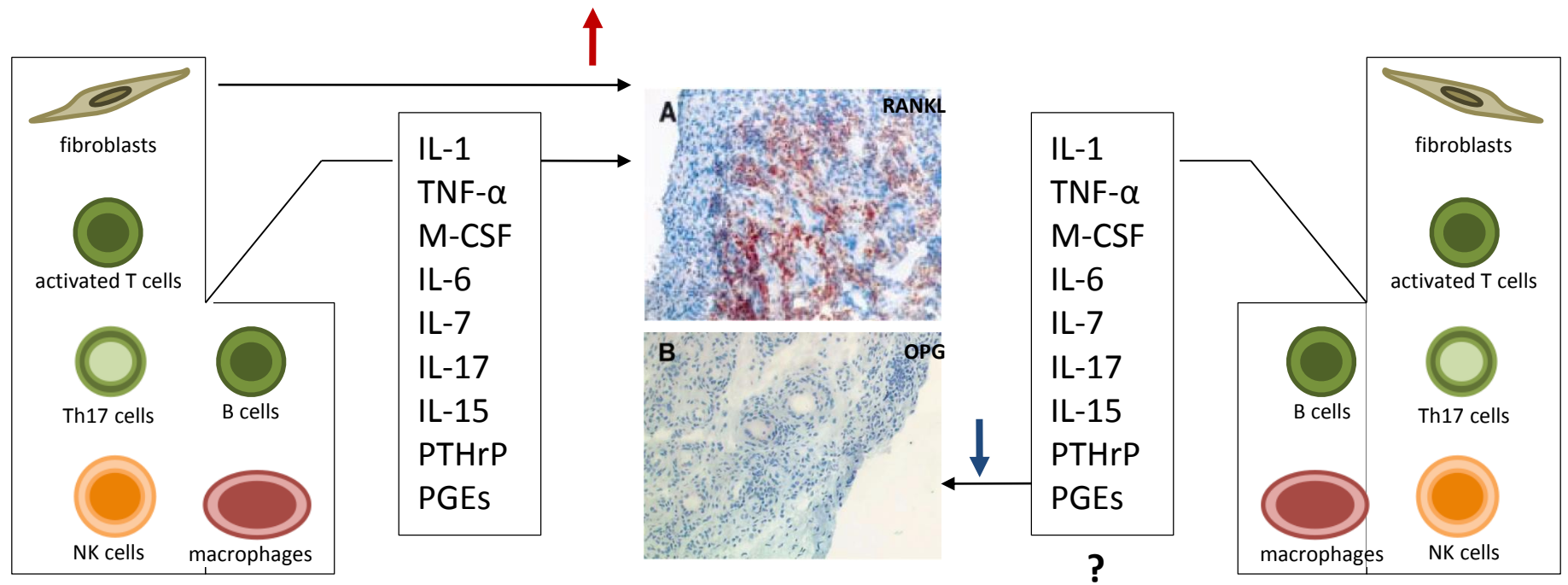
LOCAL INFLAMMATION  
(arthritis)



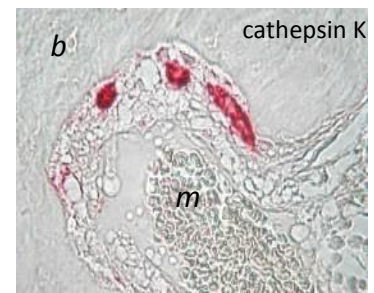
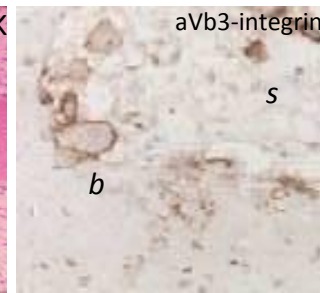
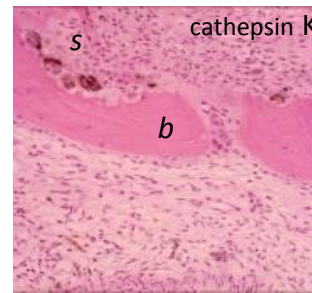
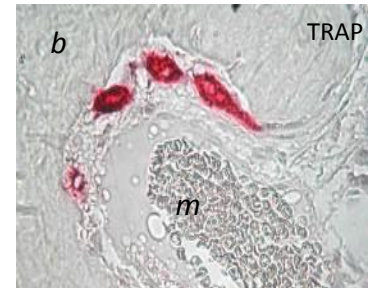
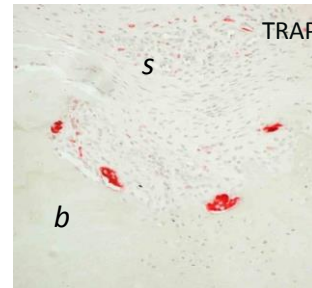
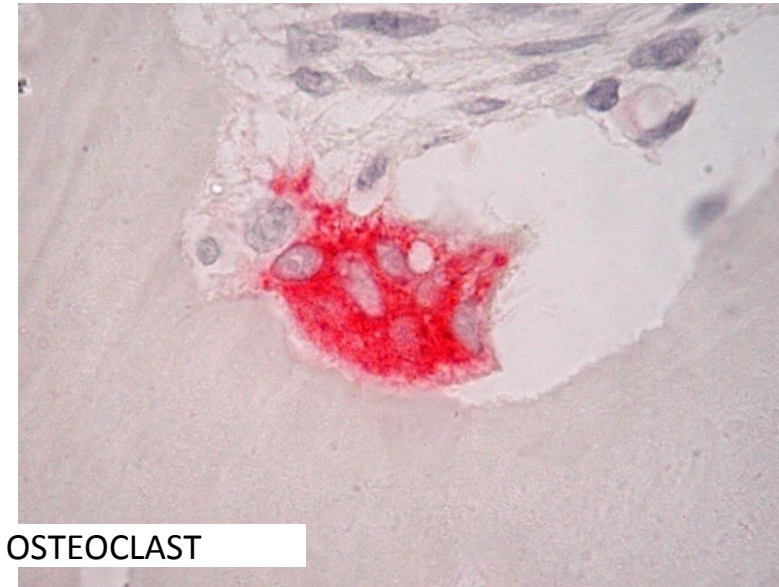
JOINT DAMAGE (EROSIONS)



# SYNOVITIS



# Osteoclasts at sites of bone erosions



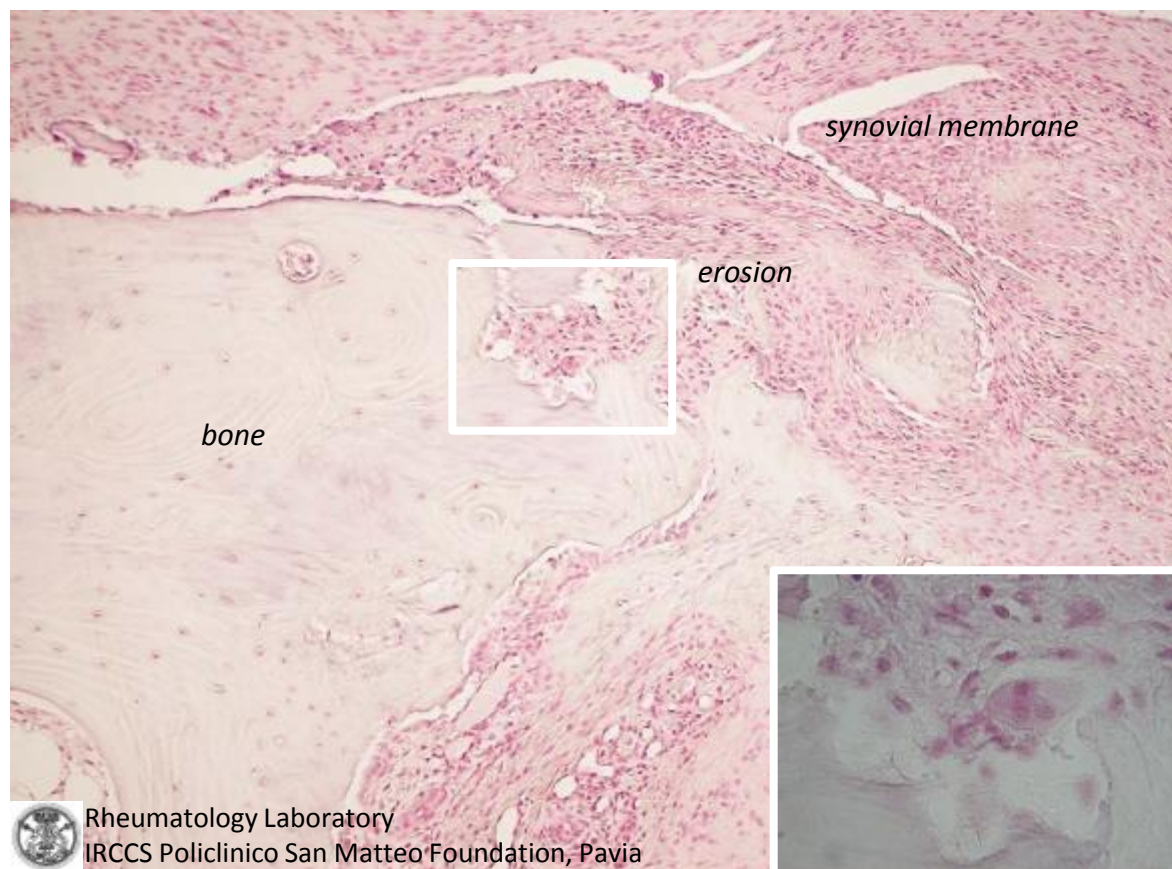
*bone-pannus interface*

*subchondral bone*

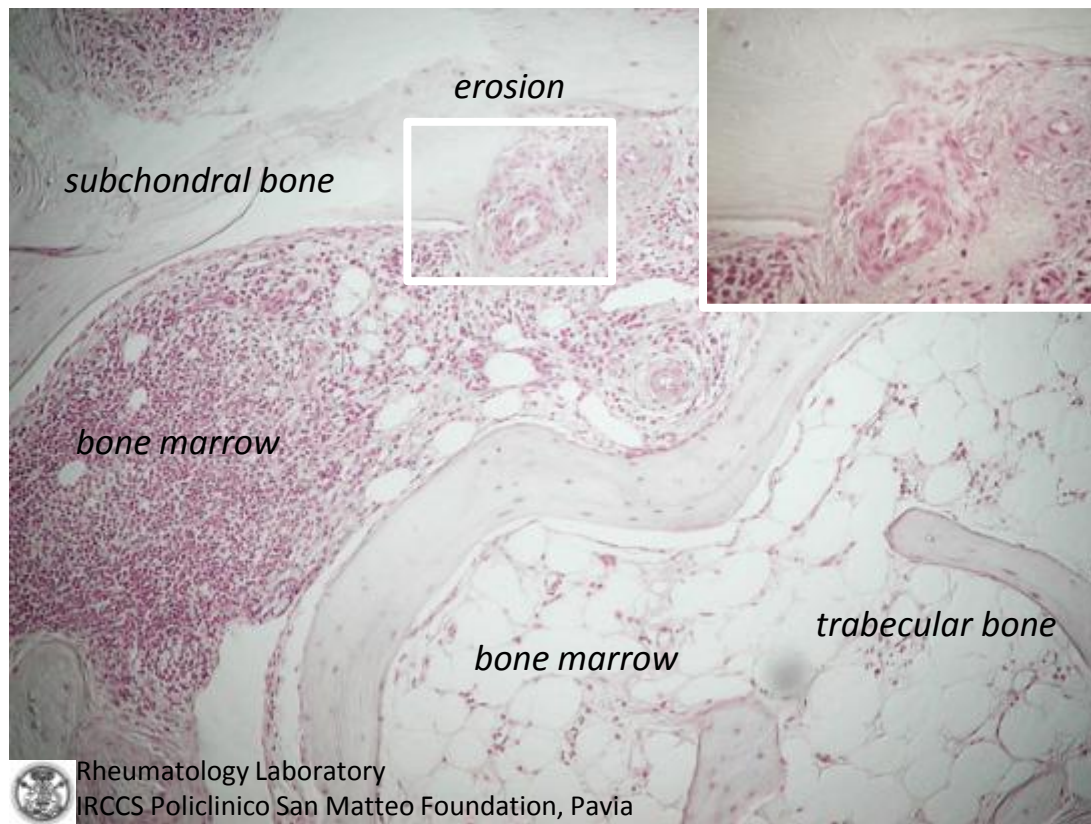
## Phenotypic markers that identify osteoclasts:

- *Multinucleation*
- *Ruffled border/clear zones of attachment*
- *Proton pump*
- *Vitronectin receptor (αVβ3 integrin)*
- *Cathepsin K activity*
- *Tartrate resistant acid phosphatase activity (TRAP)*
- *Calcitonin receptor*

# Marginal erosions (bare areas)

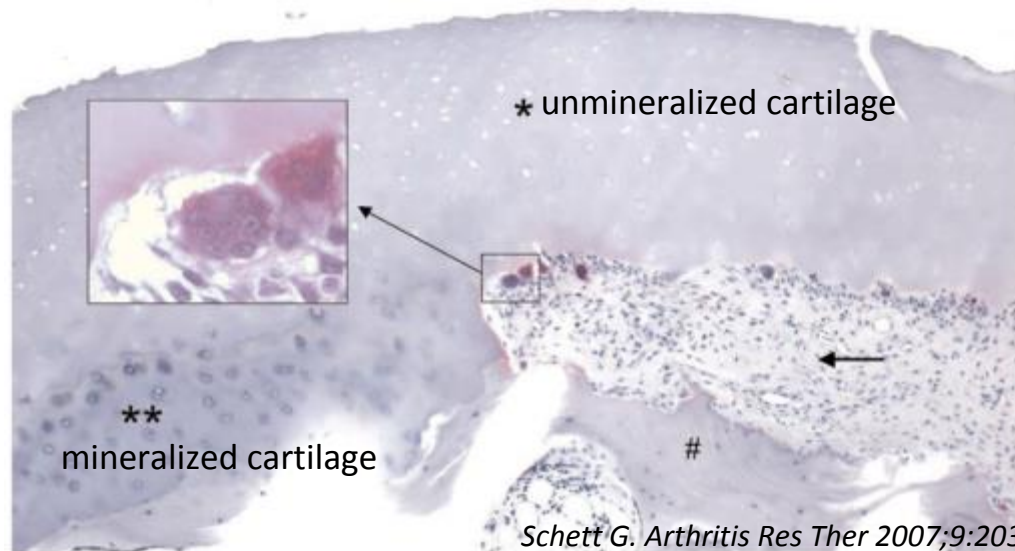


# Erosions of the subchondral bone



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IRCCS Policlinico San Matteo Foundation, Pavia

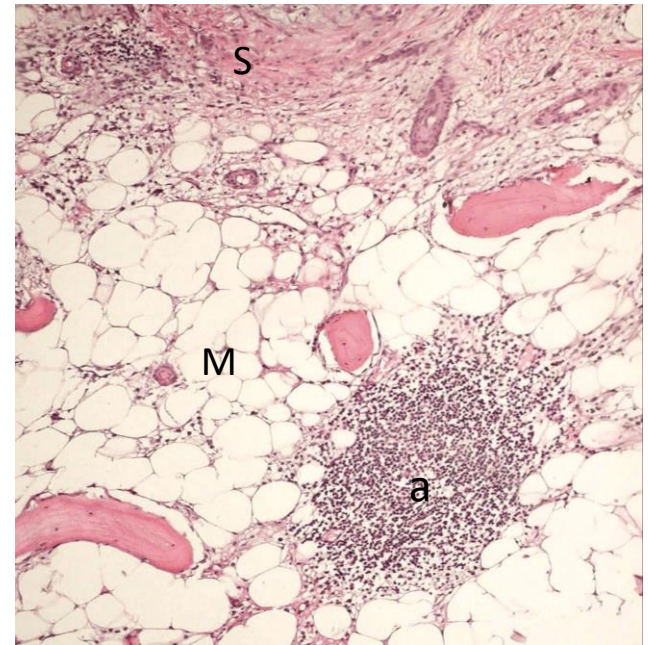
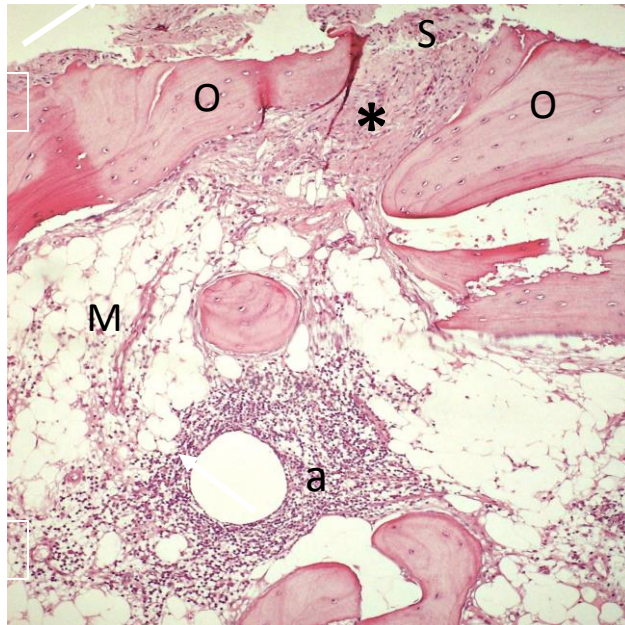
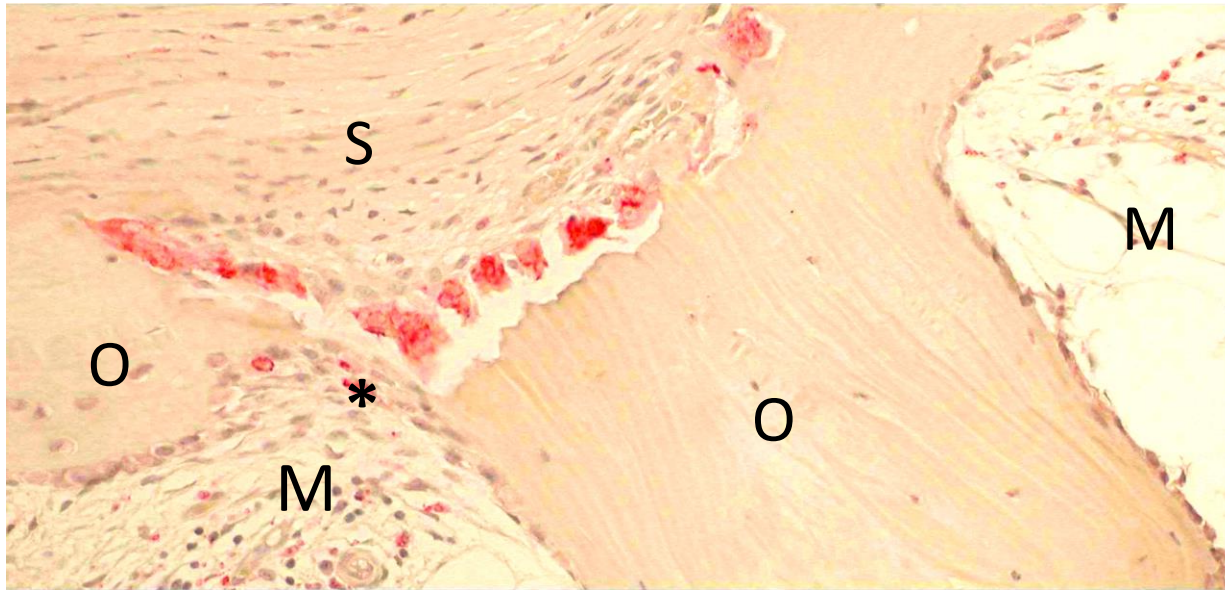
# Osteoclasts and cartilage resorption



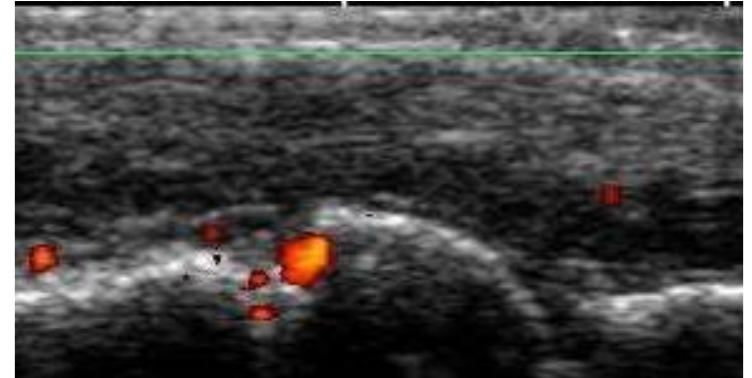
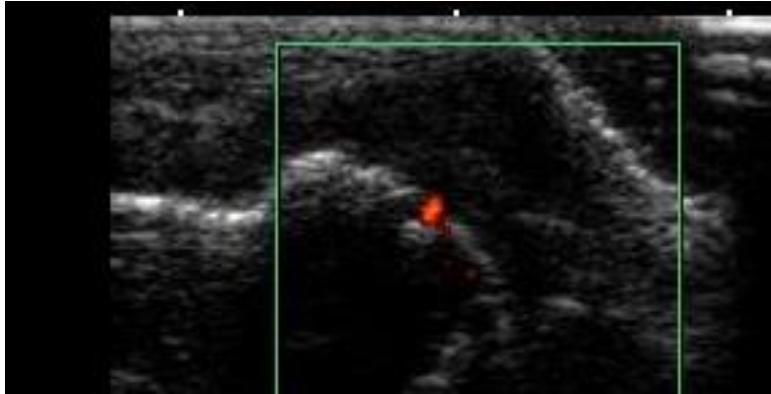
➡ Resorption of **mineralized cartilage** is **osteoclast-dependent**.

Resorption of **unmineralized surface cartilage** is **osteoclast-independent**. Invasion of synovial fibroblasts and expression of matrix-degrading enzymes (aggrecanases, matrix metalloproteinases) by synovial fibroblasts, neutrophils, and chondrocytes are key processes.

# erosion in rheumatoid arthritis



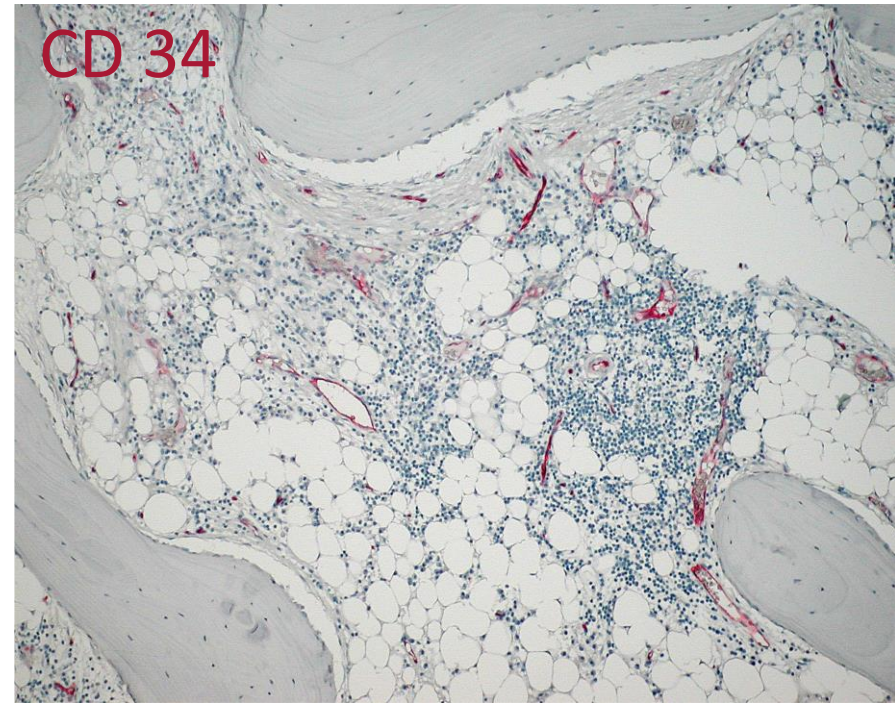
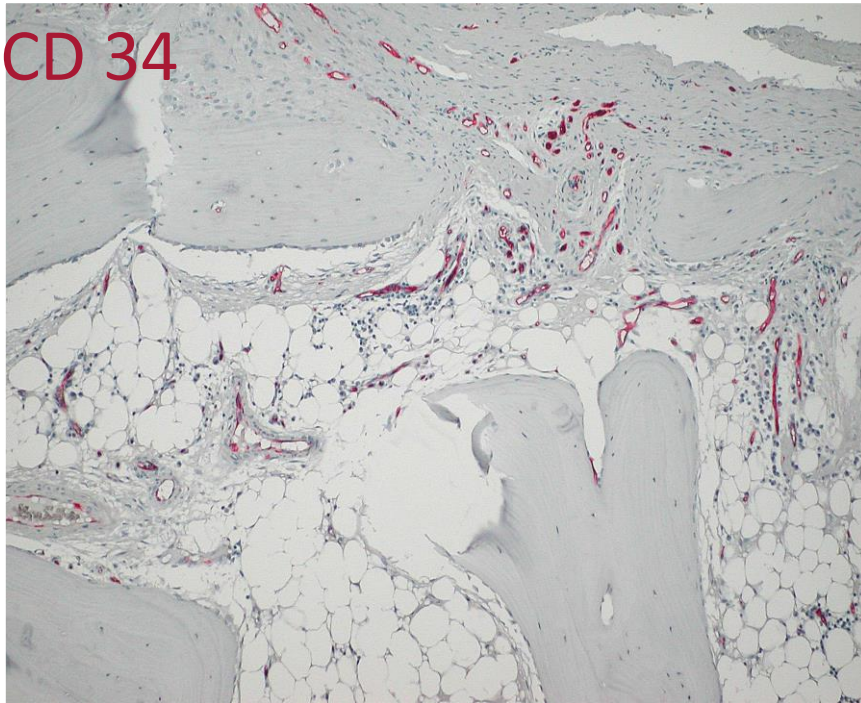
# US detectable “active” erosion



Division of Rheumatology

IRCCS Policlinico San Matteo Foundation, University of Pavia

# New vessel formation and inflammatory changes with erosion in RA



Rheumatology Laboratory

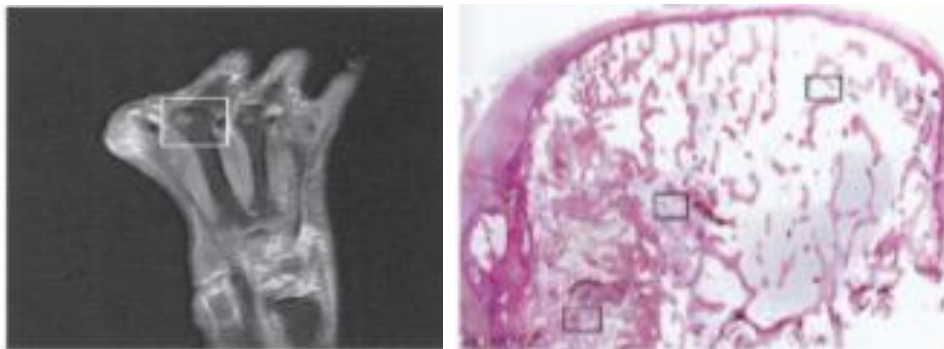
IRCCS Policlinico San Matteo Foundation, University of Pavia

# Local inflammation and bone damage: osteitis?



Magnetic resonance imaging findings in 84 patients with early RA: bone marrow oedema predicts erosive progression.

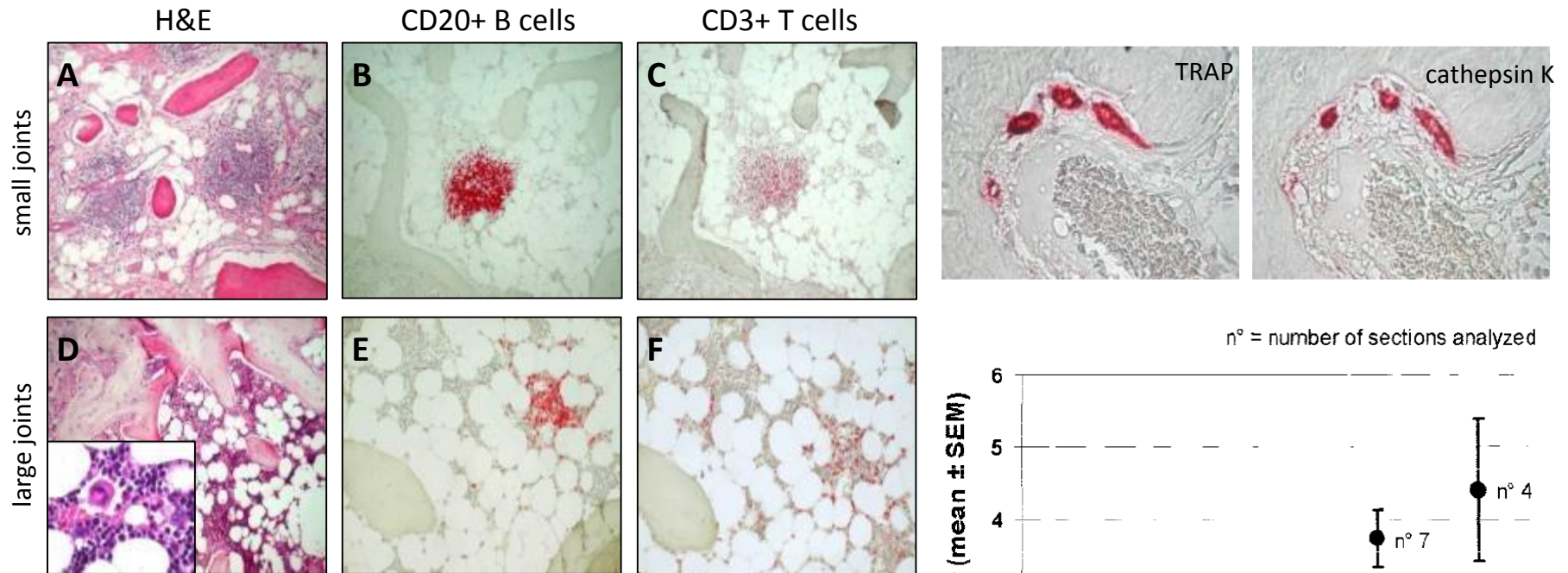
*Haavardsholm EA, et al. Ann Rheum Dis 2008;67:794-800.*



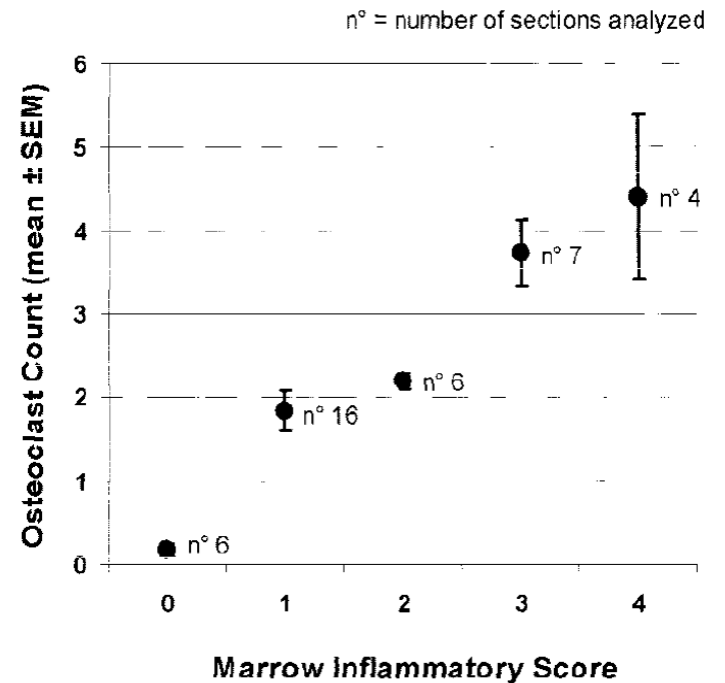
Bone marrow edema on MRI reflects true bone marrow inflammation

*Jimenez-Boj E, et al. A&R 2007.*

# Subchondral bone marrow inflammation: osteitis



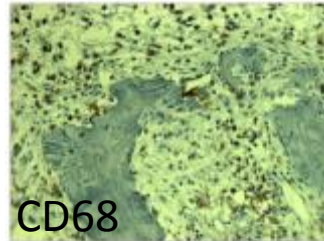
Bugatti S, et al. *Arthritis Rheum* 2005;52:3448-59.



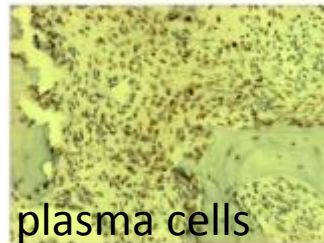
# Subchondral bone marrow inflammation: osteitis



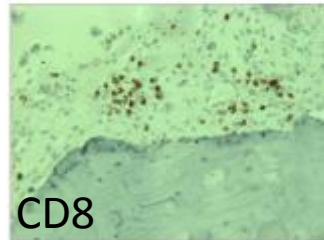
bone marrow edema



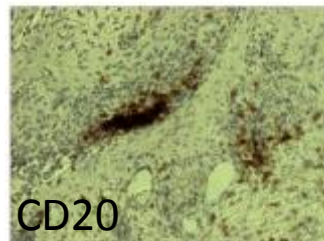
CD68



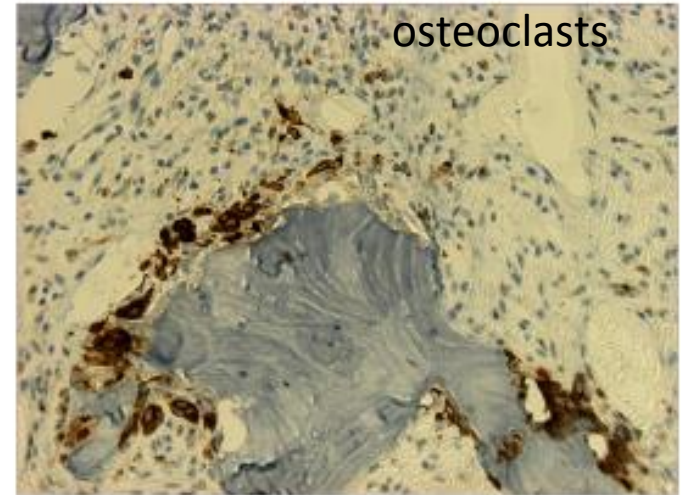
plasma cells



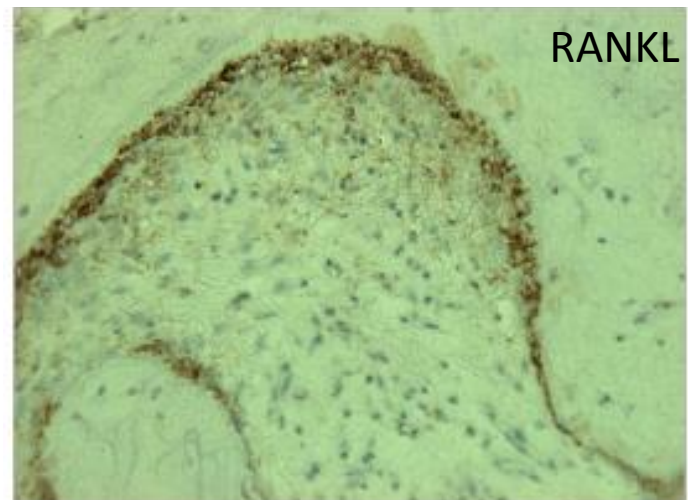
CD8



CD20



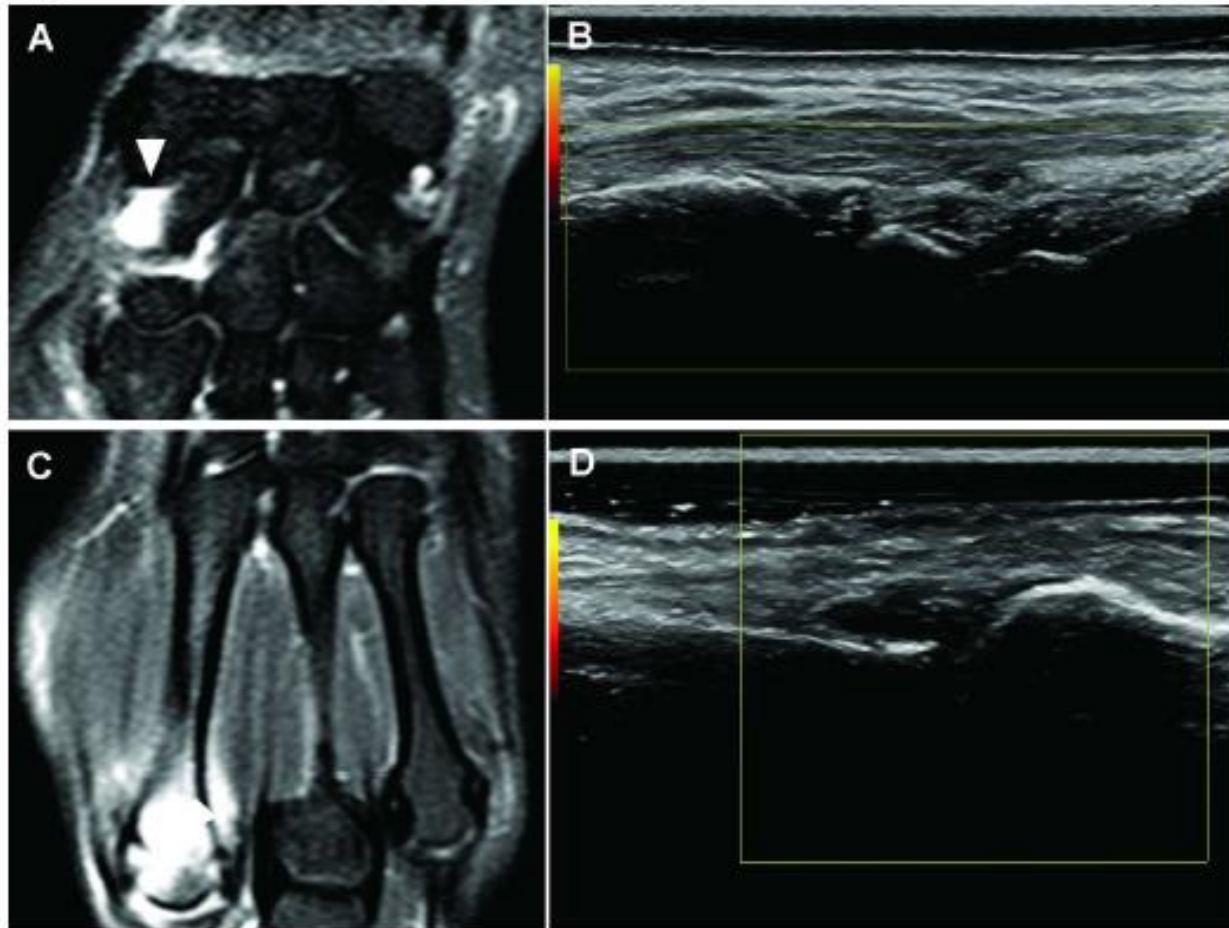
osteoclasts



RANKL

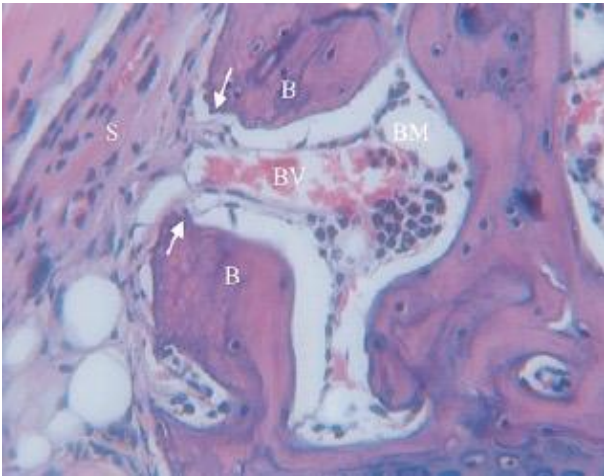
# Deas RA start in the synovium? Early bone marrow involvement

Figure 1



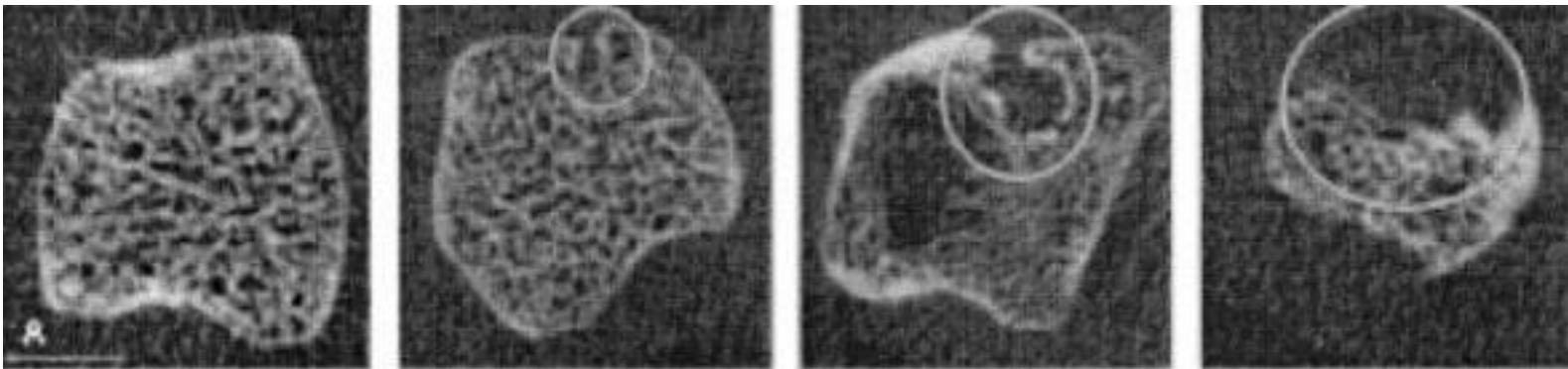
# Does the disease start in the synovium?

## Early bone marrow involvement



Before the onset of arthritis, enlarged bone canals connecting the bone marrow to the synovium allow the migration of BMPR+ mesenchymal cells from the subchondral bone to the synovium.

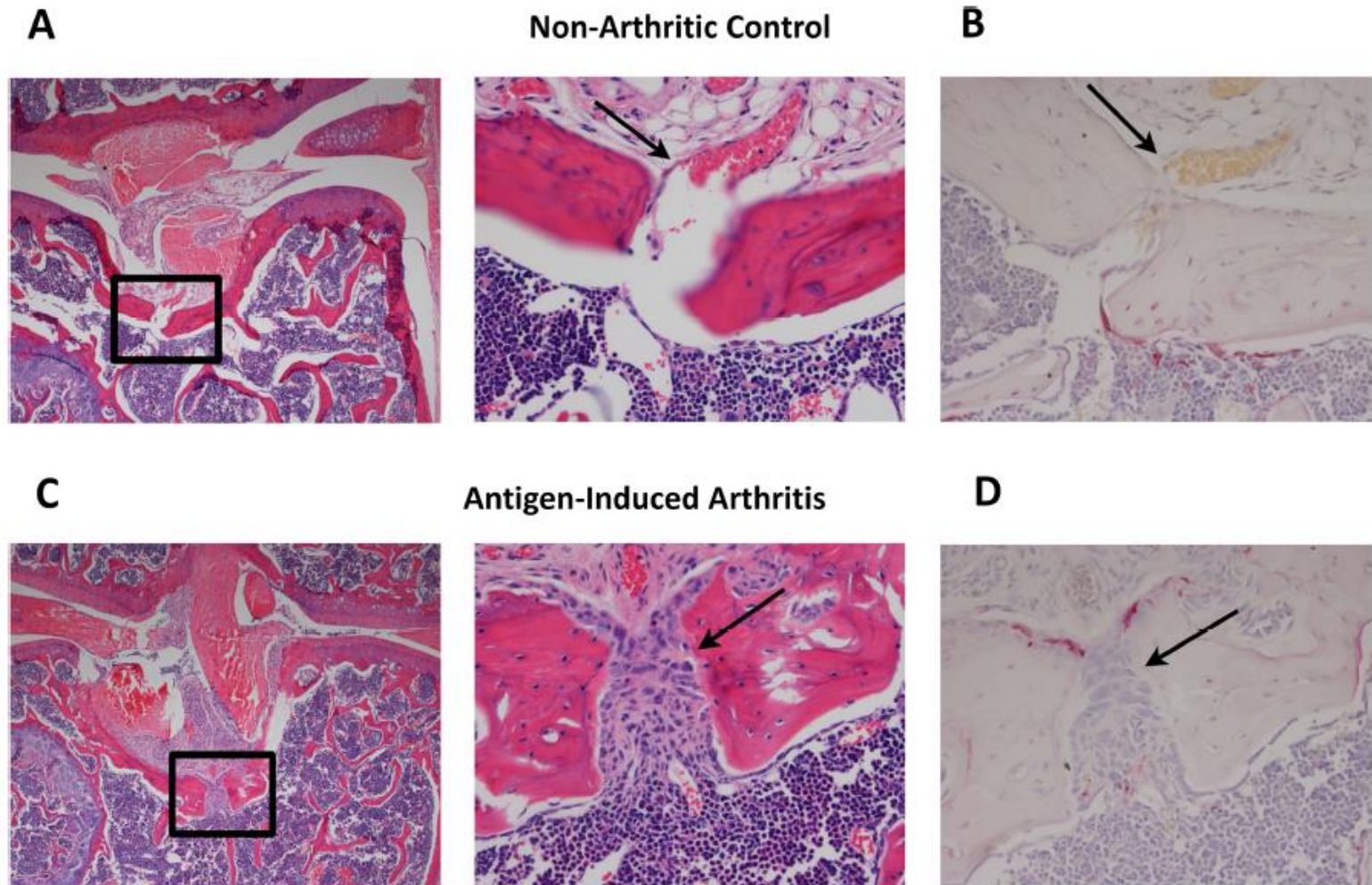
Marinova-Mutafchieva L et al. Arthritis Rheum 2002.



<1.9 mm

Stach CM et al. Arthritis Rheum 2010;62:330-9.

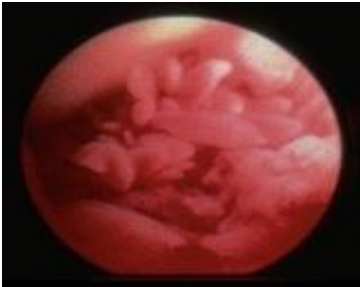
# Role of vascular channels as a novel mechanism for subchondral bone damage



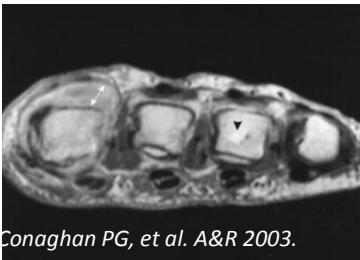
# Local inflammation and bone damage

## SYNOVITIS

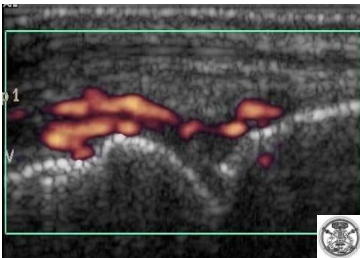
arthroscopy



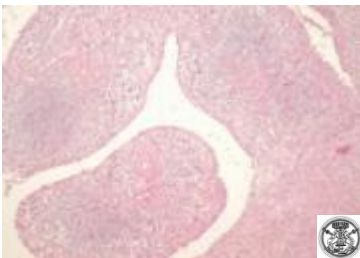
MRI



US-PD



histology



IUXTA-ARTICULAR  
OSTEOPOROSIS



JOINT SPACE  
NARROWING



EROSION OF THE  
BARE AREA



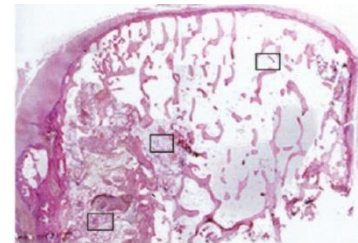
EROSION OF THE  
SUBCHONDRAL BONE



MRI

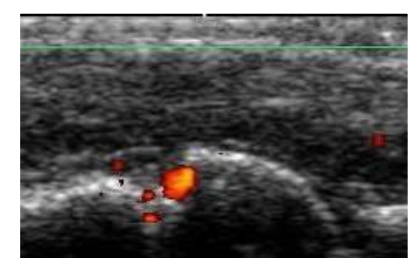
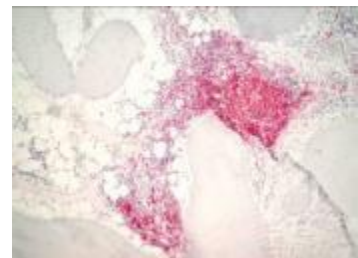


histology



## OSTEITIS

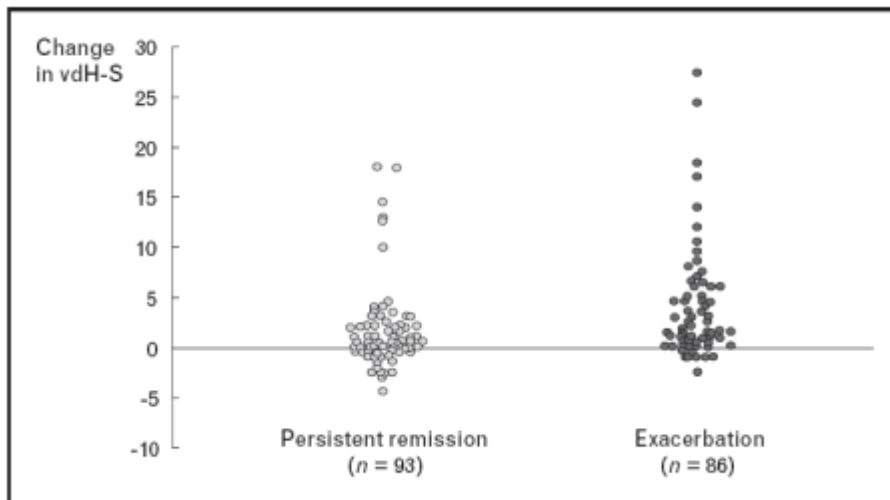
IHC



# Is inflammation necessary ?

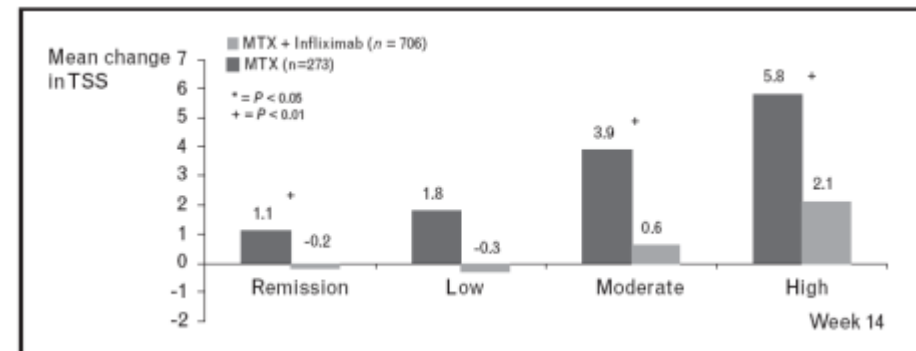
Apparent **disconnect** between clinical and radiographic outcomes

radiographic progression in patients without clinical evidence of synovitis



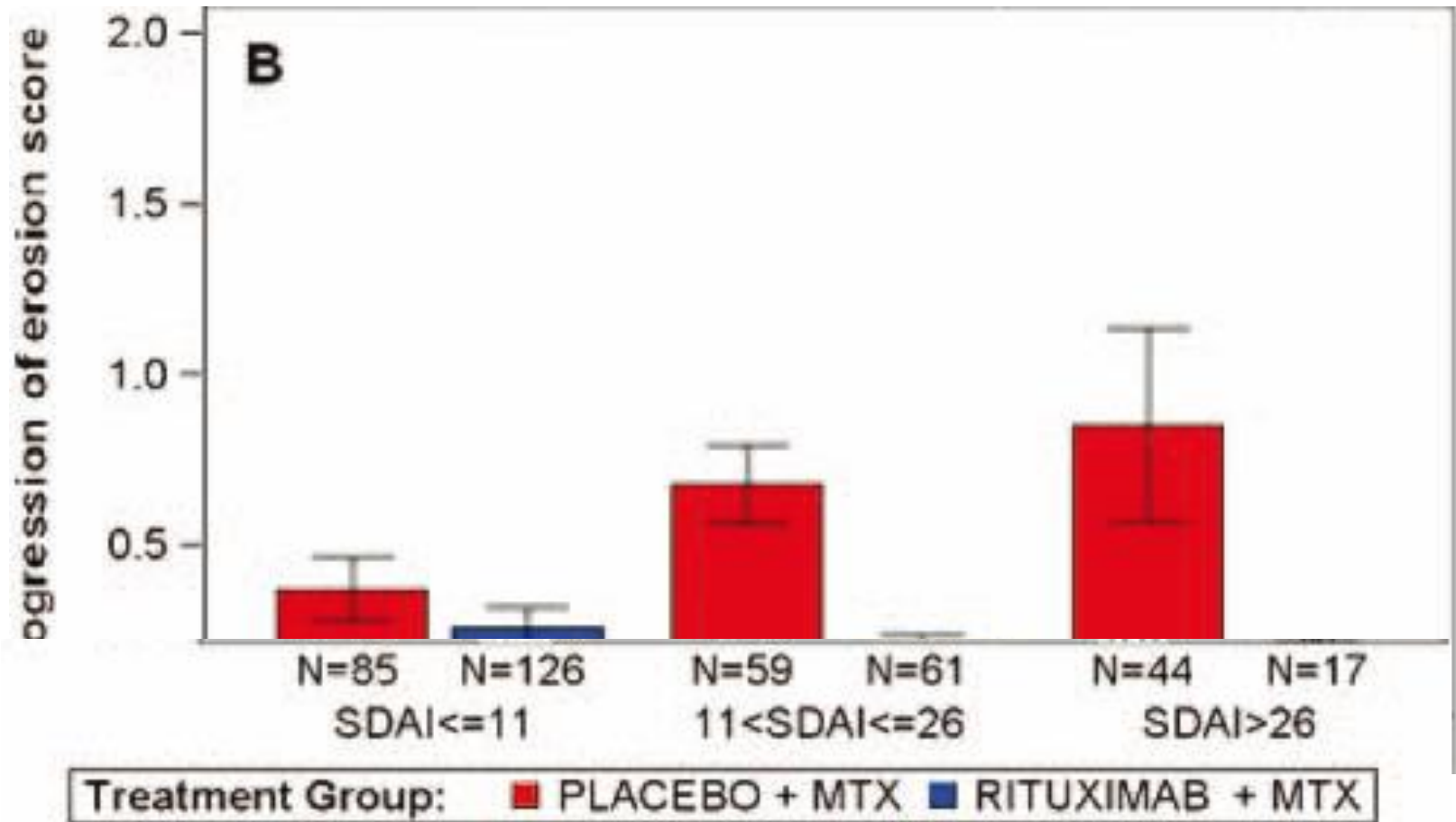
adapted from Molenaar ET, et al. *Arthritis Rheum* 2004;50:36–42.

Inhibition of radiographic progression in patients with clinically active disease



Keystone E. *Curr Opin Rheumatol* 2009;21:231-7.

# Rituximab dissociates the tight link between disease activity and joint damage in RA patients



# Radiographic progression in clinical remission

**Table 3.** Associations between clinical, laboratory, and imaging findings at baseline and radiographic progression in both hands and feet over 12 months\*

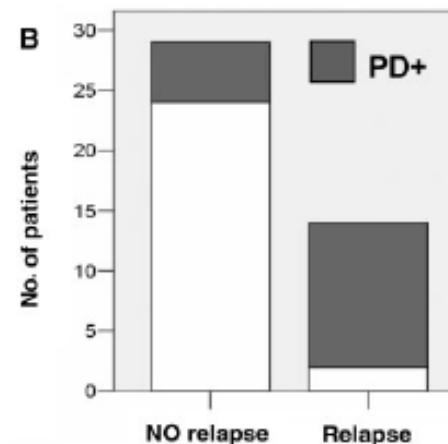
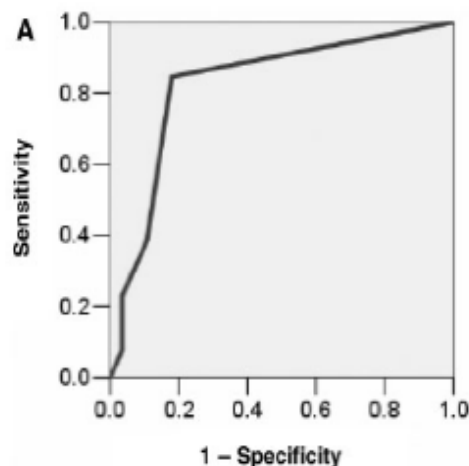
Baseline variable	No radiographic progression (n = 73)	Radiographic progression (n = 17)	OR (95% CI)	P
No. (%) RF positive	28 (38)	11 (65)	2.95 (0.98, 8.86)	0.054
ESR, median (IQR) mm/hour	10 (6–18)	13 (8–18)	1.01 (0.96, 1.06)	0.667
CRP, median (IQR) mg/liter	5 (0–9)	0 (0–12)	1.01 (0.93, 1.10)	0.765
No. (%) meeting ACR remission criteria	41 (56)	5 (29)	0.33 (0.10, 1.02)	0.054
No. (%) in DAS28 remission (score <2.6)	44 (60)	6 (35)	0.36 (0.12, 1.08)	0.068
DAS28 score, mean (95% CI)	2.48 (2.26, 2.71)	2.89 (2.40, 3.38)	1.54 (0.89, 2.65)	0.122
Total US PD score, median (IQR)	1 (0–2)	1 (0–3.5)	1.36 (1.02, 1.81)	0.038
Dominant-hand US PD score, median (IQR)	0 (0–0.75)	0 (0–2)	1.64 (1.03, 2.61)	0.036

*Brown AK, et al. Arthritis Rheum 2008.*

# Ultrasonographic evaluation of joint involvement in early rheumatoid arthritis in clinical remission: power Doppler signal predicts short-term relapse

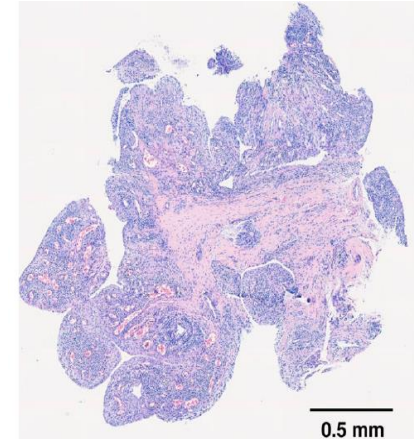
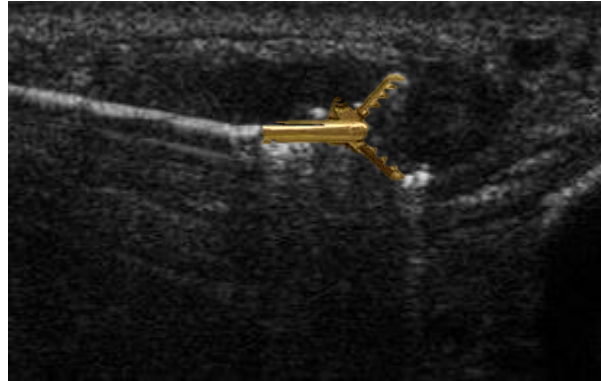
Carlo Alberto Sciré<sup>1</sup>, Carlomaurizio Montecucco<sup>1</sup>, Monica Todoerti<sup>1</sup>, Oscar Epis<sup>1</sup>, Roberto Caporali<sup>1</sup>

	No relapse, <i>n</i> = 29	Relapse, <i>n</i> = 14	OR	95% CI
DAS > 1.1	13	11	9	0.7, 110.3
SJC > 1	13	9	0.6	0.1, 5.5
US-JC > 2	10	11	4.6	0.4, 49.5
US-PD > 0	5	12	12.8*	1.6, 103.5



# **Immunohistological assessment of the synovial tissue in small joints in rheumatoid arthritis: validation of a minimally invasive ultrasound-guided synovial biopsy procedure**

Carlo Alberto Scirè<sup>1</sup>, Oscar Epis<sup>1</sup>, Veronica Codullo<sup>1</sup>, Frances Humby<sup>2</sup>, Patrizia Morbini<sup>3</sup>, Antonio Manzo<sup>2</sup>, Roberto Caporali<sup>1</sup>, Costantino Pitzalis<sup>2</sup> and Carlomaurizio Montecucco<sup>1</sup>



*Arthritis Res Ther 2007.*

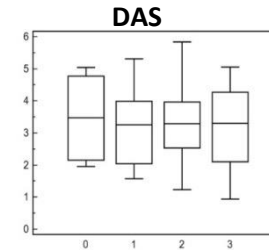
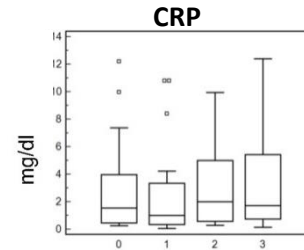
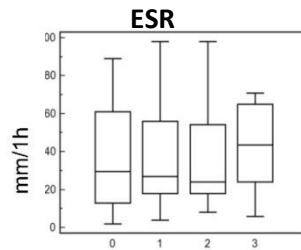
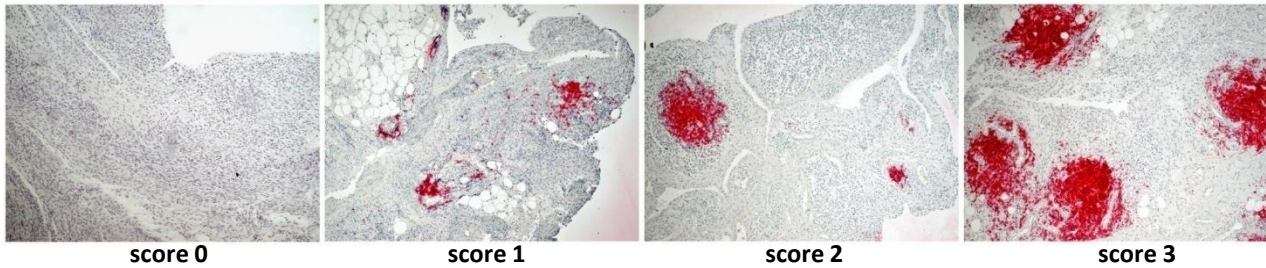
## **Evaluating Antirheumatic Treatment Using Synovial Biopsy: a Guideline for Standardisation to Be Used in Clinical Trials**

**Marleen G.H. van de Sande<sup>1</sup>, Danielle M. Gerlag<sup>1</sup>, Beatrijs M. Lodde<sup>1</sup>, Lisa G.M. van Baarsen<sup>1</sup>, Stefano Alivernini<sup>2</sup> Veronica Codullo<sup>3</sup>, Ioana Felea<sup>4</sup>, Elsa C.V. de Sousa<sup>5</sup>, Richard Reece<sup>6</sup>, Carlomaurizio Montecucco<sup>3</sup>, Doug J. Veale<sup>7</sup>, Costantino Pitzalis<sup>8</sup>, Paul Emery<sup>6</sup>, Lars Klareskog<sup>9</sup>, Iain B. McInnes<sup>10</sup>, Paul P. Tak<sup>1</sup>** EULAR Synovitis Study Group – AutoCure Project

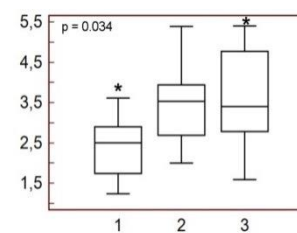
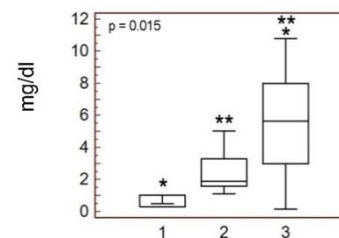
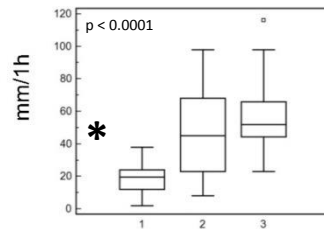
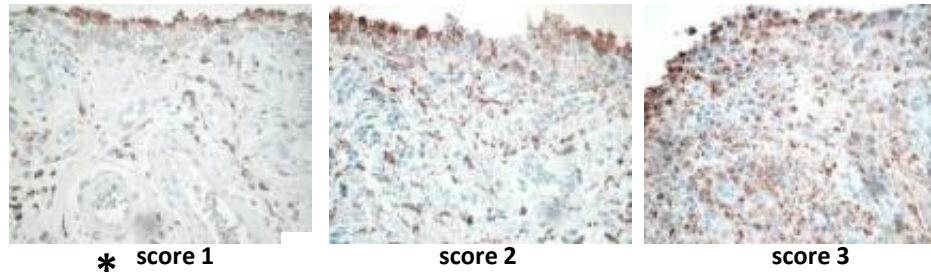
*Ann Rheum Dis 2011*

# Histological patterns of synovial inflammation

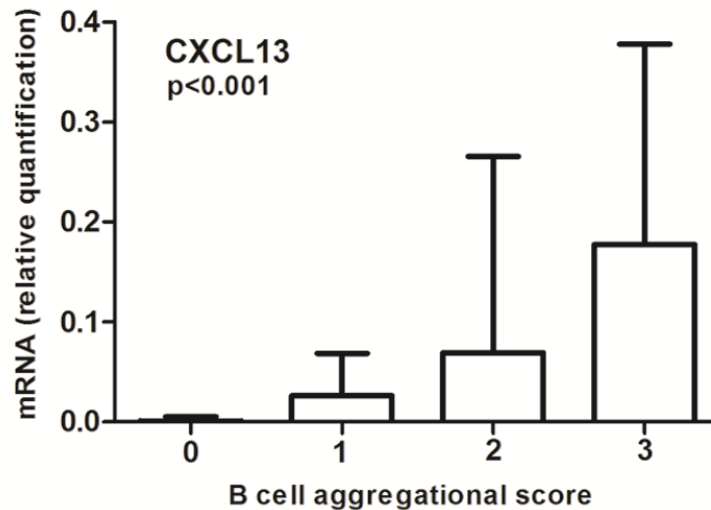
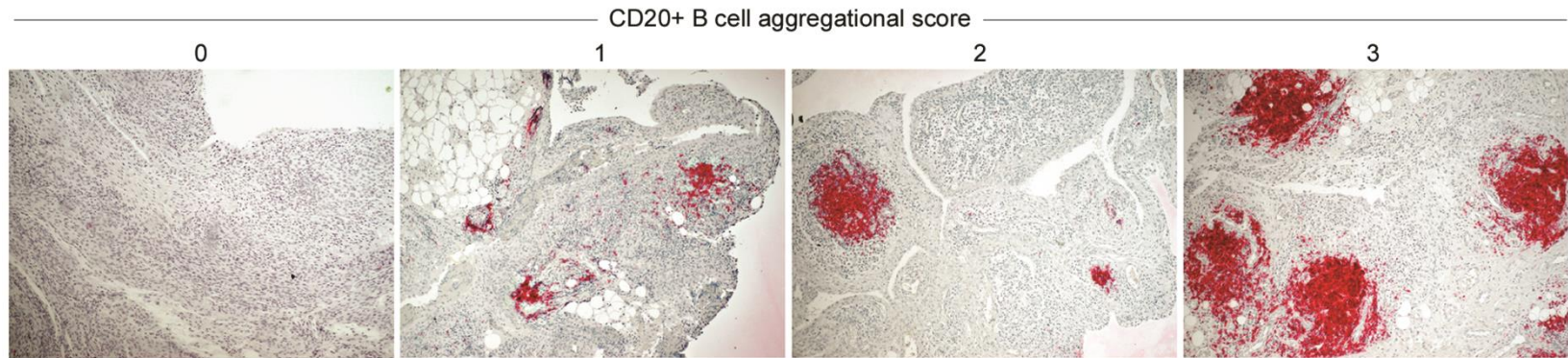
CD20+ B cell aggregational score



CD68+ sublining macrophage score

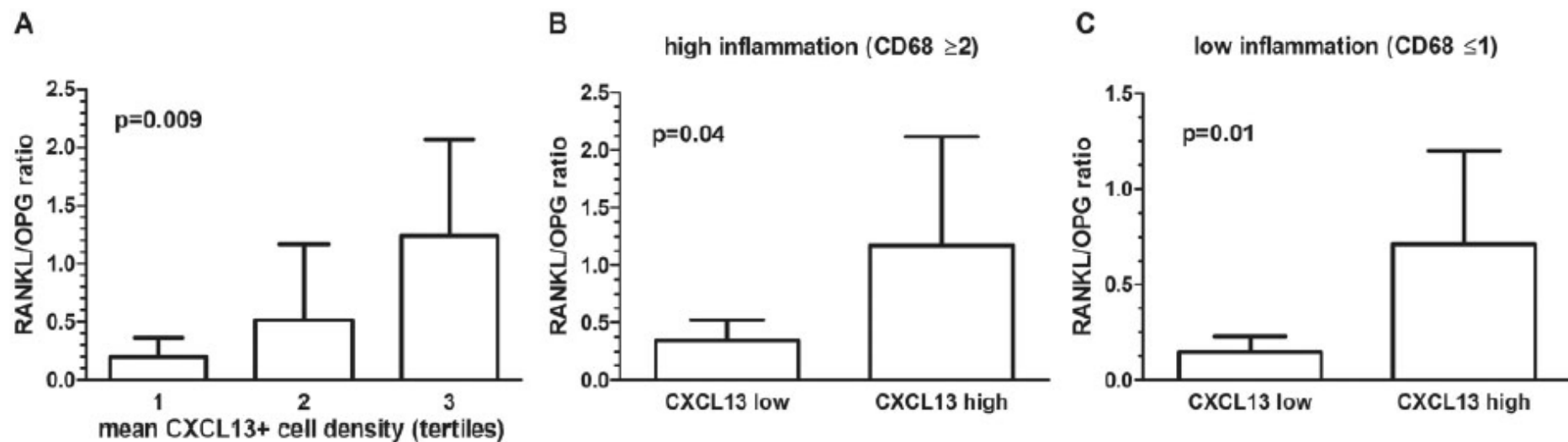


# Lymphoid pattern is strongly associated with CXCL13 expression



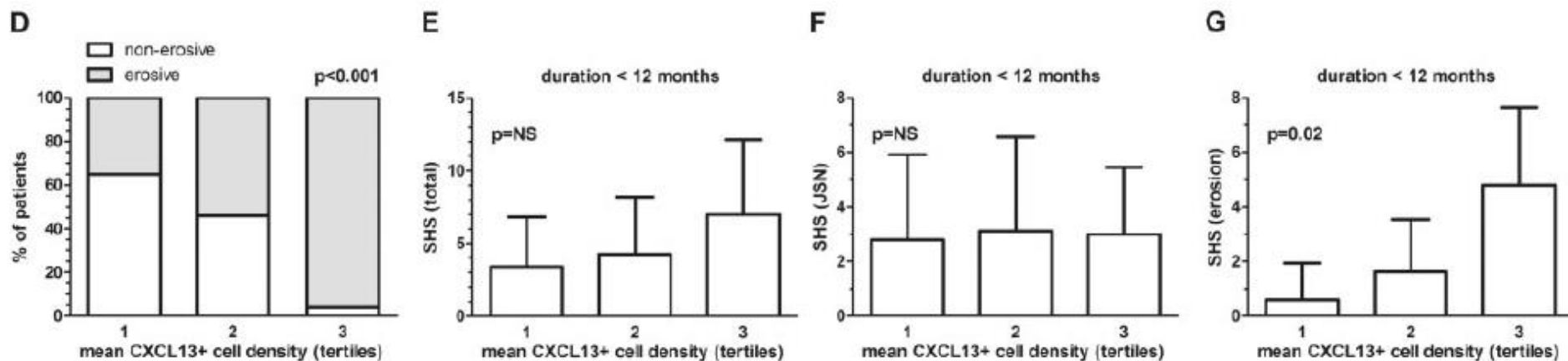
# Synovial expression of CXCL13 is increased in more severe RA

FIG. 4 Association of CXCL13 expression levels with bone damage

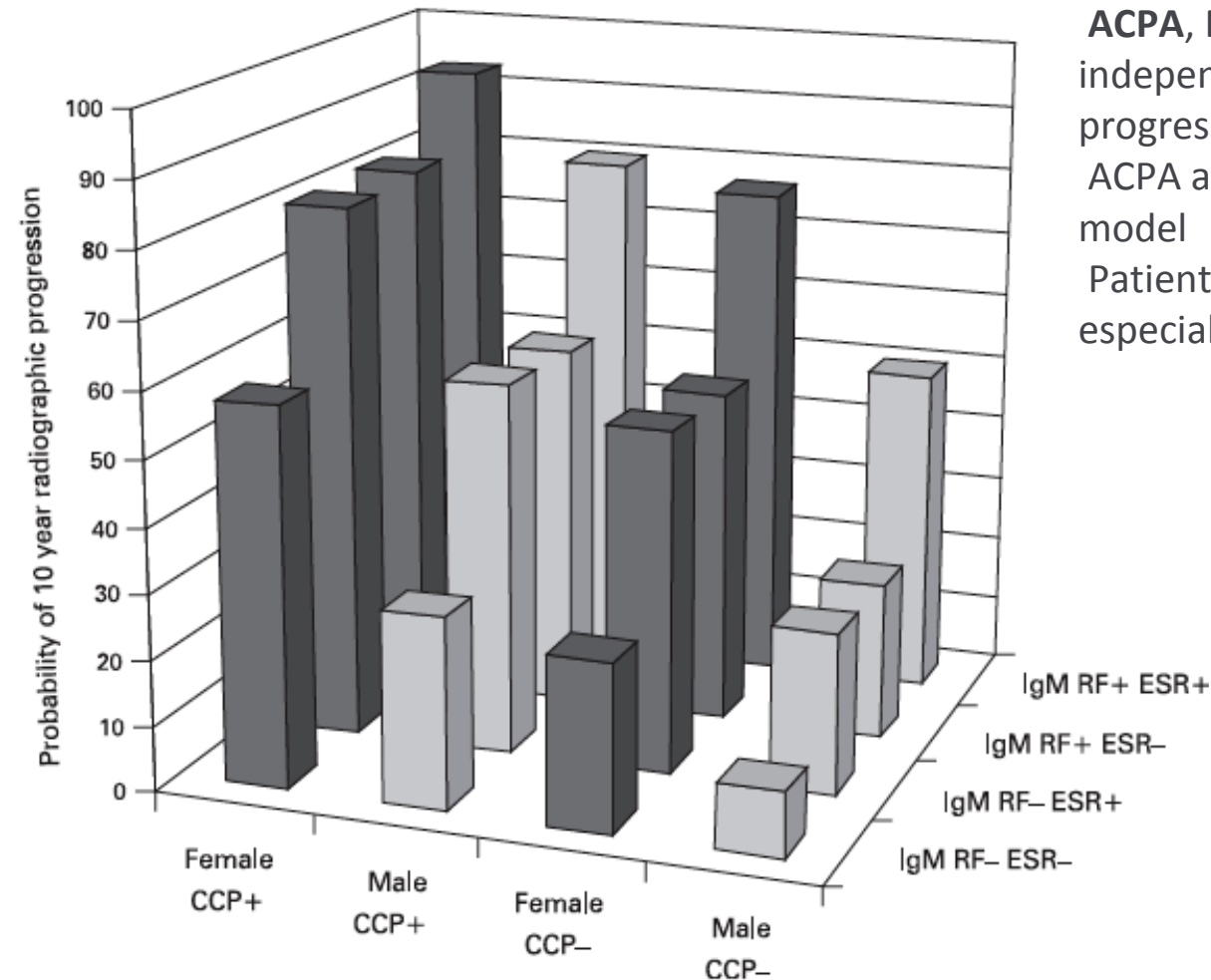


# Synovial expression of CXCL13 is increased in more severe RA

FIG. 4 Association of CXCL13 expression levels with bone damage



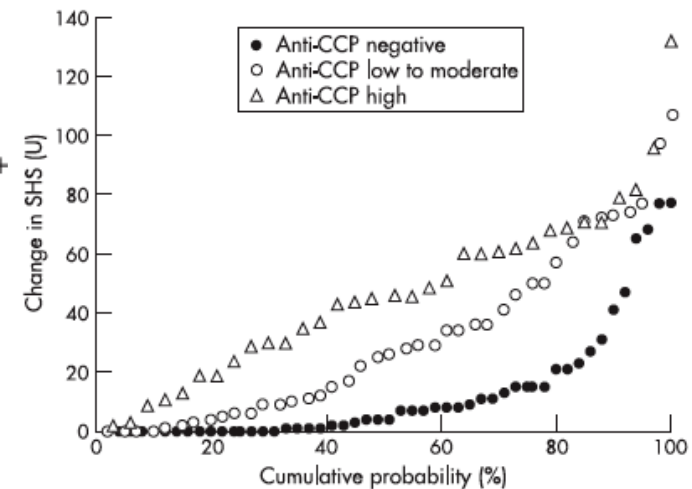
# Radiographic progression



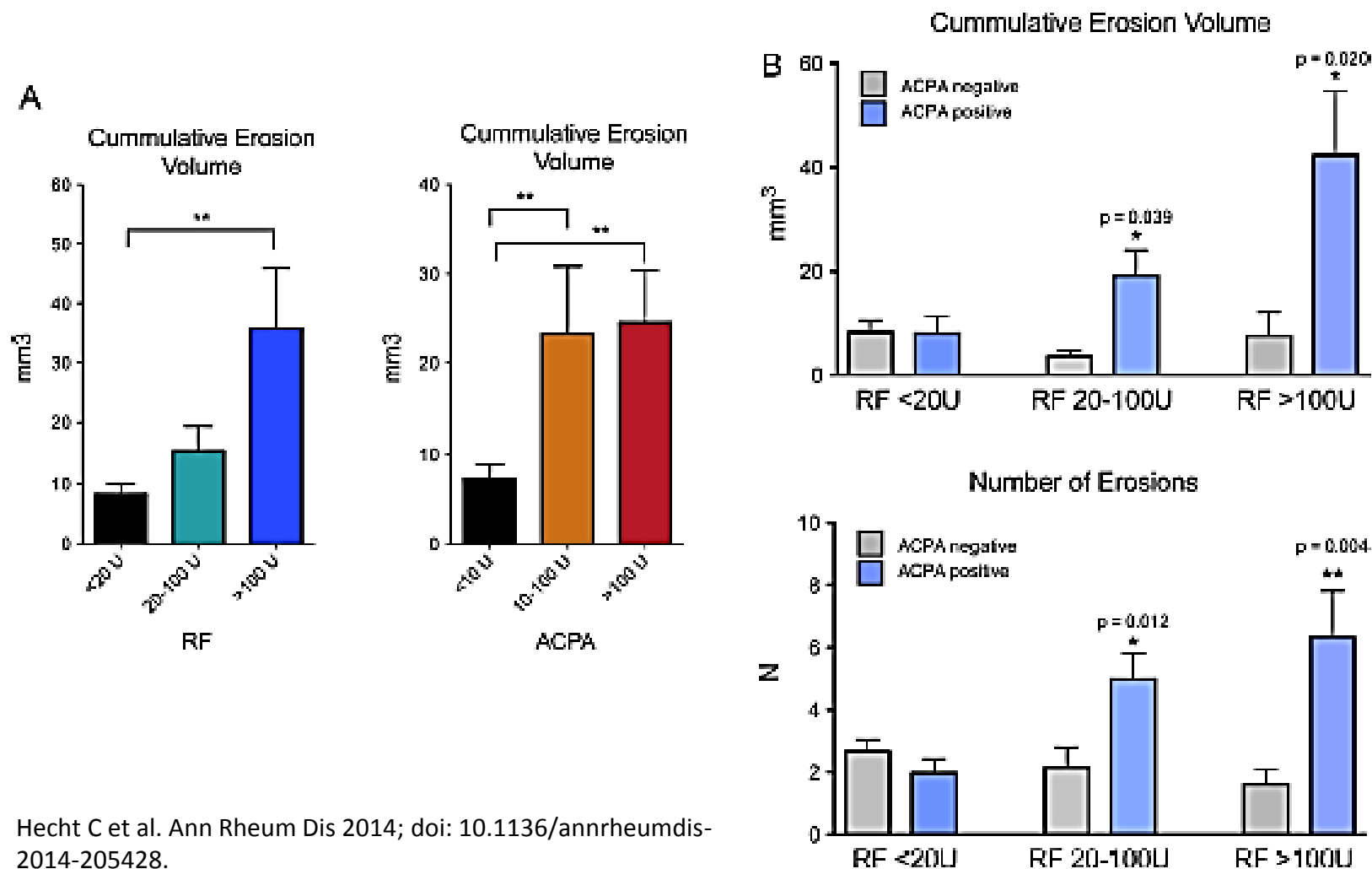
**ACPA, RF IgM, ESR and female sex** are all independent predictors of radiographic progression.

ACPA are the strongest predictors in this model

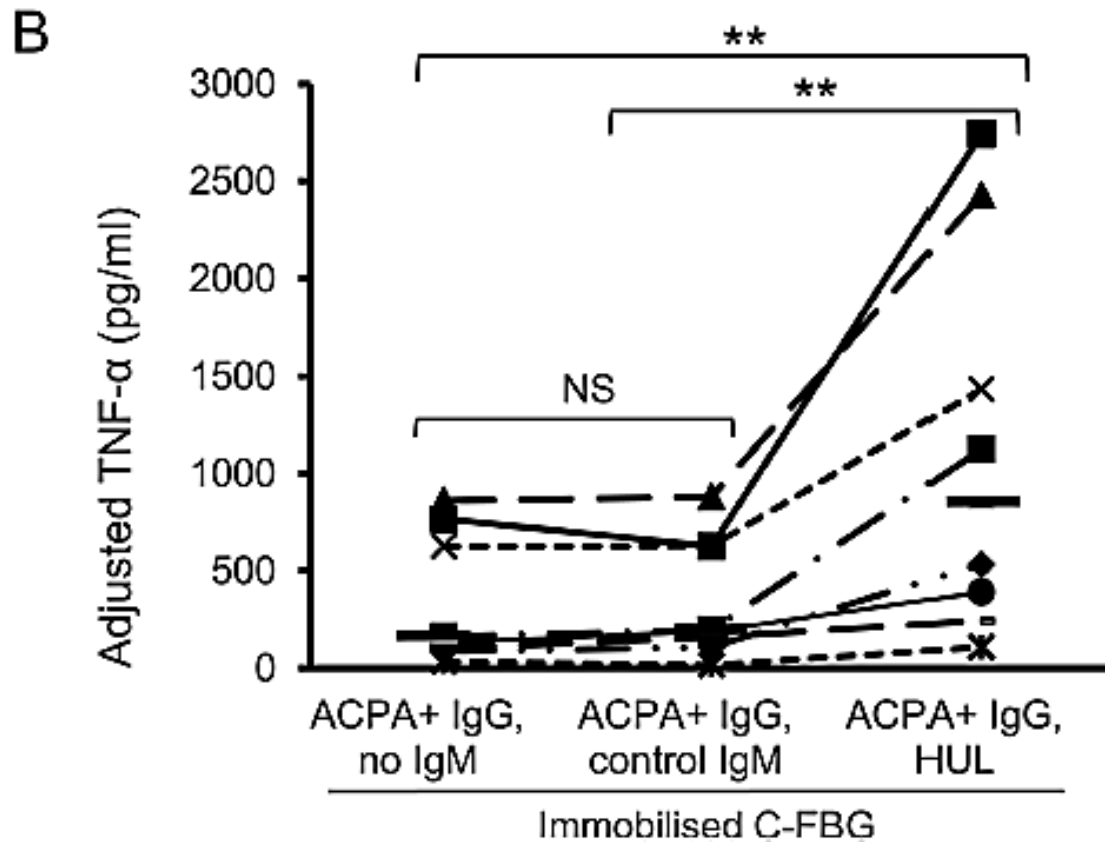
Patients with **high levels of ACPA** are especially prone to radiographic progression



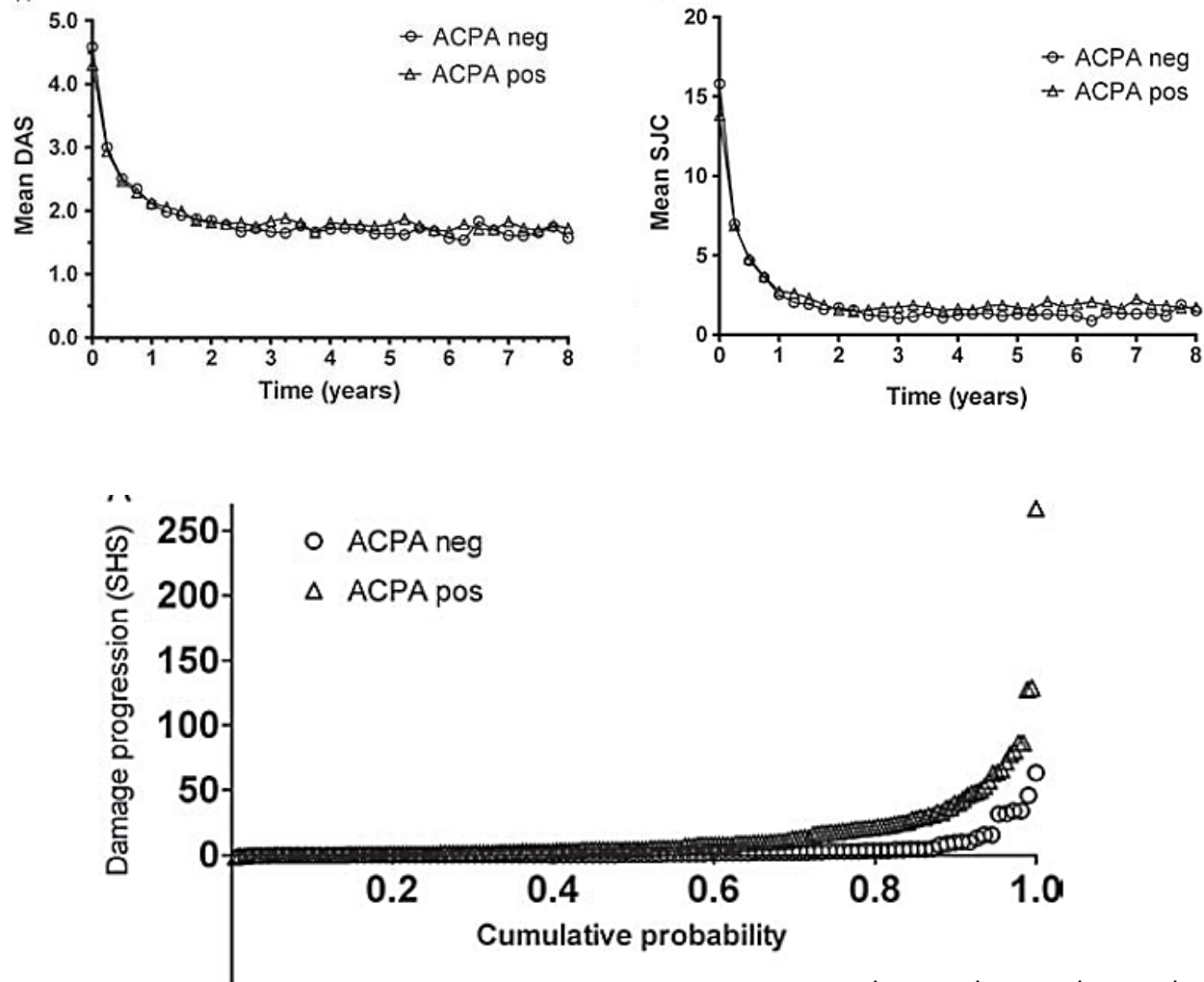
# ACPA and RF show an additive effect on erosion number and erosion size



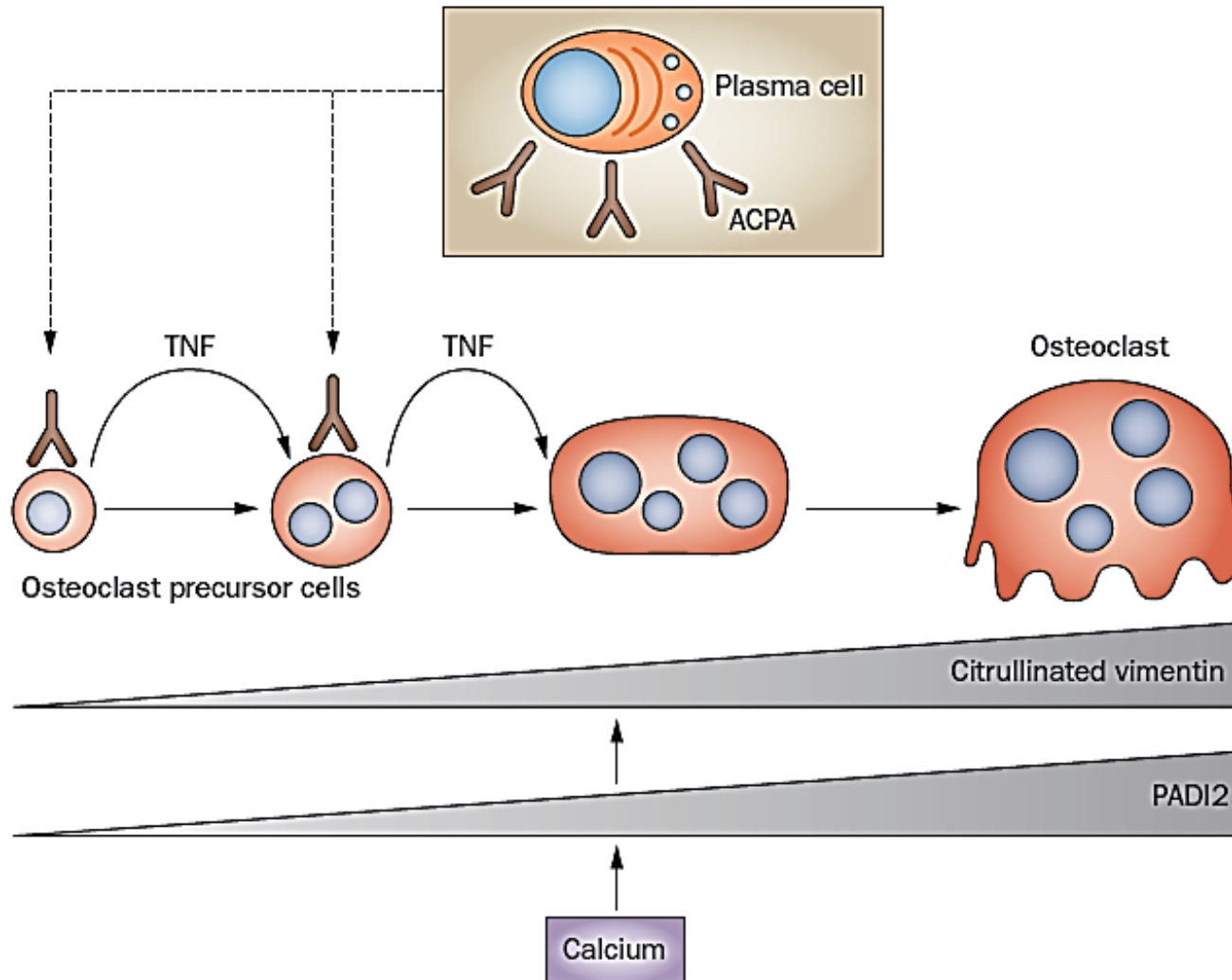
# IgM RF amplifies the inflammatory response of macrophages induced by ACPA-IC



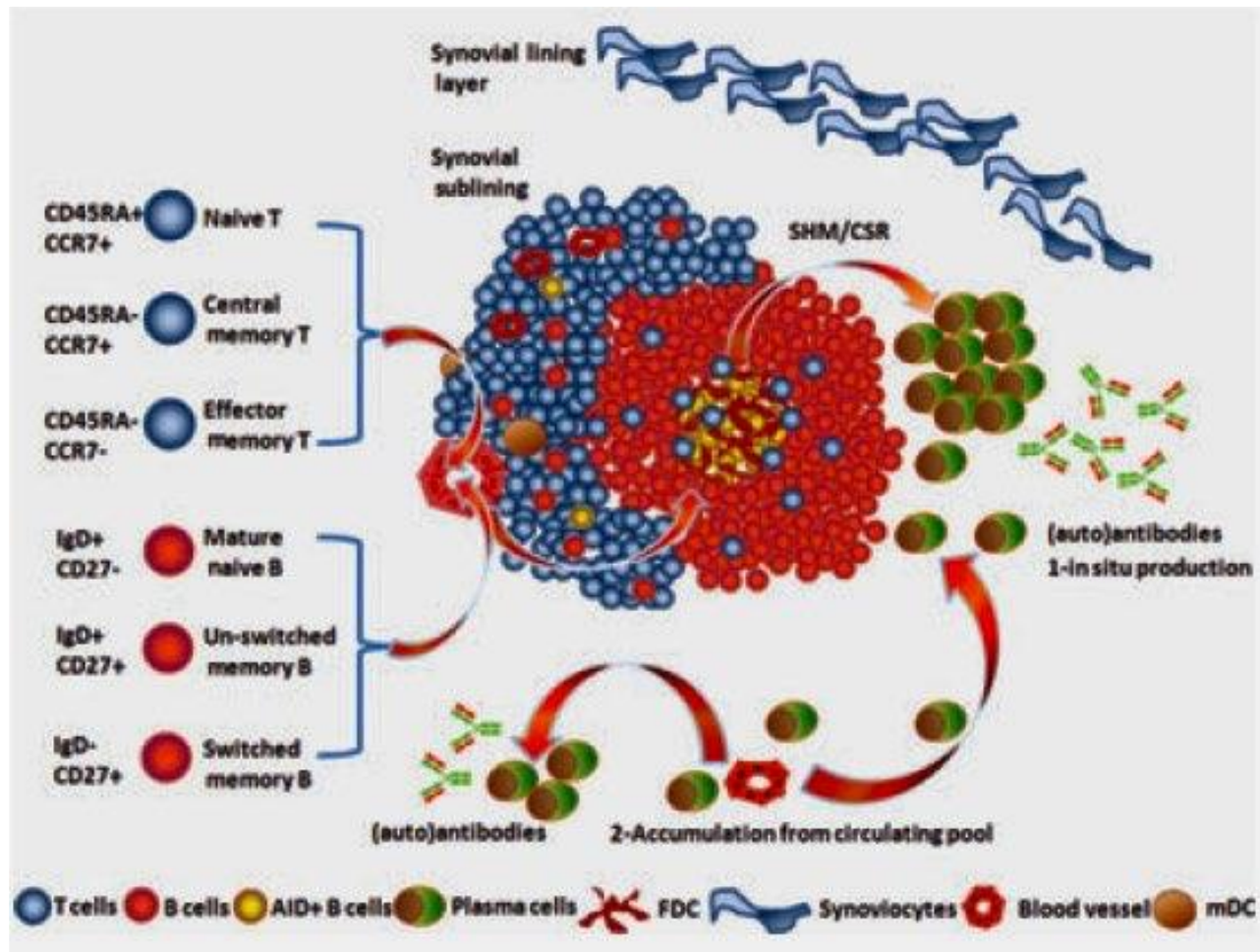
# ACPA predict radiographic progression irrespective of clinical response



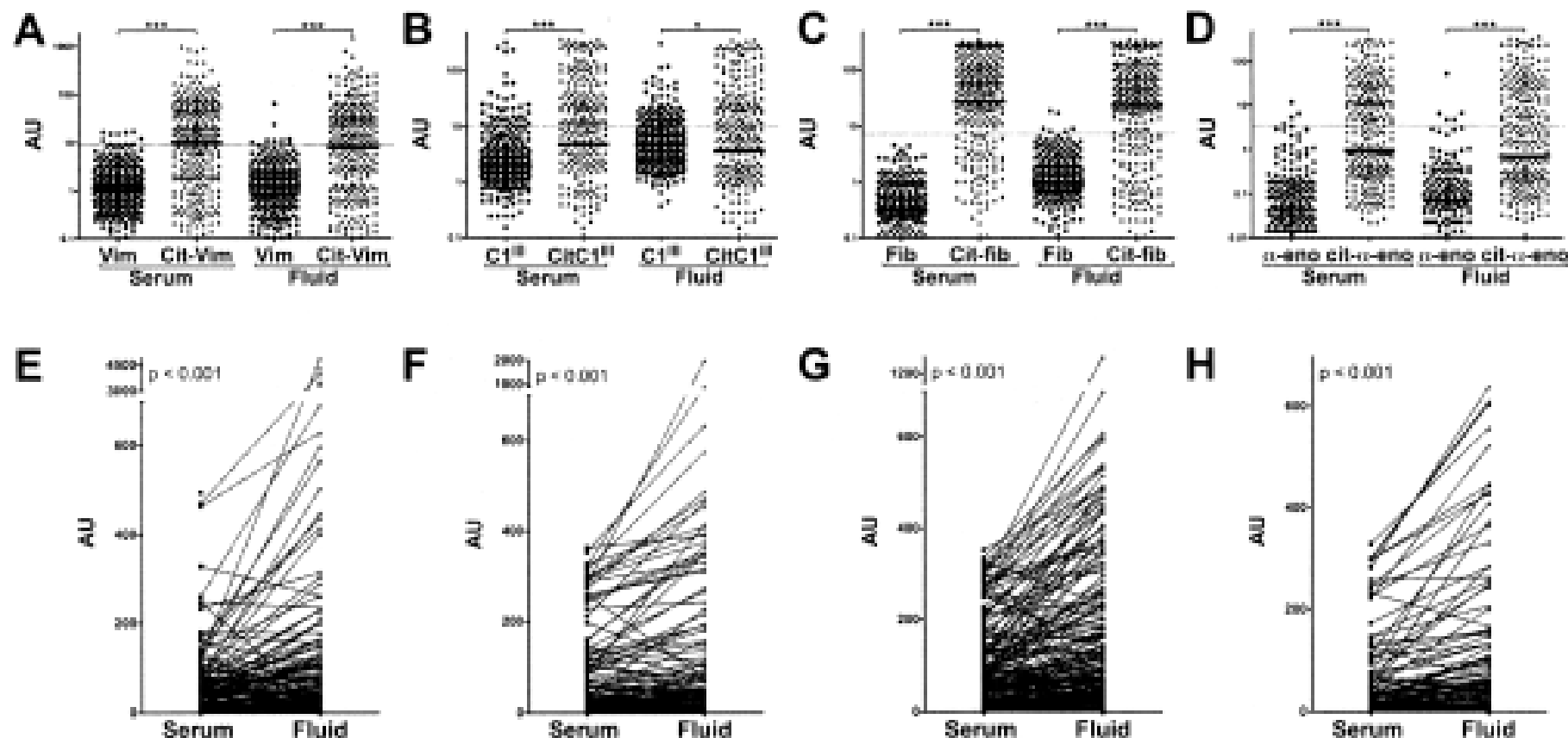
# ACPA are pathogenic: osteoclast activation



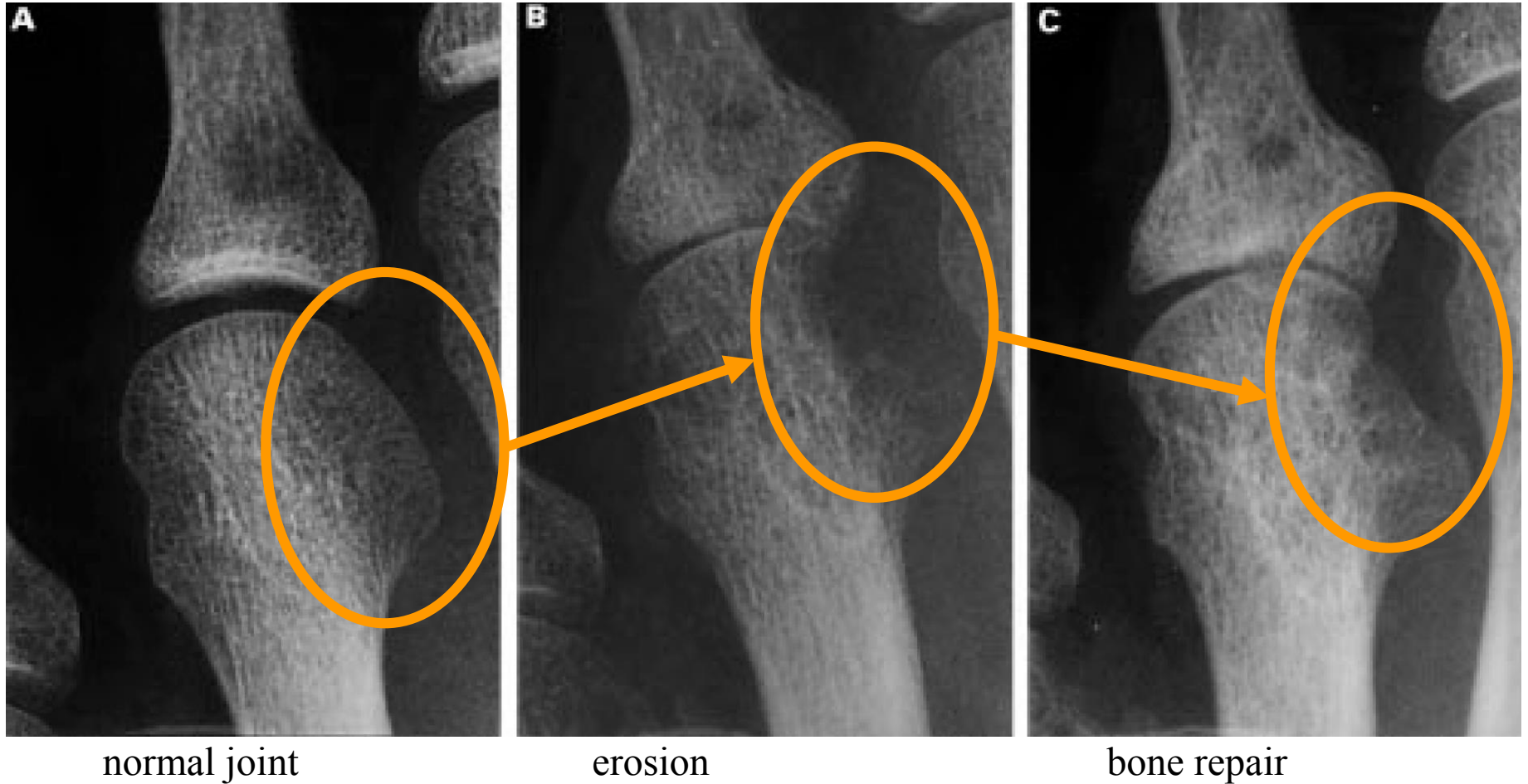
# Synovial B cells: production of autoantibodies



# Antibodies to several citrullinated antigens are enriched in the joints of rheumatoid arthritis patients



# Can erosions heal?





# Repair of joint erosions in rheumatoid arthritis: prevalence and patient characteristics in a large inception cohort

Michael P M van der Linden, Ramona Boja, Naomi B Klarenbeek, Tom W J Huizinga, Désirée M van der Heijde and Annette H M van der Helm-van Mil

*Ann Rheum Dis* published online 18 May 2009;  
doi:10.1136/ard.2009.108332

250 RA pts, Leiden Early Arthritis Clinic; yearly made radiographs

**REPAIR** = agreement of two readers in having a negative change in the Sharp–van der Heijde erosion scores that persisted for at least two years

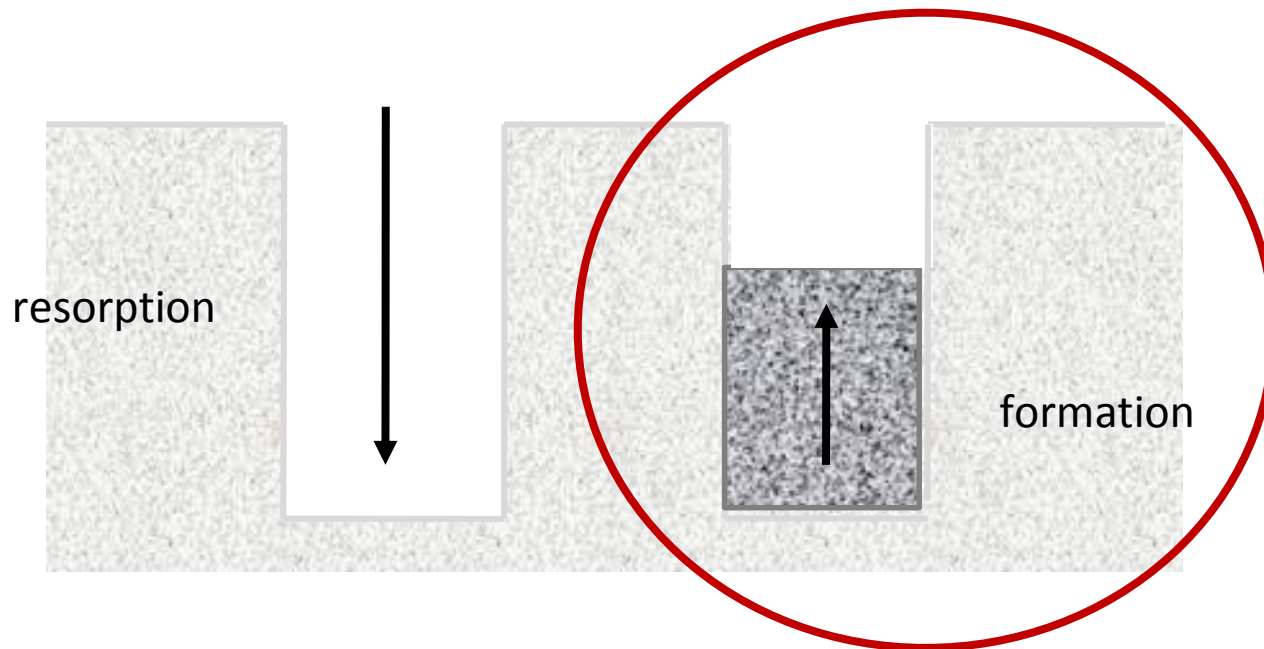
**32 joints with repair identified in 18 (7.2%) patients**

highest frequency of repair occurring after 4 to 6 years follow-up

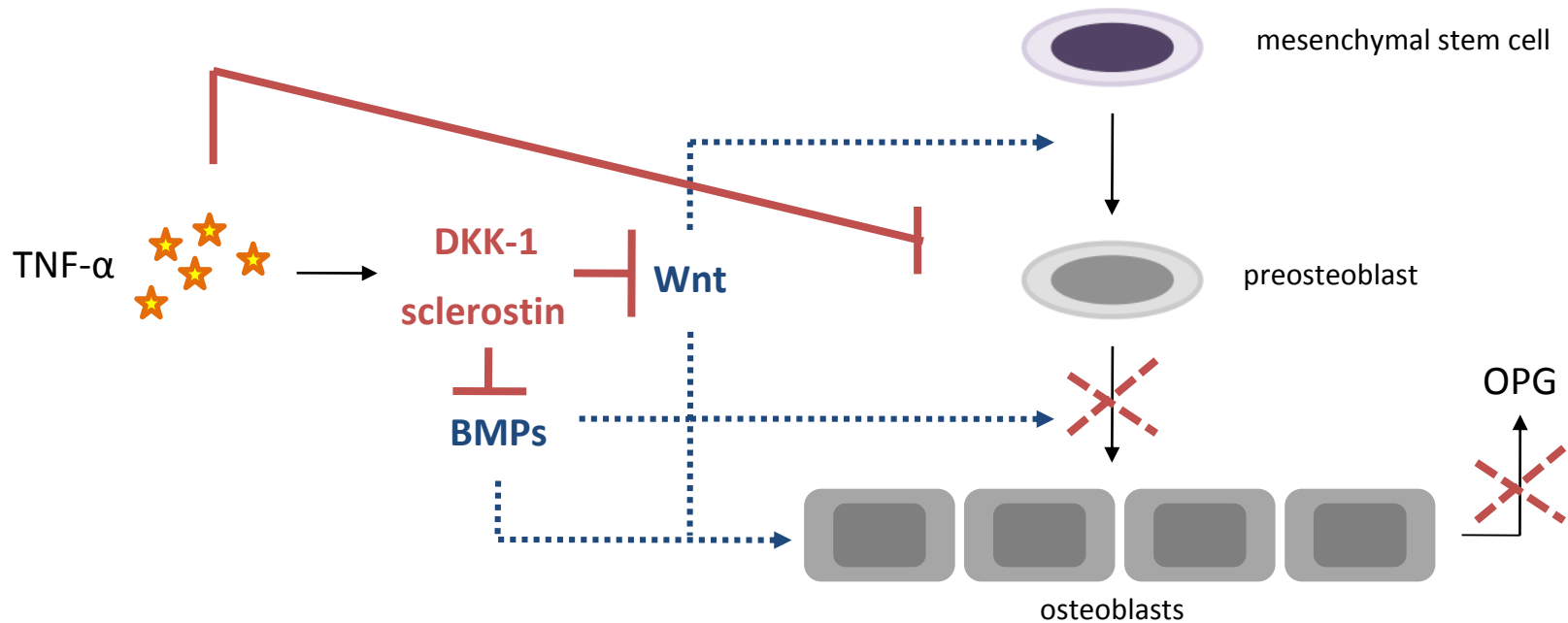
significant higher Sharp-van der Heijde scores in pts with repair compared to patients without repair in the disease course



*Implicit in the loss of articular and juxta-articular bone is that there is a dysregulation in bone remodeling such that **resorption** exceeds **formation**.*



# blunted osteoblast activity in RA synovitis

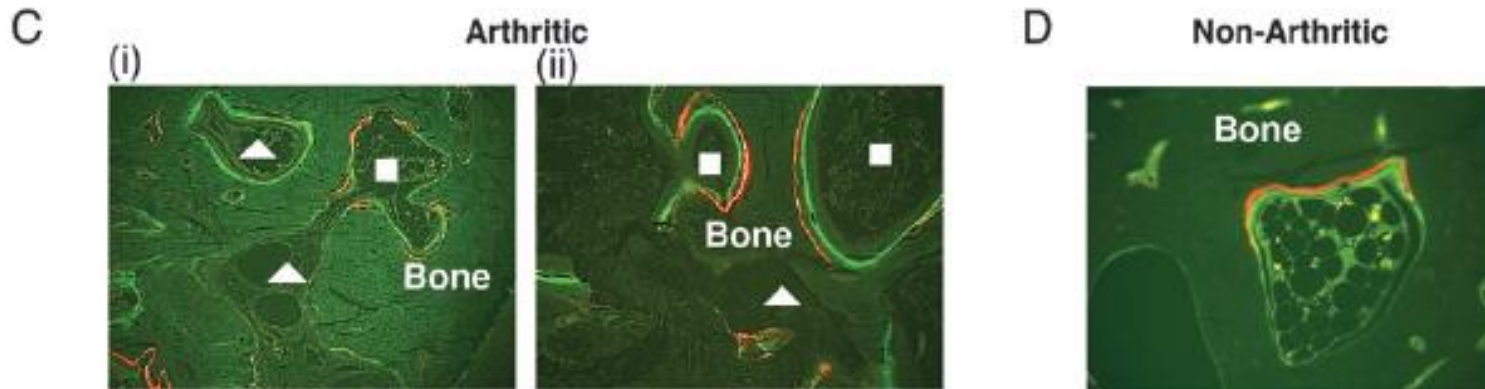


*Gilbert L et al. J Biol Chem 2002.*

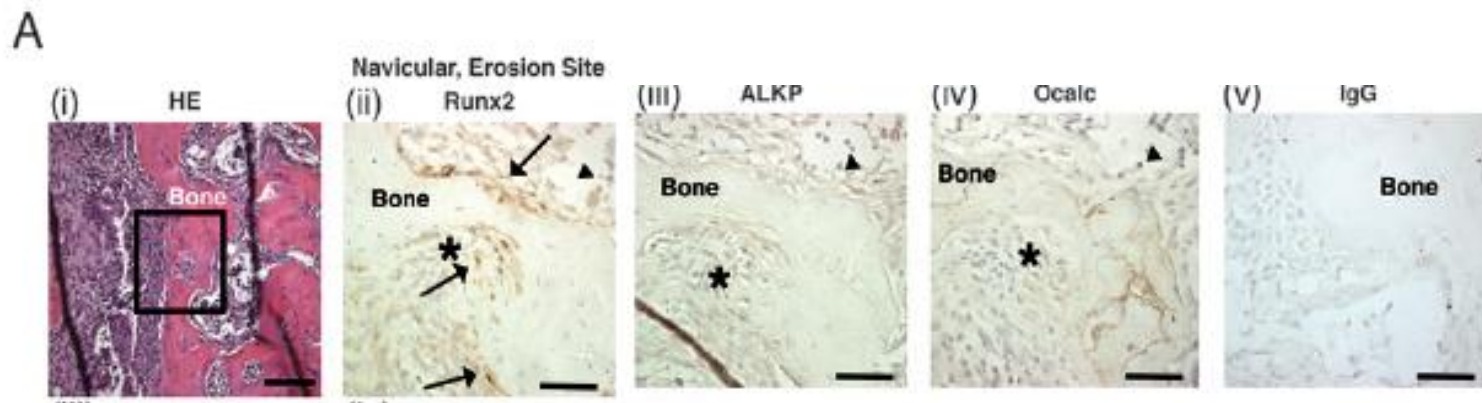
*Diarra D, et al. Nat Med 2007;13:156-63.*

*Vincent C, et al. J Bone Miner Res 2009;24:1434-49.*

# Osteoblast function is compromised at sites of focal bone erosion in inflammatory arthritis

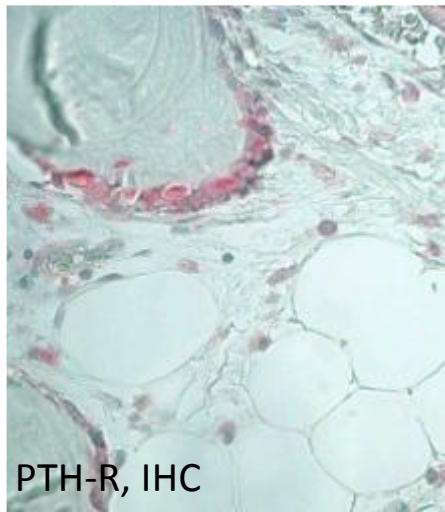


Formation of mineralized bone is reduced at bone surfaces directly adjacent to inflammation

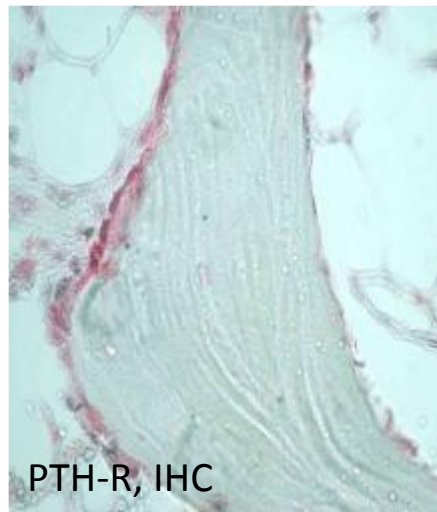


Paucity of cells expressing the mid/late stage osteoblast marker alkaline phosphatase

## Subchondral repair in RA



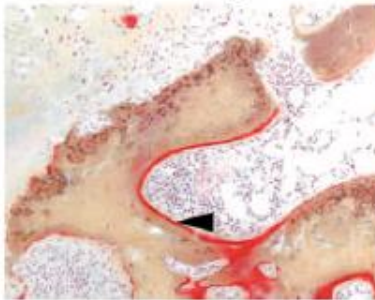
PTH-R, IHC



PTH-R, IHC

*Bugatti S, et al. Arthritis Rheum 2005.*

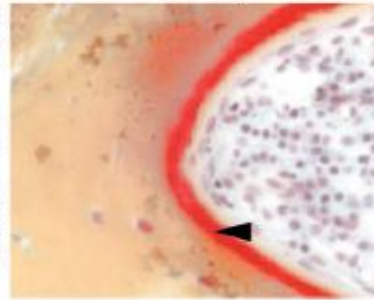
A Osteoid deposits



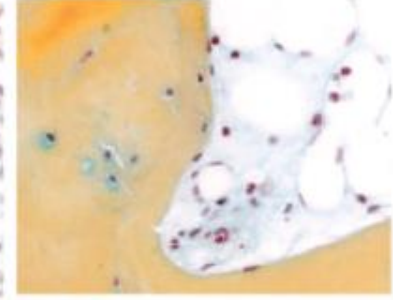
B Control



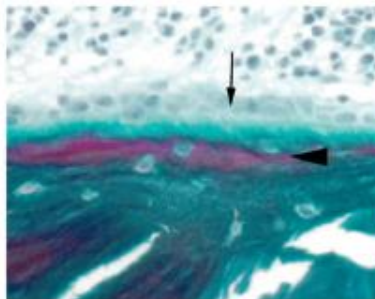
C Osteoid deposits



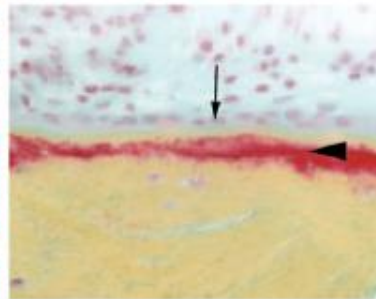
D Control



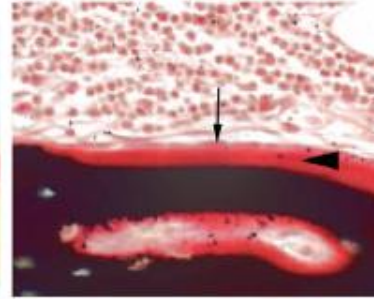
E Goldner



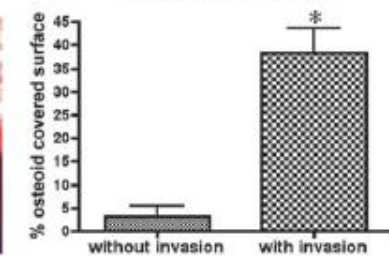
F Movat



G Von Kossa



H Osteoid deposition  
in subcortical bone

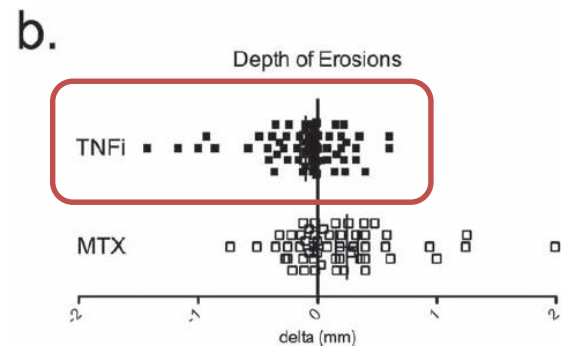
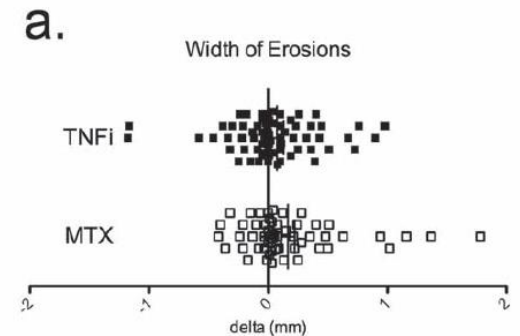
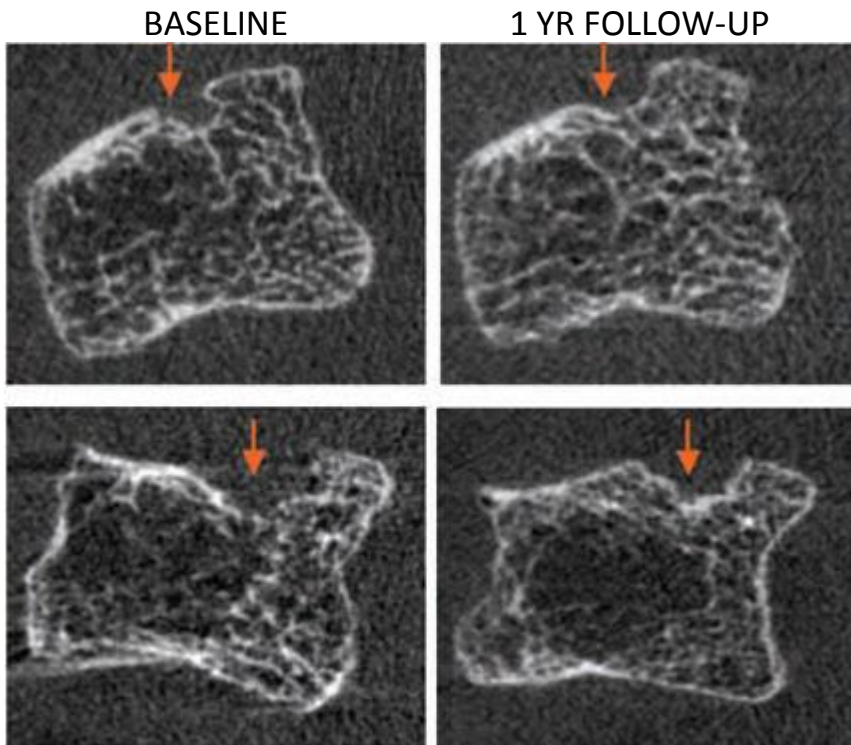


*Jimenez-Boj E, et al. J Imm 2005.*

# Repair of bone erosions

Bone erosions in RA patients treated with TNFi show evidence of repair in contrast to bone erosions in patients treated with MTX.

Repair is associated with a decrease in the depth of lesions and sclerosis at the bases of the lesions. Repair thus emerges from the endosteal rather than periosteal bone compartment and probably involves the bone marrow.



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