Le sindromi da edema midollare dell'osso

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Disclosures

- ***Invited speaker for:***
  - ***Amgen***
  - ***Ely Lilly***
  - ***UCB***
  - ***Abbvie***
  - ***Roche***
  - ***BMS***

Transient Osteoporosis: transient bone marrow oedema?

Wilson AJ, Murphy WA, Hardy DC, Totty WG

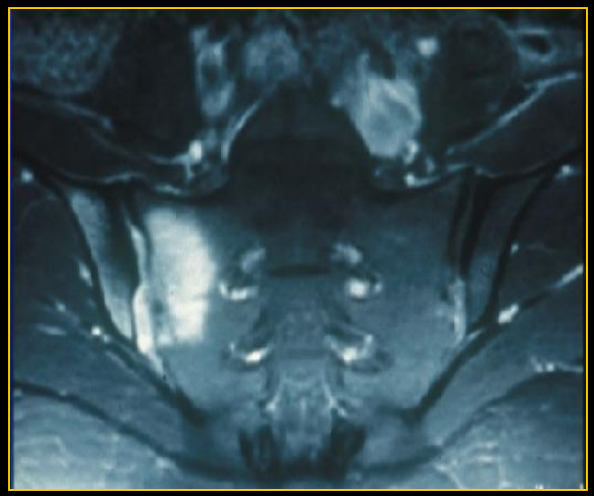
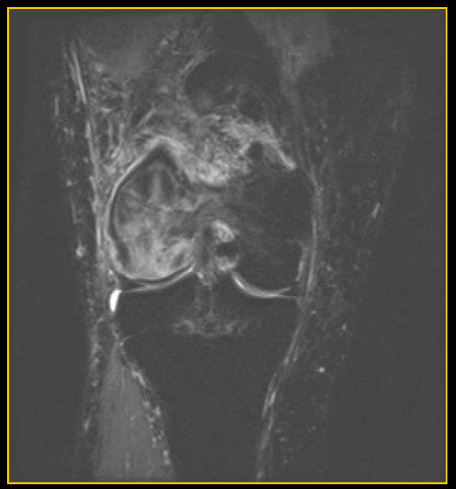
Radiology 1988; 167:757-60

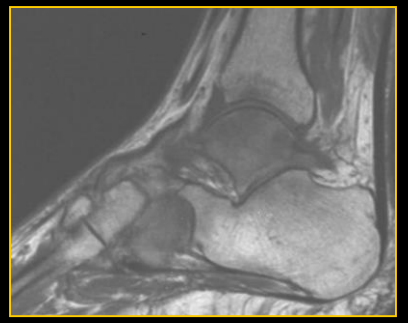
"….ill-defined bone marrow hyperintensities on T2-weighted MR images in patients ***with debilitating knee and hip pain ……"***

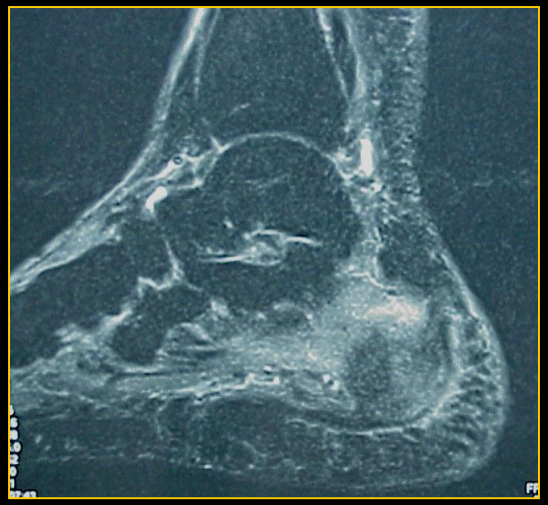
" Corresponding standard radiographs were ***normal or demonstrated nonspecific osteopenia ……"***

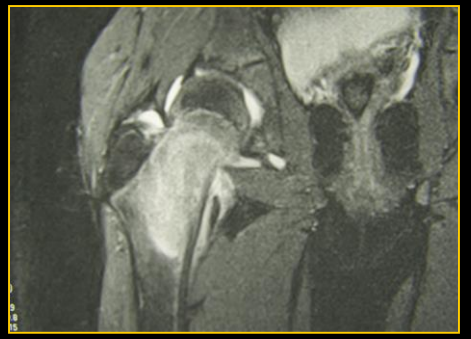
"The term Bone Marrow Oedema reflects a lack of a better term and emphasizes ***the generic character of the condition ……."***

Bone marrow edema : a final common pathway for extremely different conditions

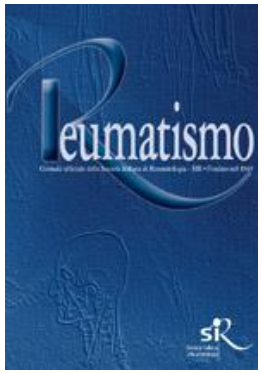






Bone Marrow Edema:
List of various terms found in the Literature

- Acute bone marrow edema
- Bone bruising
- Bone marrow lesions
- Bone marrow edema syndrome
- Edema-like bone marrow abnormality
- Migratory transient Osteoporosis
- Post-transplant distal limb syndrome
- Regional migratory Osteoporosis
- Regional transient Osteoporosis
- Shifting bone marrow edema of the knee
- Transient bone marrow edema syndrome
- Transient osteoporosis
- Transient migratory Osteoporosis
- Transient bone marrow edema



REVIEW *Reumatismo, 2014; 66 (2): 184-196*

A clinical overview of bone marrow edema

M. Manara, M. Varenna
Division of Rheumatology, Gaetano Pini Institute, Milan, Italy

<u>Bone Marrow Edema</u> is a descriptive term which identifies a specific Magnetic Resonance Imaging pattern that can be observed in a number of clinical entities, often characterized by pain as their main symptom, but show significant differences in terms of histopathological findings, causal mechanisms and prognosis.

Bone Marrow Edema

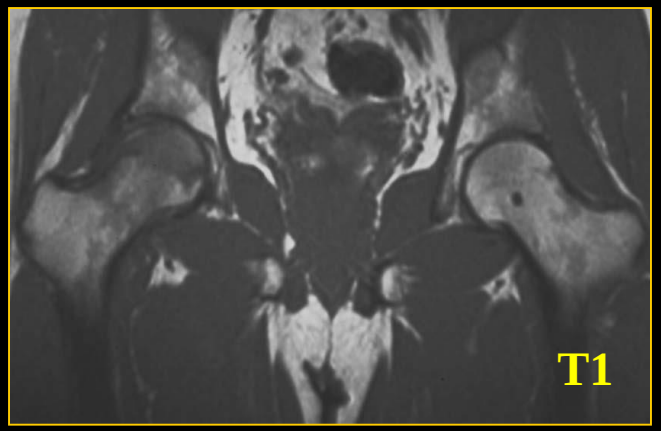
- **Diagnosis**
- **Pathophysiology**
- **Clinical relevance**
- **Predictive role**

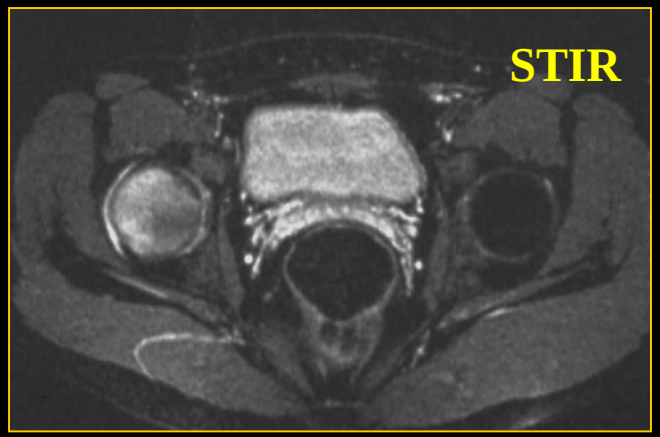
Bone Marrow Edema

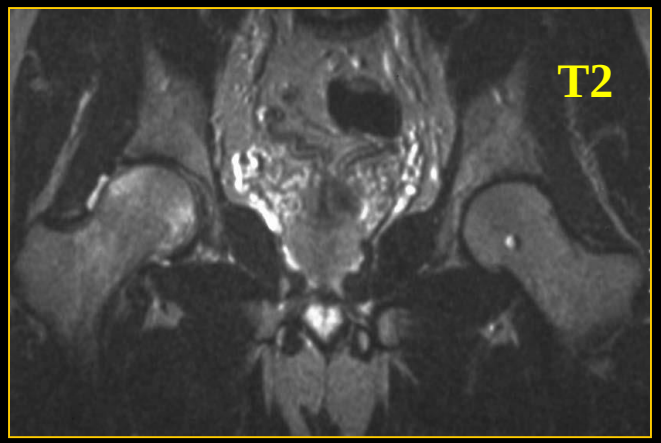
- **Diagnosis**
- **Pathophysiology**
- **Clinical relevance**
- **Predictive role**

Signal characteristics of bone oedema at MR imaging

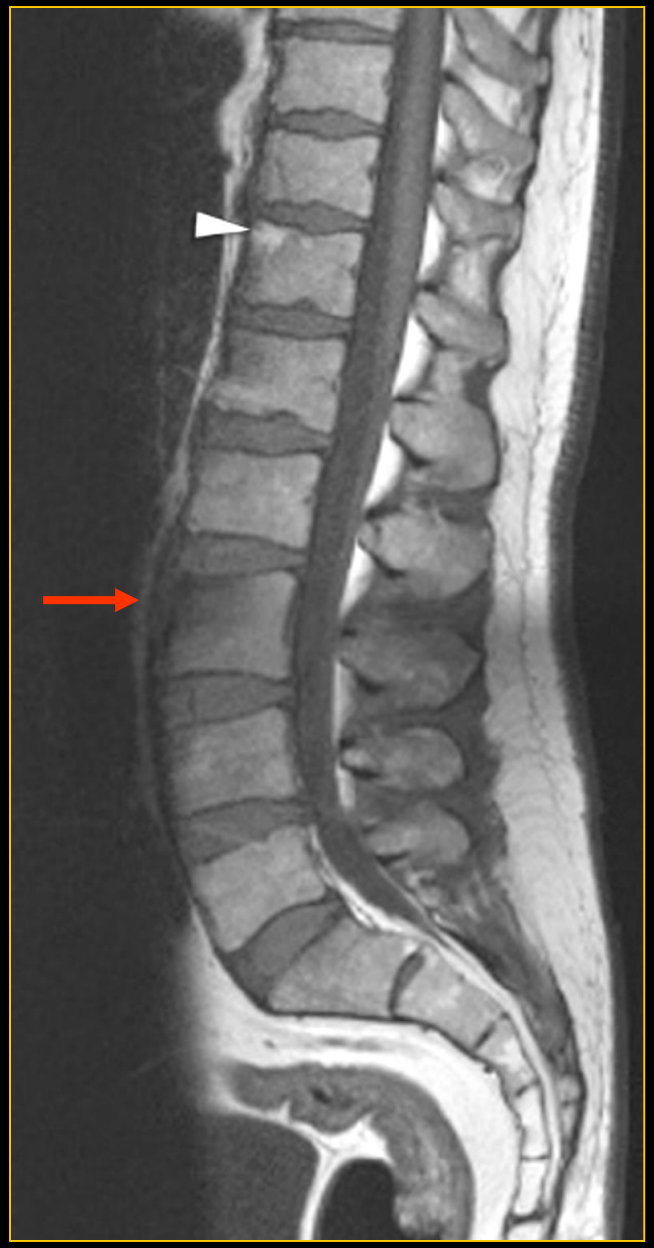
T1 weighted	Hypointense
T2 weighted	Hyperintense
T2 Fat suppressed (STIR)	Hyperintense
Post - i.v. gadolinium	Enhancement



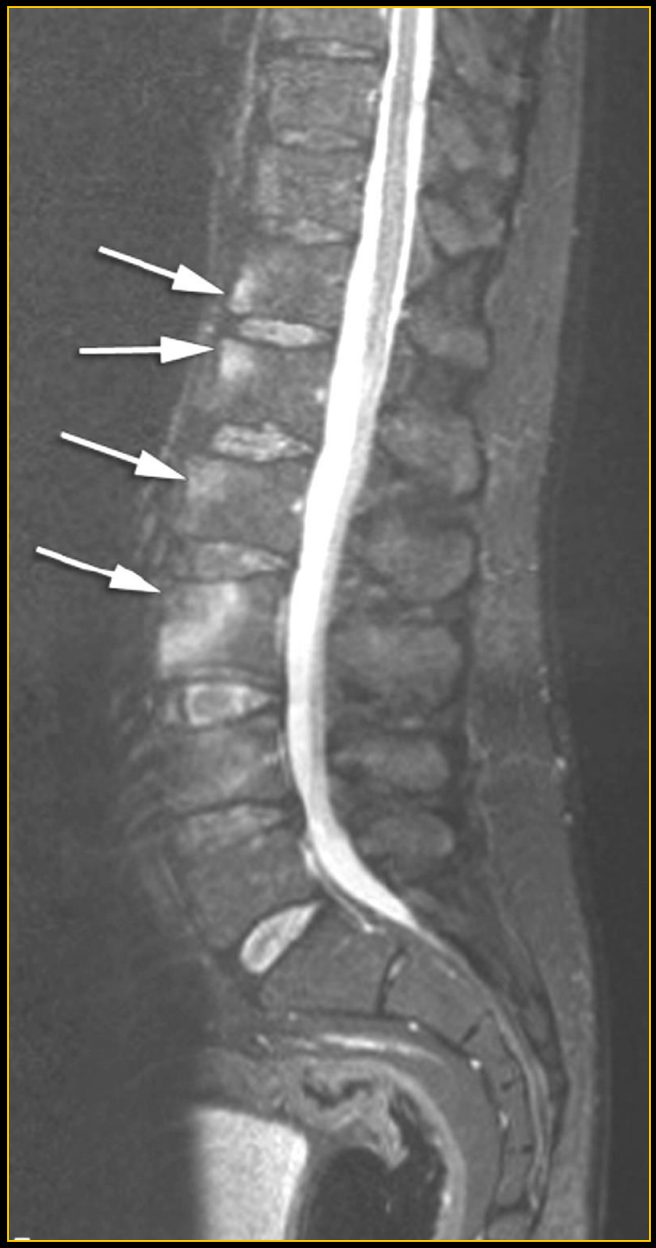




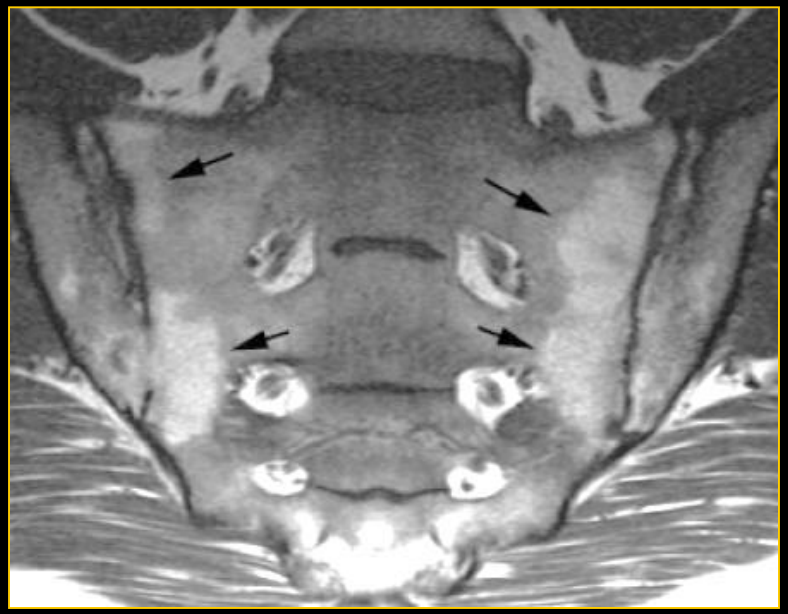
T 1



T 2



T1 : Chronic, not Active Sacroiliitis



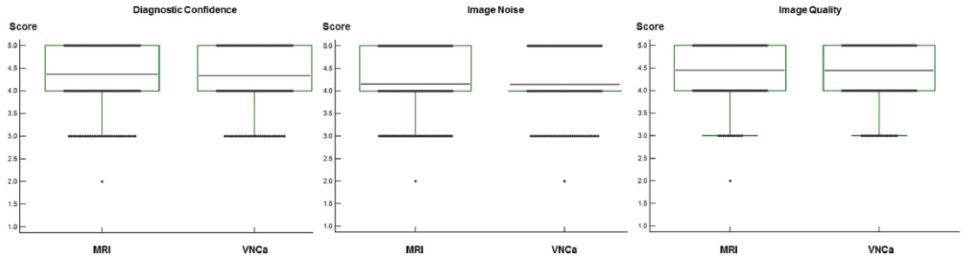
T2 STIR: Active Sacroiliitis

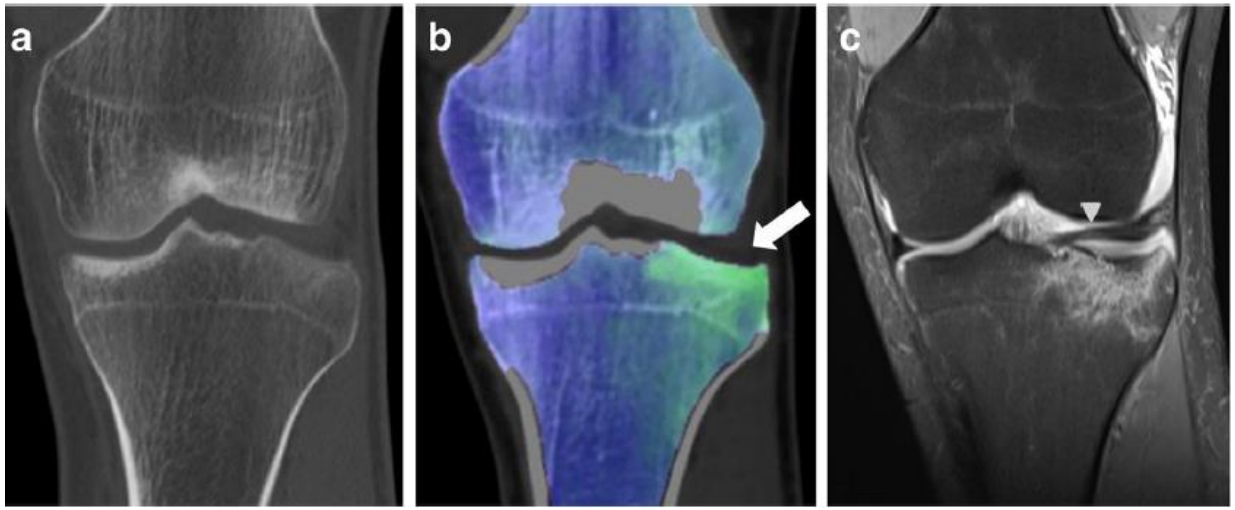
European Radiology
https://doi.org/10.1007/s00330-019-06304-7

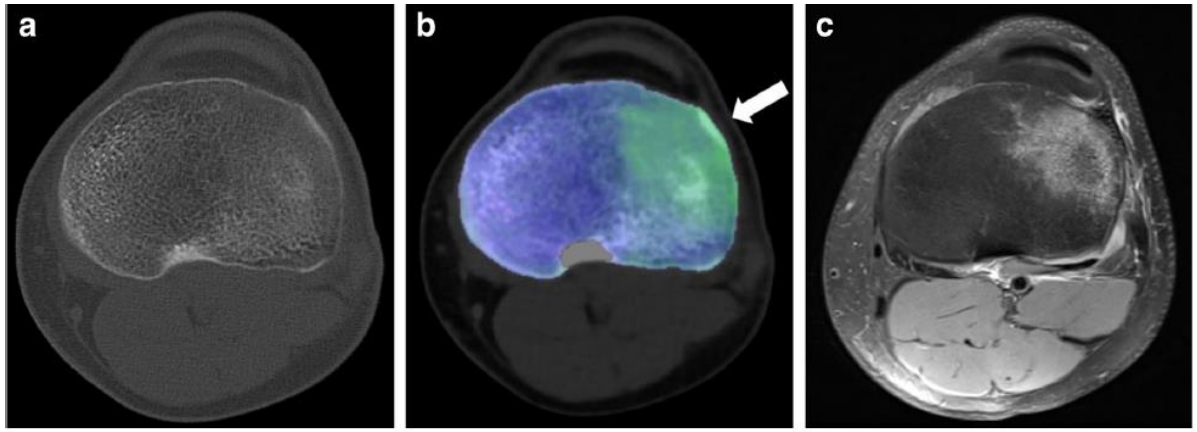
MUSCULOSKELETAL

Color-coded virtual non-calcium dual-energy CT for the depiction of bone marrow edema in patients with acute knee trauma: a multireader diagnostic accuracy study

Christian Booz[1] · Jochen Nöske[1] · Lukas Lenga[1] · Simon S. Martin[1] · Ibrahim Yel[1] · Katrin Eichler[2] · Tatjana Gruber-Rouh[2] · Nicole Huizinga[3] · Moritz H. Albrecht[1] · Thomas J. Vogl[2] · Julian L. Wichmann[1,4]





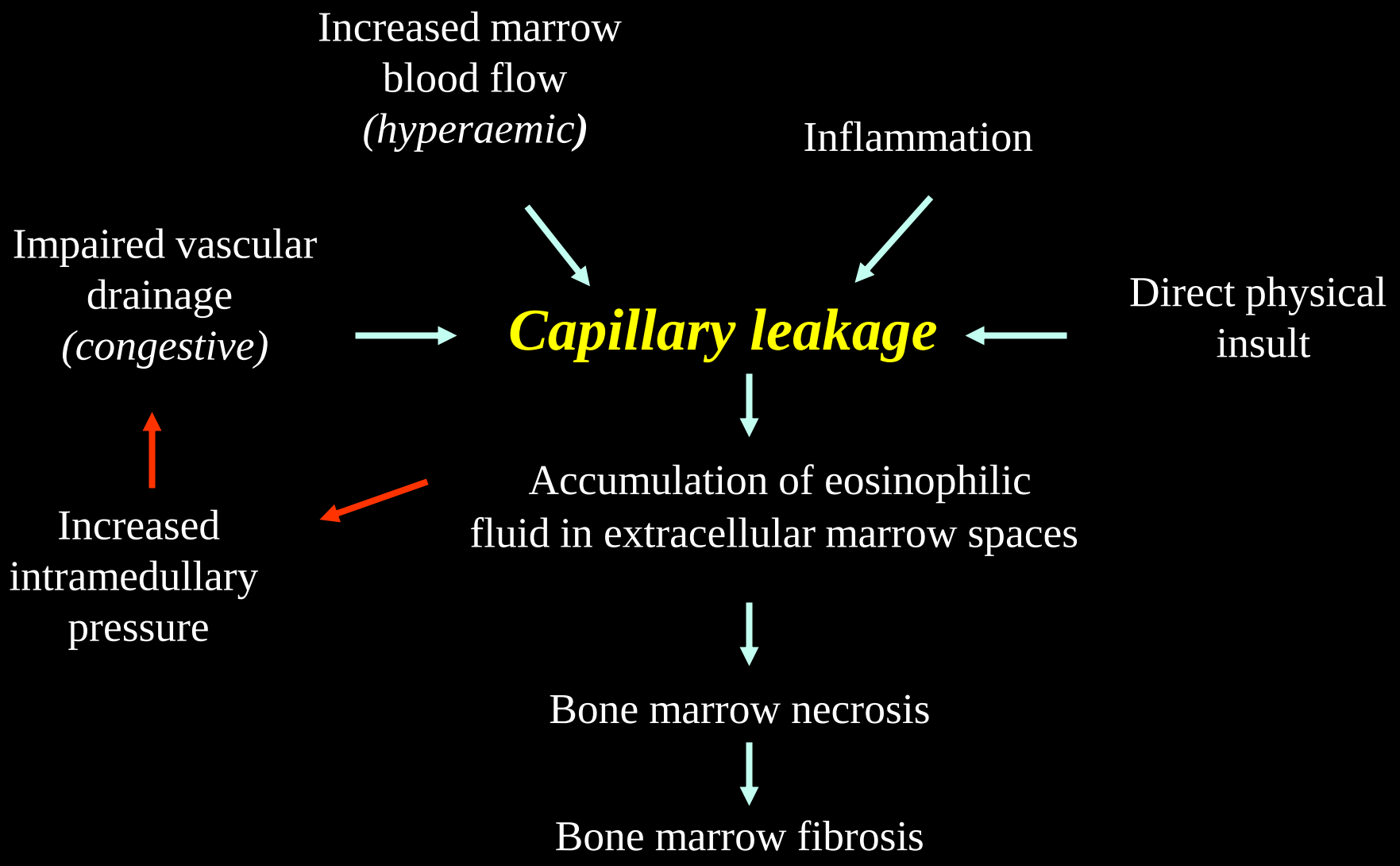


Booz C et al. *Eur Radiol* 2019

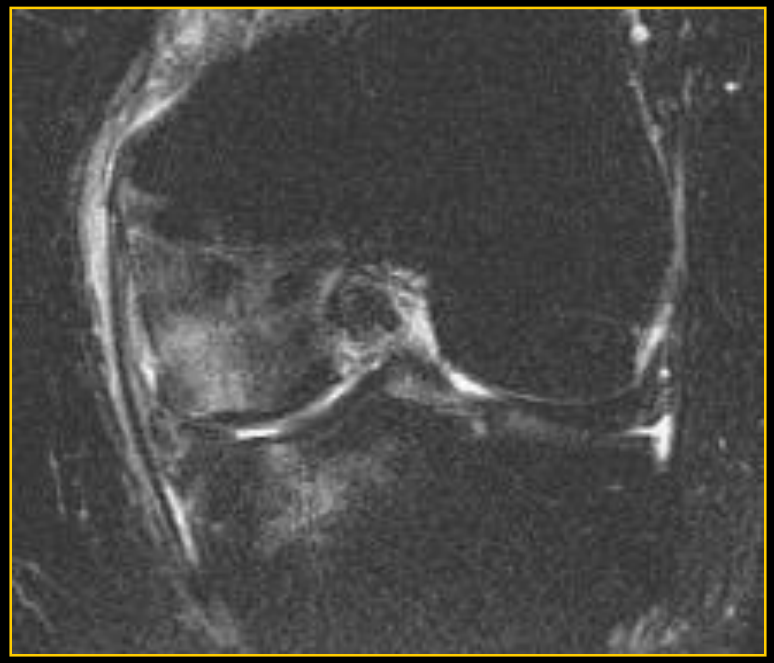
Bone Marrow Edema

- Diagnosis
- **Pathophysiology**
- Clinical relevance
- Predictive role

The pathophysiology of Bone Marrow Edema

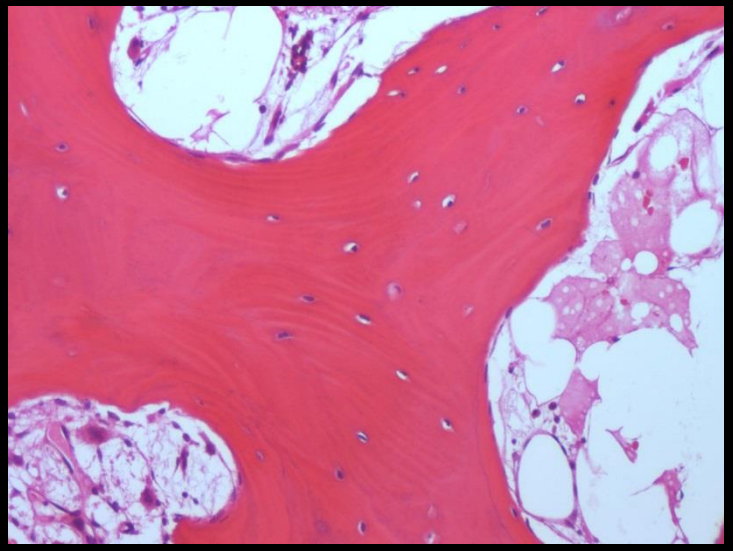


BME = BMA = BML

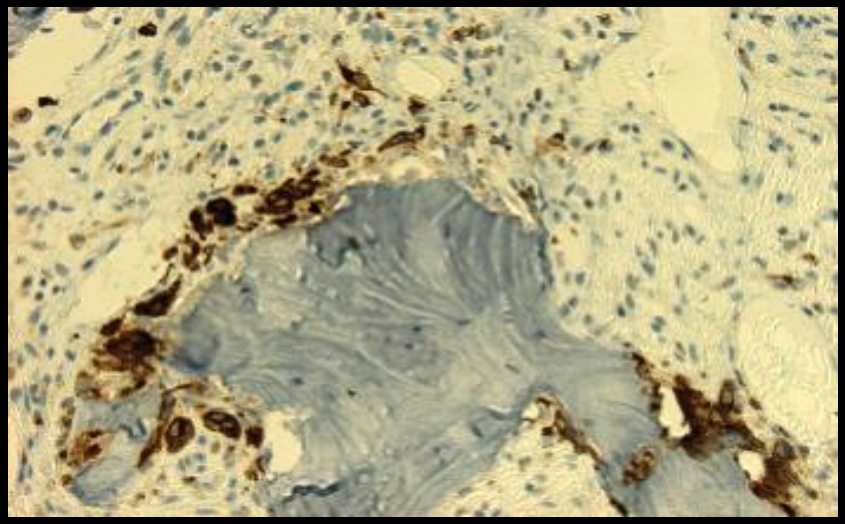


Histopathology shows fibrosis, osteonecrosis and bone remodeling but little actual edema

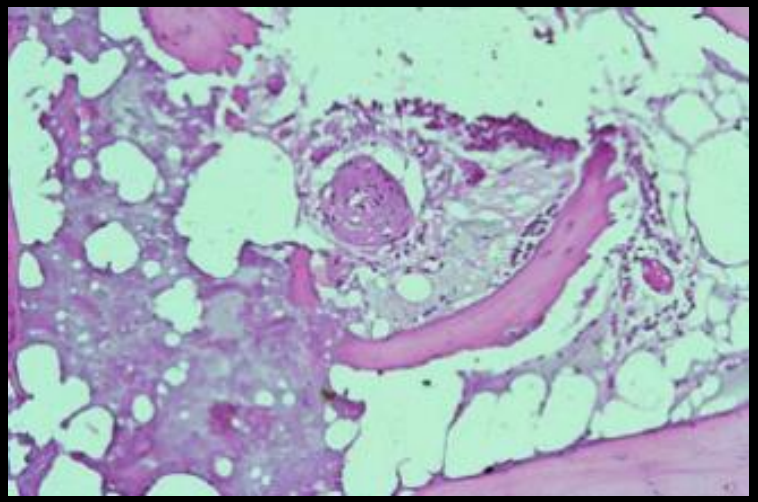
Bone marrow “abnormality” (BMA) or Bone Marrow “lesion” (BML) preferred term



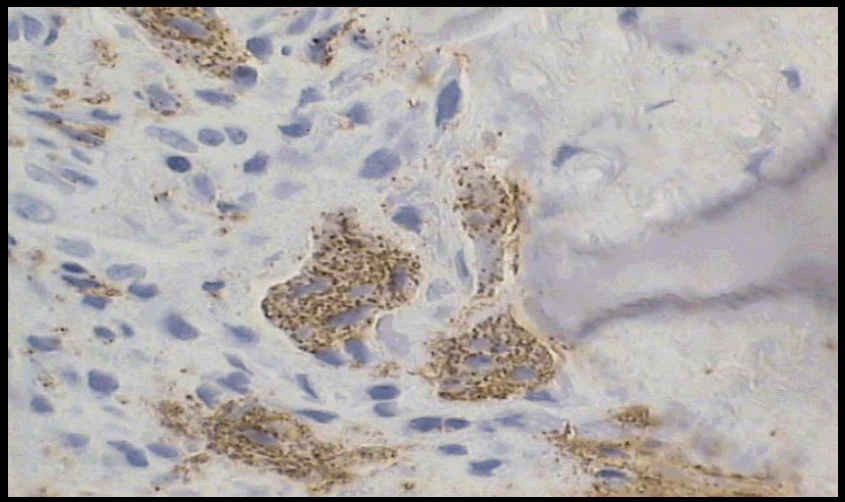
CRPS-I: Personal observation



RA: Dalbeth N et al. *Ann Rheum Dis* 2009



OA: Hunter DJ et al. *Arthritis Res Ther* 2009



SA: Marzo-Ortega H et al. *Rheumatology* 2008

Rheumatol Int (2012) 32:575–584
DOI 10.1007/s00296-011-2141-2

REVIEW ARTICLE

Bone marrow lesions: a universal bone response to injury?

Erik Fink Eriksen · Johan Diederich Ringe

Rheumatol Int **2012**

Bone Marrow Lesions Etiology

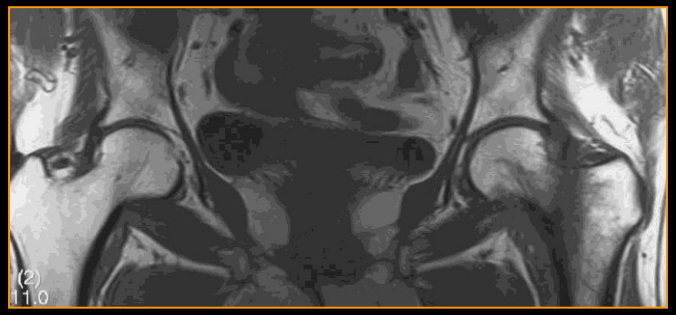
- ***Trauma***
  - Fracture (acute, osteoporotic, stress)
  - Local transient Osteoporosis
  - Bone bruise
  - Osteochondral injuries
- ***Degenerative lesions***
  - Osteoarthritis
- ***Inflammatory lesions***
  - Inflammatory arthropaties and enthesitis
- ***Ischemic lesions***
  - Avascular necrosis
  - CRPS type I
  - Sickle cell anemia
- ***Infectious lesions***
  - Osteomyelitis
  - Diabetic foot, Charcot Arthropaty
  - Sepsis
- ***Metabolic/Endocrine lesions***
  - Hydroxyapatite deposition disease (HADD)
  - Gout
- ***Iatrogenic lesions***
  - Local surgery
  - Radiotherapy
- ***Neoplastic (and neoplastic-like) lesions***

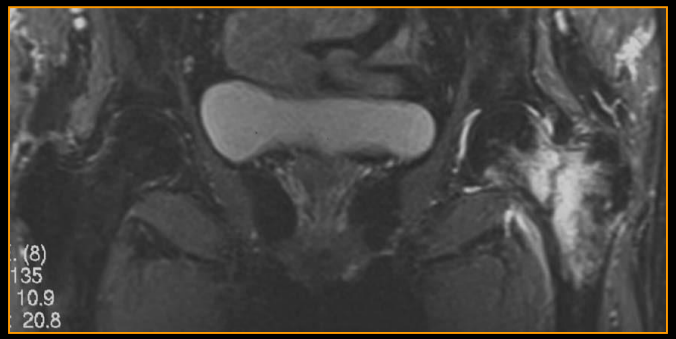
Bone marrow oedema : a final common pathway

- **Traumatic**
- **Neoplastic**
- **Vascular**
- **Degenerative**
- **Inflammatory**

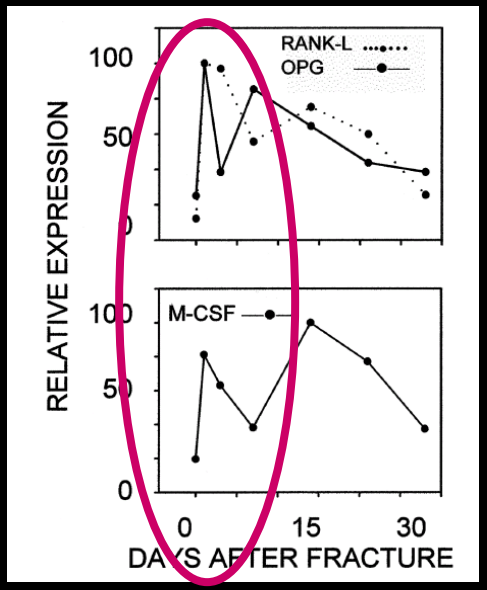
Traumatic Bone Edema

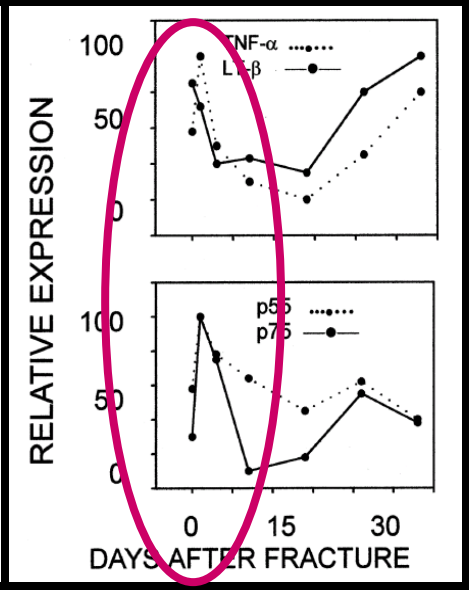
Condition	Proposed pathophysiology
Trauma	Fracture/microfracture



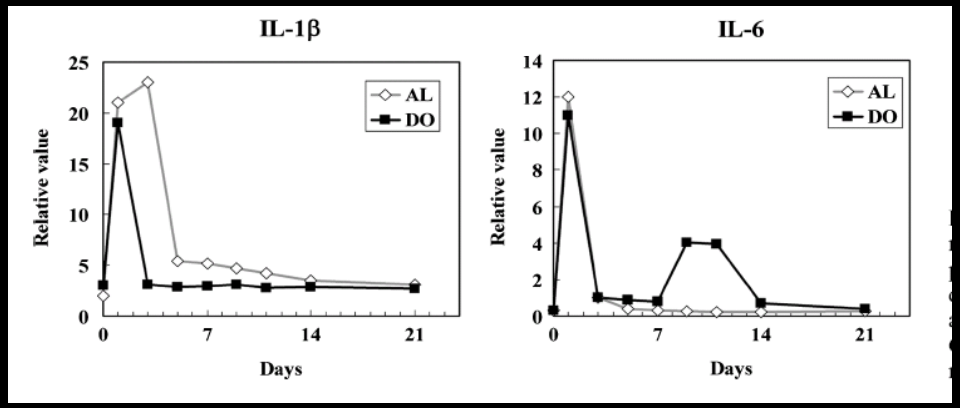


The local expression of inflammatory cytokines peaks within 24 hours after a fracture in models of distraction Osteogenesis





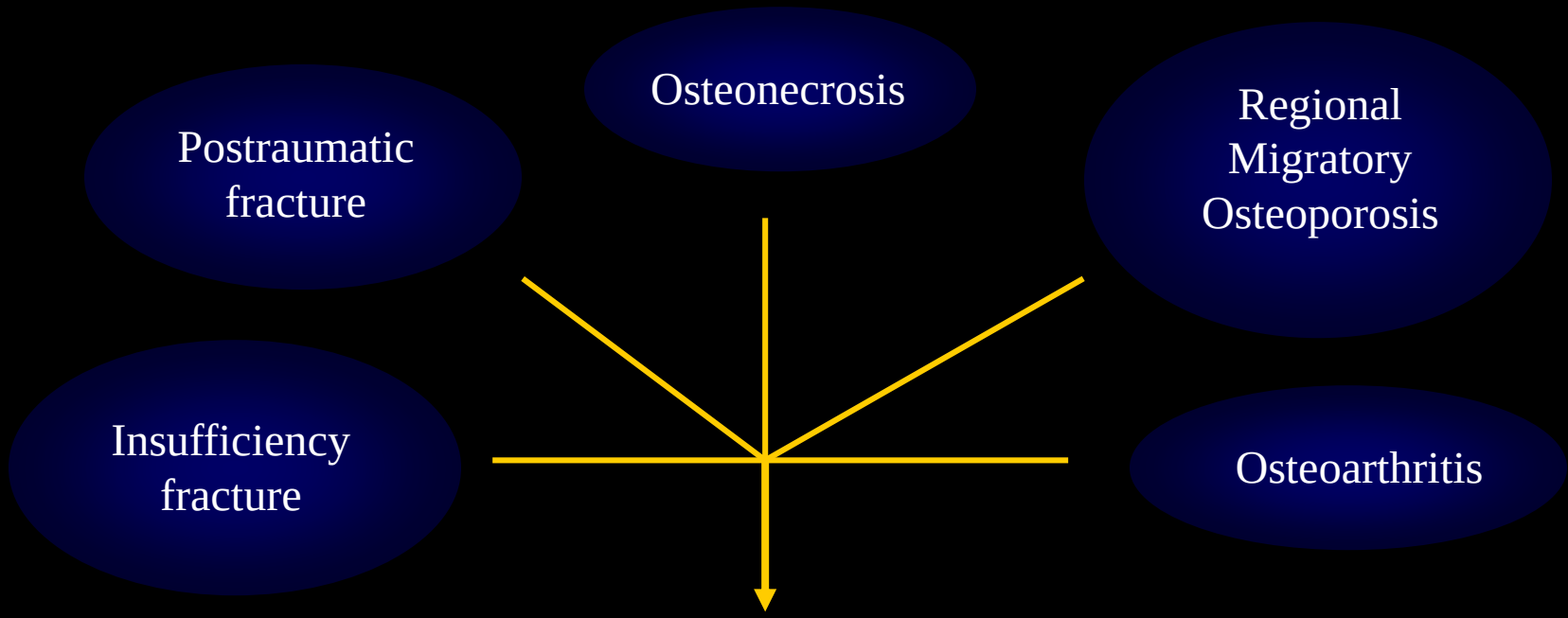
Kon T et al *JBMR* 2001



Cho TJ et al *Calcif Tissue Int* 2007

Bone edema in Atraumatic Osteoporotic fracture

Possible diseases underlying traumatic Bone Marrrow Edema

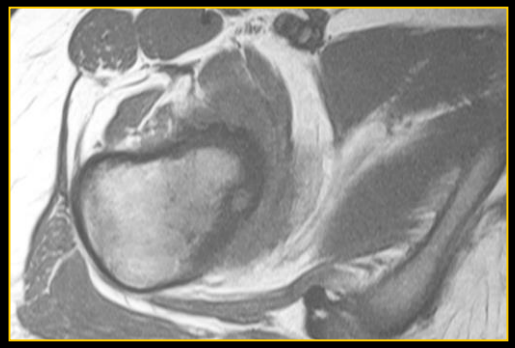


Trabecular microfractures

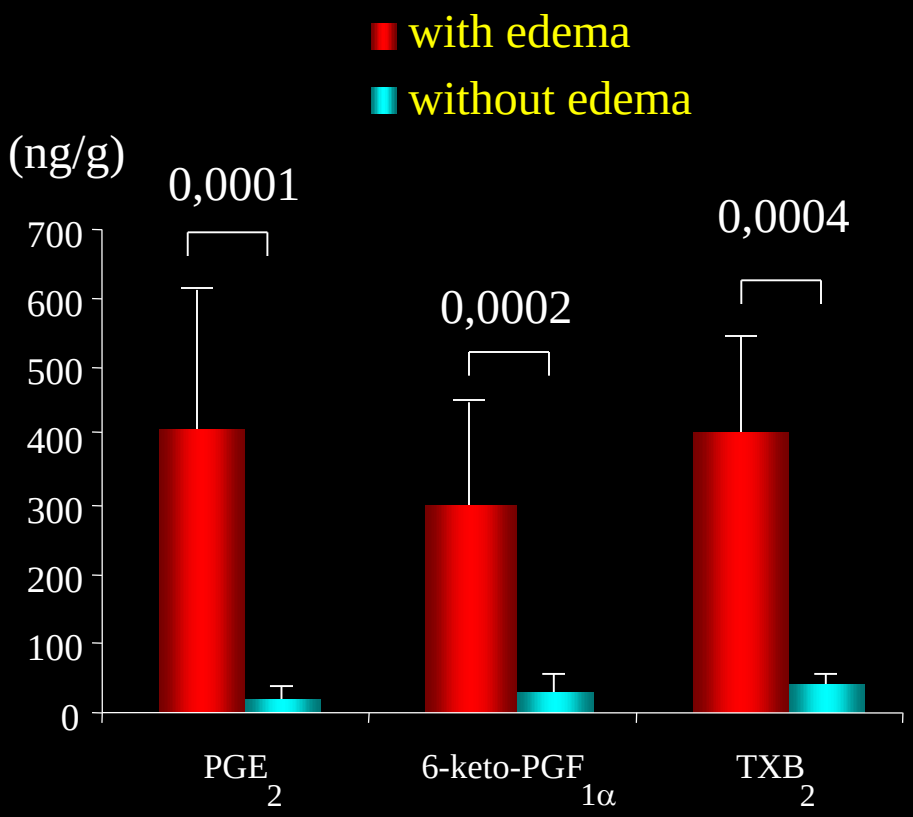
Bone Marrow Edema

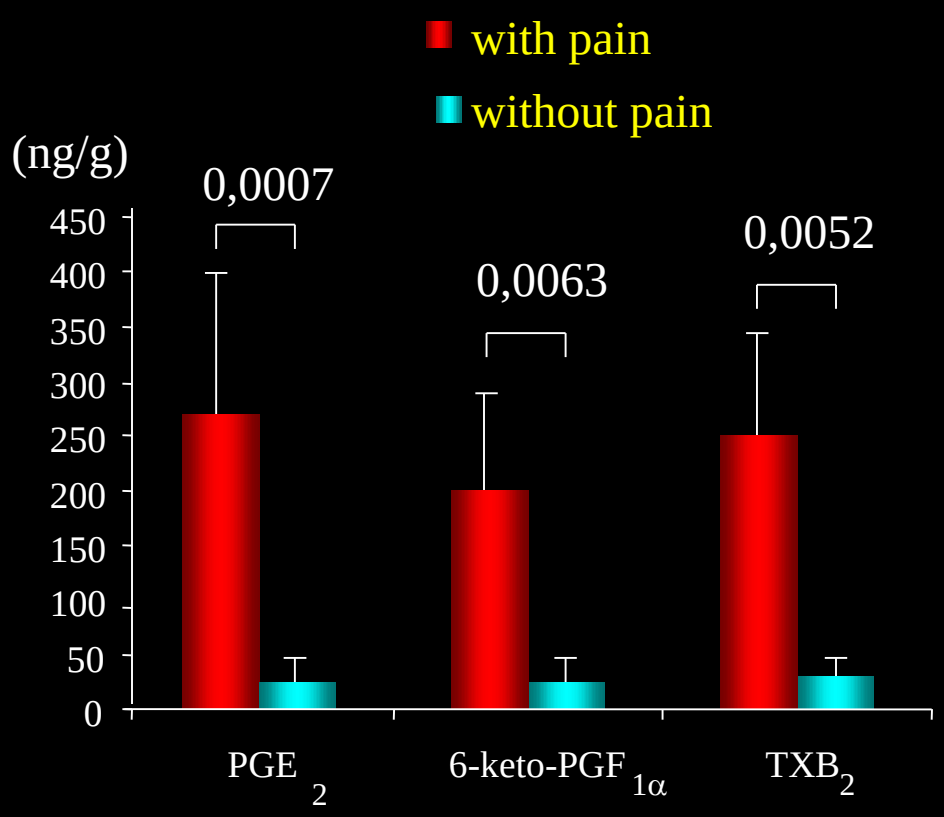
Neoplastic Bone Edema

Condition	Proposed pathophysiology
Tumor	Bone damage/vasoactive mediators



Prostaglandin Levels of Primary Bone Tumor tissues correlate with marrow edema and pain





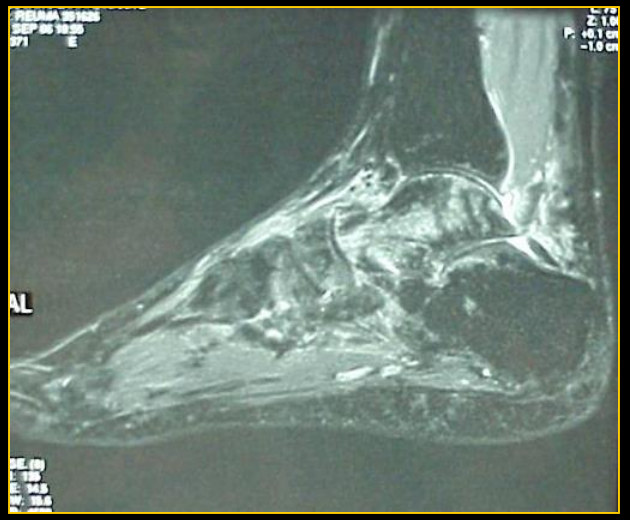
Yamamura S et al. *Cancer,* 1997

Vascular Bone Edema

Bone Vascular Syndromes

- **Reflex Sympathetic Dystrophy Syndrome (CRPS-I)**
- **Bone Marrow Oedema Syndrome**
- **Aseptic Necrosis**

Condition	Proposed pathophysiology
CRPS-I	Tissue hypoxia, acidosis



PAIN MEDICINE
Volume 8 • Number 4 • 2007

REVIEW ARTICLE

Proposed New Diagnostic Criteria for Complex Regional Pain Syndrome

R. Norman Harden, MD,* Stephen Bruehl, PhD,†
Michael Stanton-Hicks, MB, BS, DMSc, FRCA, ABPM,‡ and Peter R. Wilson, MB, BS§

General definition of the syndrome

CRPS describes an array of painful conditions characterized by a continuing (spontaneous and/or evoked) regional pain that is disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor,vasomotor and/or trophic findings. The syndrome shows variable progression over time.

Table 3 Proposed clinical diagnostic criteria for CRPS

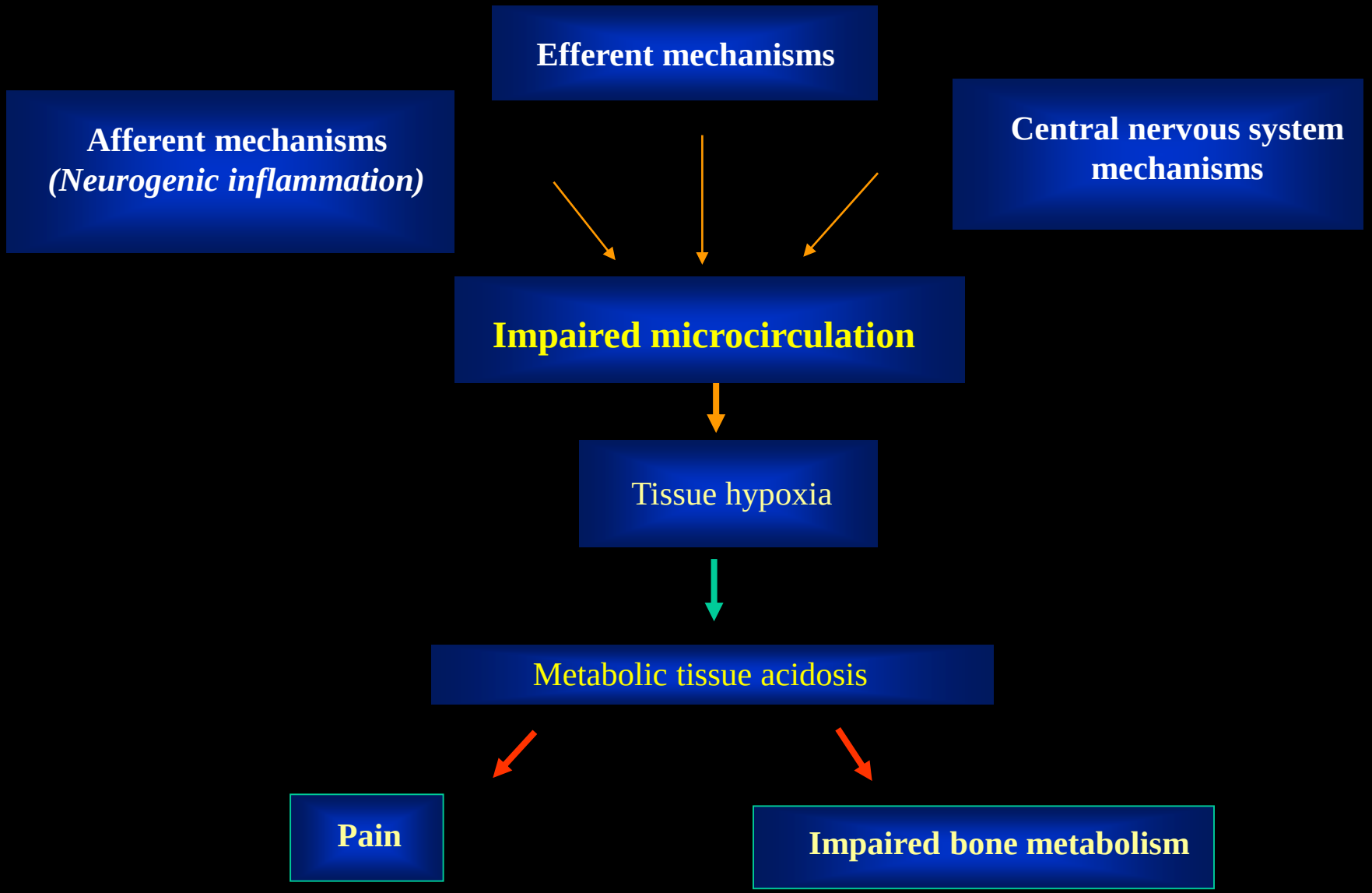
General definition of the syndrome:
CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time

To make the *clinical* diagnosis, the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three of the four* following categories:
   Sensory: Reports of hyperesthesia and/or allodynia
   Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign **at time of evaluation** in *two or more* of the following categories:
   Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
   Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

Harden MR et al. *Pain Med* 2007

The pathophysiology of CPRS-I

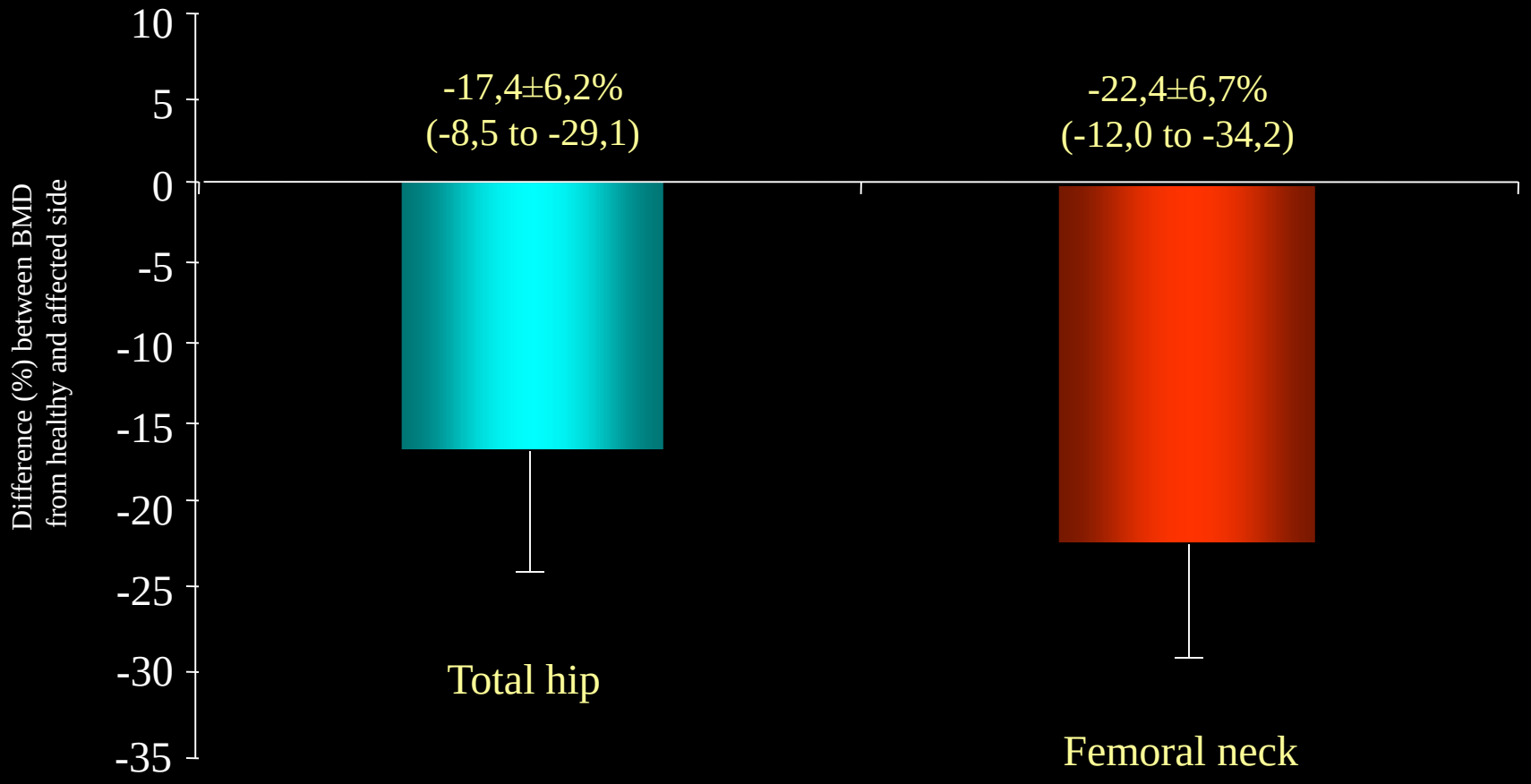


Bone Marrow Oedema Syndrome (Transient Osteoporosis of the Hip)

- Predominantly middle-aged men and pregnant female at third trimester of pregnancy
- Usually monolateral (90% of cases)
- **Disabling hip joint pain**
- Focal loss of radiodensity on plain X-ray
- Increased radio-tracer uptake in bone scintigraphy
- Characteristic pattern of BMOS on MRI
- Self-limiting clinical course (6-24 months)
- History of unusual activity before the onset (5-10%)

BMD measurements in 16 patients with BMES of the hip

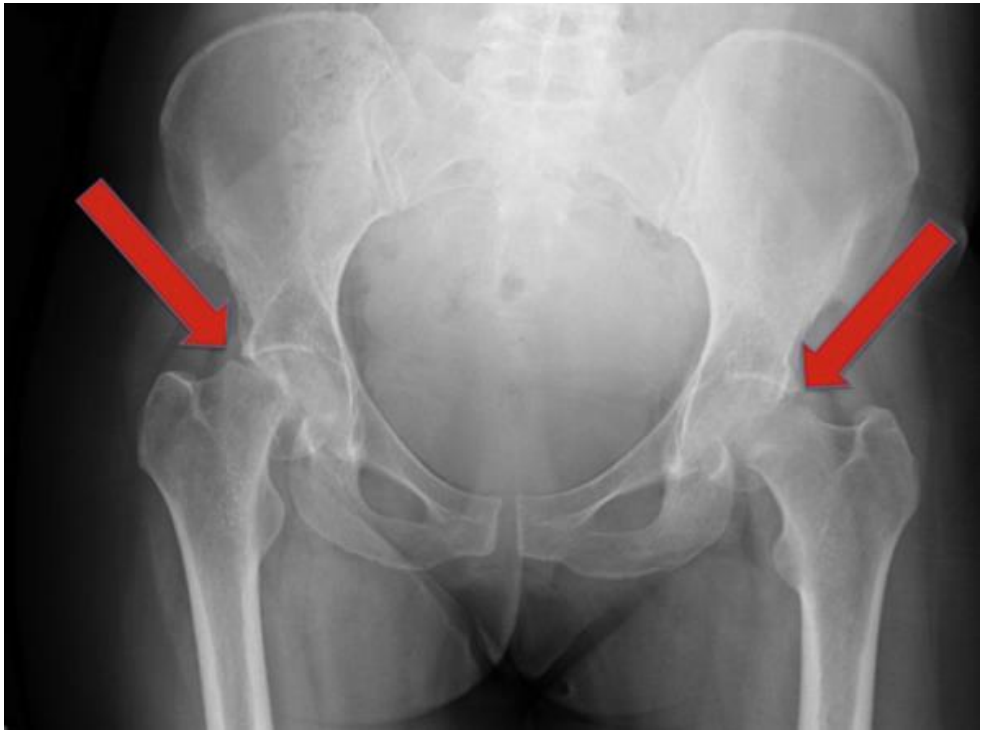
(mean disease duration 8 ± 3.8 weeks)

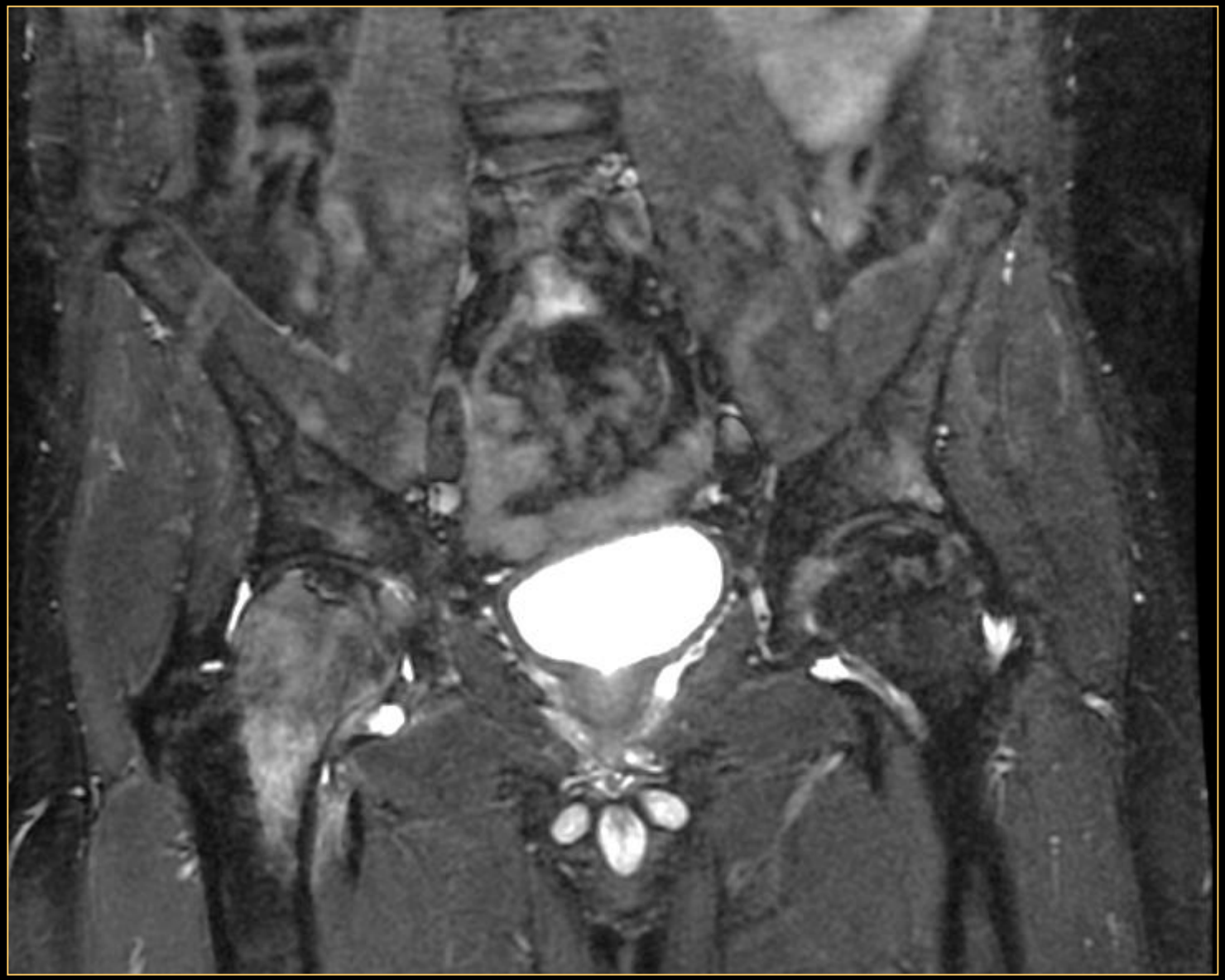


Varenna M et al. *Bone* 2002

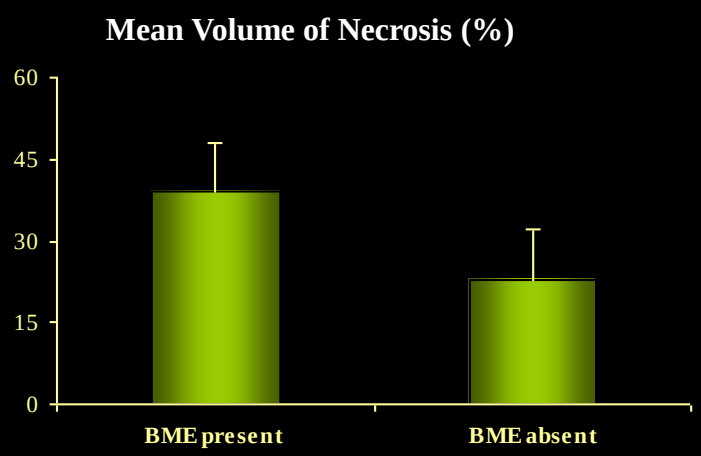
Transient osteoporosis of the hip in pregnancy resulting in bilateral fracture of the neck of the femur

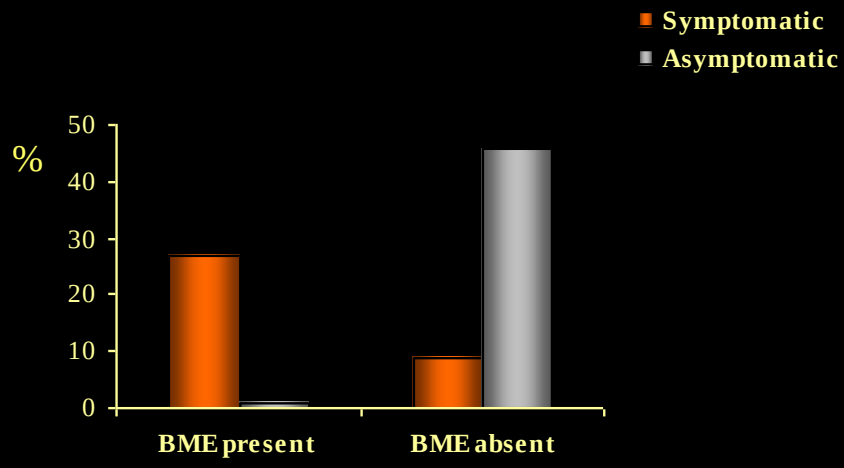
Charles Bircher [a,*], Karolina Afors [b], Martin Bircher [c]

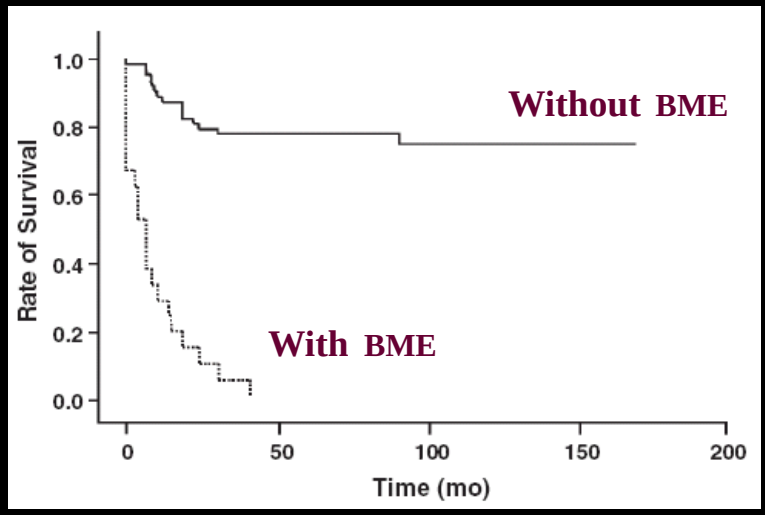




Relationship between BME and development of symptoms and prognosis in patients with ON of the femoral head







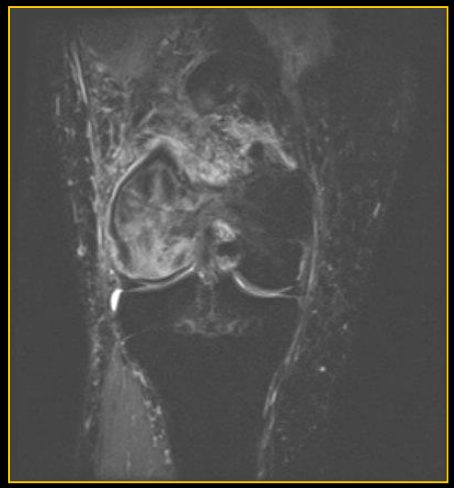
Ito H et al. *AJR* 2006

Distinguishing features of Bone Marrow Edema Syndromes and Avascular Osteonecrosis

	Bone Marrow Edema Syndromes	Avascular Necrosis
Incidence	Rare	15.000 cases per yr
Male/Female Ratio	3 to 1	1 to 1
Etiology	Unknown (variant of RSDS)	Interruption of bone supply
Laterality	Unilateral, may be recurrent	Bilateral in more than 50 % of cases
Onset of symptoms	Acute	Insidious
MRI	Diffuse bone edema pattern	Focal lesion
Prognosis	Resolution	Progressive in 70-80 % of patients

Degenerative Bone Edema

Condition	Proposed pathophysiology
Osteoarthritis	Microdamage in subchondral bone



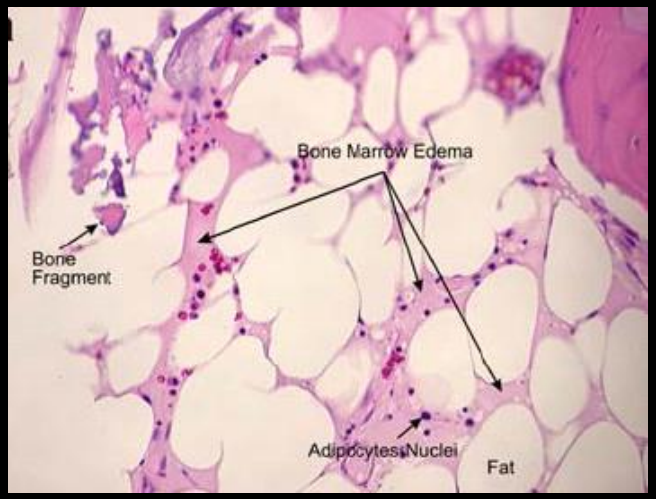
ARTHRITIS & RHEUMATISM
Vol. 54, No. 5, May 2006, pp 1529–1535
DOI 10.1002/art.21789

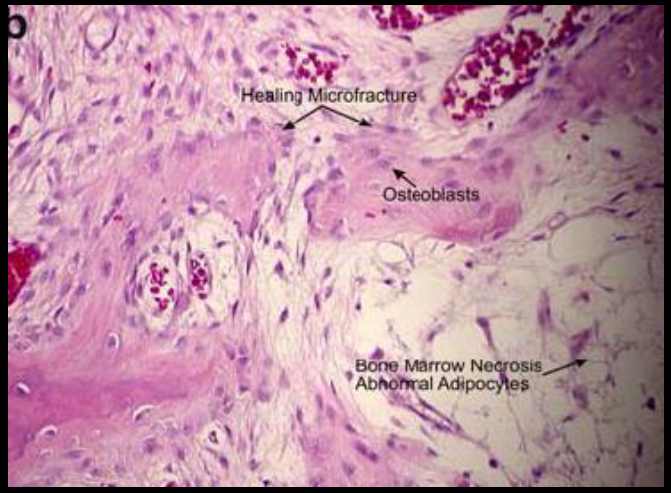
Increase in Bone Marrow Lesions Associated With Cartilage Loss

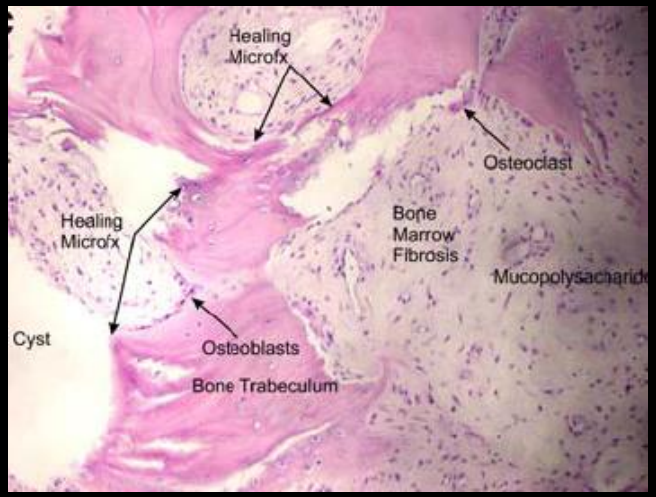
A Longitudinal Magnetic Resonance Imaging Study of Knee Osteoarthritis

David J. Hunter,[1] Yuqing Zhang,[1] Jingbo Niu,[1] Joyce Goggins,[1] Shreyasee Amin,[2] Michael P. LaValley,[1] Ali Guermazi,[3] Harry Genant,[3] Daniel Gale,[4] and David T. Felson[1]

The amount of Bone Marrow Edema in Hip OA correlates with the severity of pain, radiographic findings and number of microfractures







Taljanovic MS et al. *Skeletal Radiol* 2008

ARTHRITIS & RHEUMATISM
Vol. 50, No. 2, February 2004, pp 341–344
DOI 10.1002/art.20051

Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

EDITORIAL

Osteoarthritis: Is It a Disease of Cartilage or of Bone?

David T. Felson and Tuhina Neogi

EDITORIAL

Osteoarthritis is not a cartilage disease

Yet more evidence that osteoarthritis is not a cartilage disease

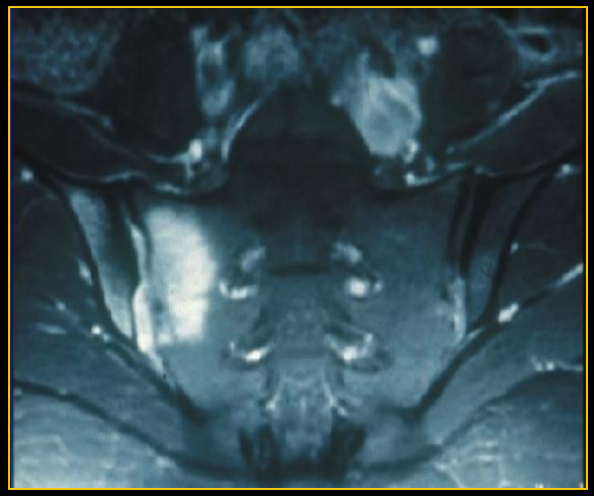
K D Brandt, E L Radin, P A Dieppe, L van de Putte

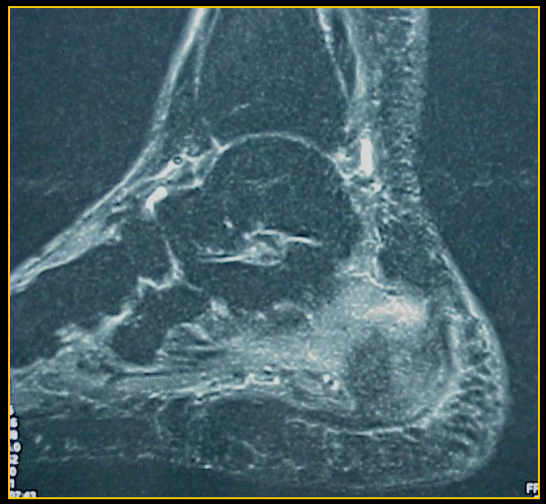
A better insight into the realities behind osteoarthritis

Brandt K et al. *ARD* 2006

Inflammatory Bone Edema

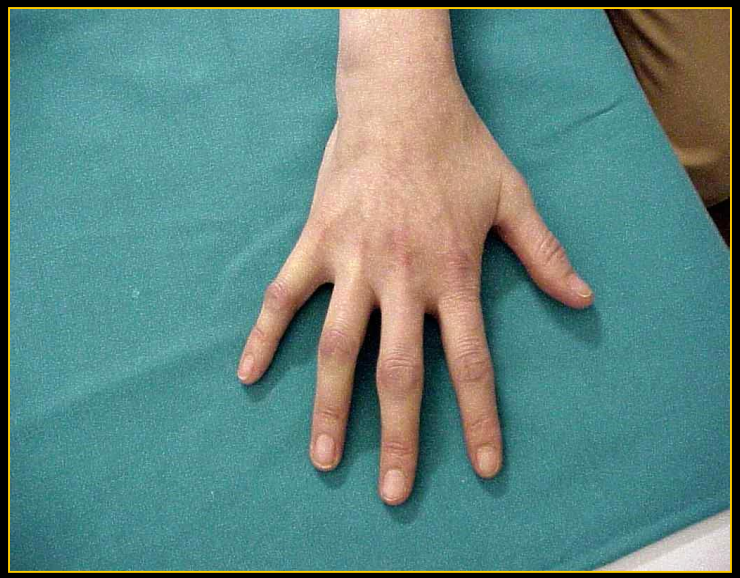
Condition	Proposed pathophysiology
Inflammation : RA,SpAs	Pro-inflammatory (osteoclastogenic) Cytokines





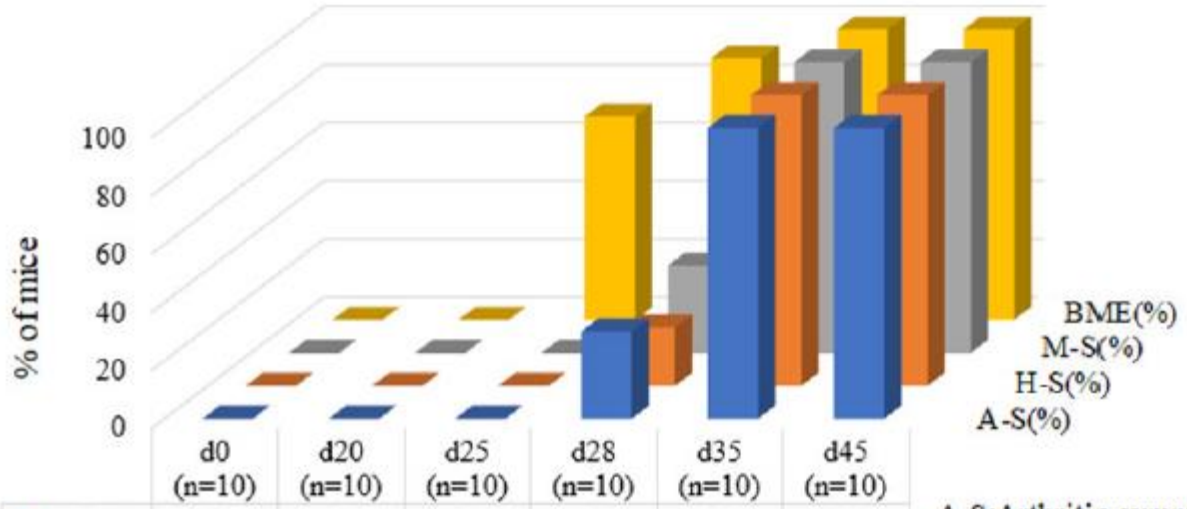
Non-radiographic axial SpA

Bone edema, pain and joint swelling in early Rheumatoid Arthritis



The Bone Marrow Edema Links to an Osteoclastic Environment and Precedes Synovitis During the Development of Collagen Induced Arthritis

Fang Wang[1†], Aishu Luo[2†], Wenhua Xuan[2], Liang Qi[3], Qing Wu[2], Ke Gan[4], Qiande Zhang[5], Miaojia Zhang[2] and Wenfeng Tan[2]*

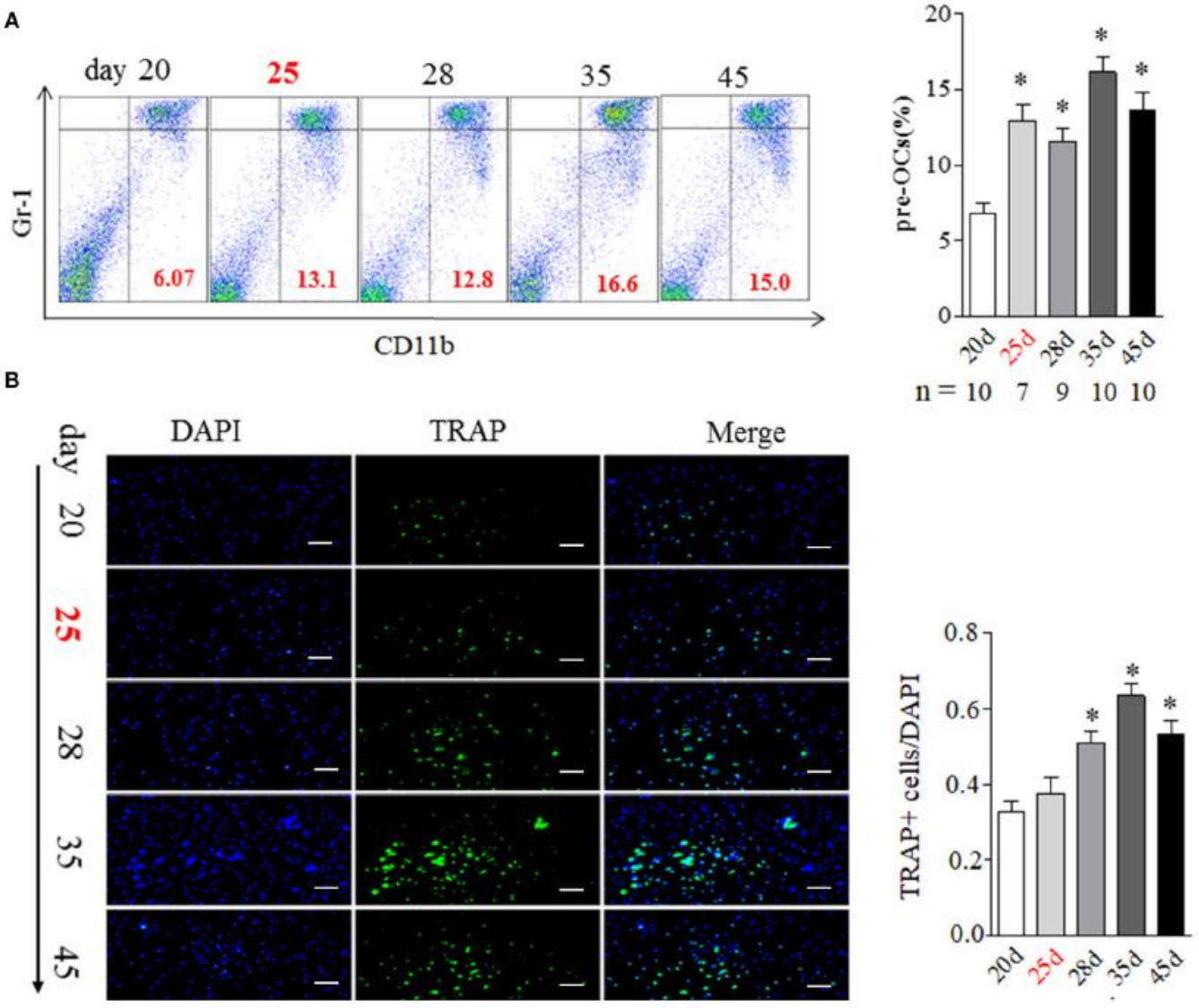


	d0 (n=10)	d20 (n=10)	d25 (n=10)	d28 (n=10)	d35 (n=10)	d45 (n=10)
A-S(%)	0	0	0	30	100	100
H-S(%)	0	0	0	20	100	100
M-S(%)	0	0	0	30	100	100
BME(%)	0	0	70	90	100	100

A-S:Arthritic symptom
H-S:Histological synovitis
M-S:MRI-Synovitis
BME:Bone marrow edema

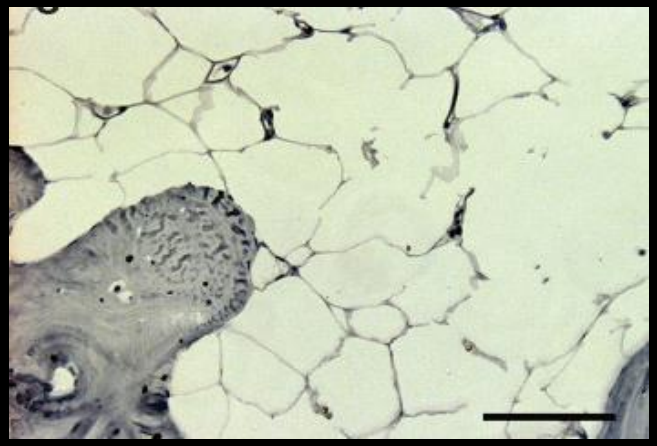
Wang F et al. *Front Immunol* 2019

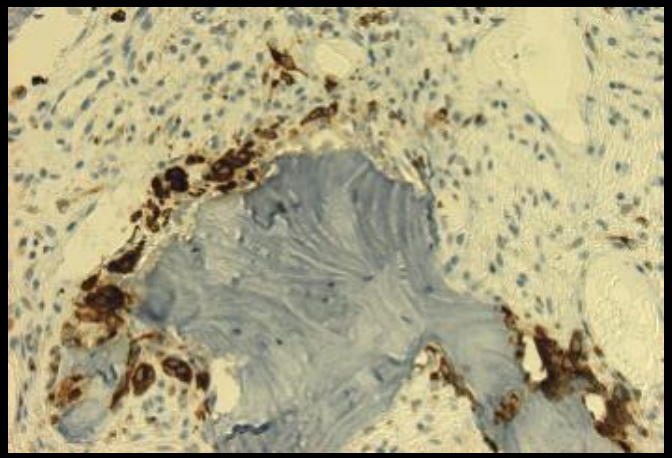
Bone marrow edema links to increased Osteoclast formation in bone marrow during the development of CIA



Wang F et al. *Front Immunol* 2019

Bone edema in RA is associated with inflammatory infiltrates and increased osteoclast number



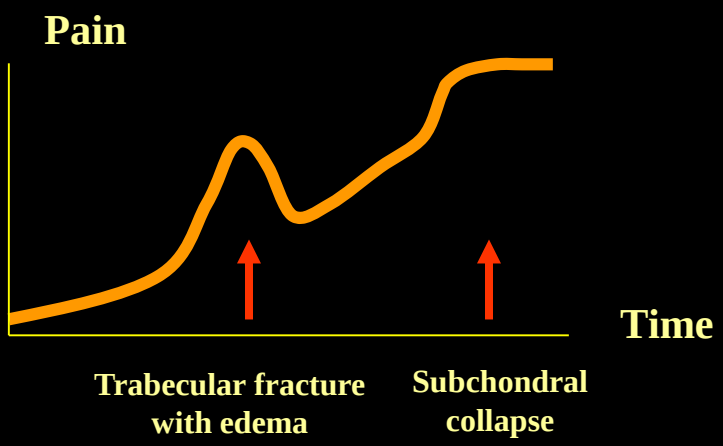


Dalbeth N et al. *Ann Rheum Dis* 2009

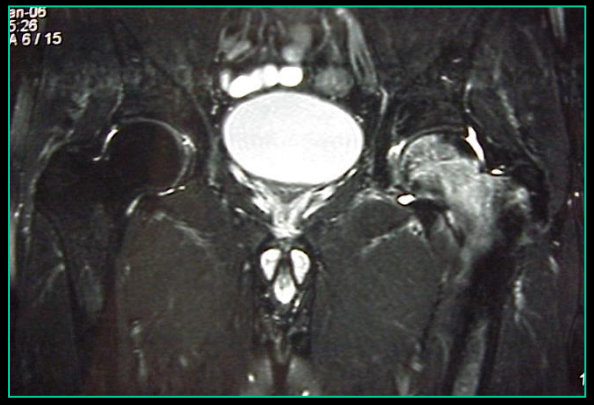
Bone Marrow Edema

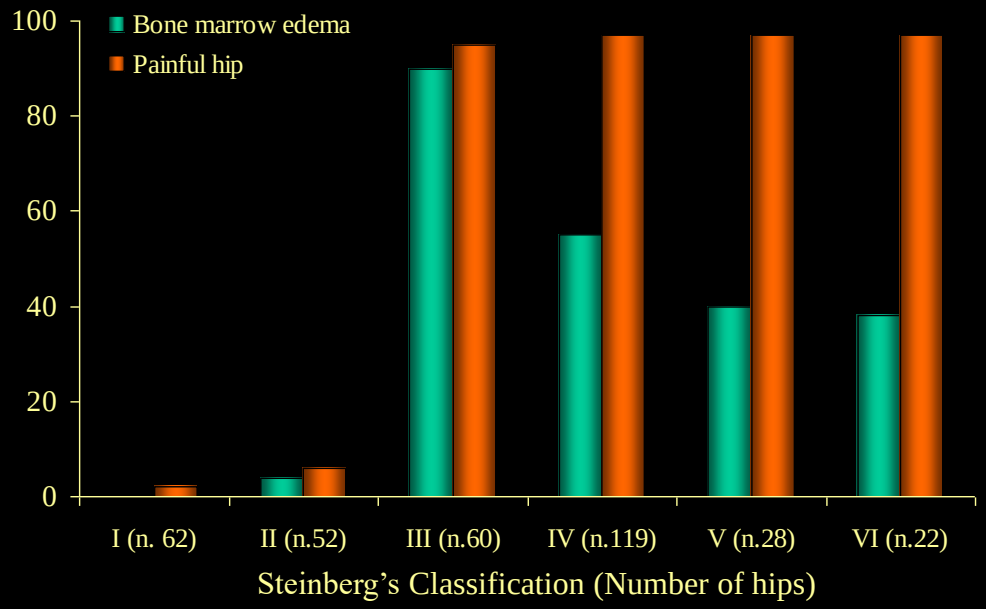
- Diagnosis
- Pathophysiology
- **Clinical relevance**
- Predictive role

Natural history of pain in Osteonecrosis of the femoral head



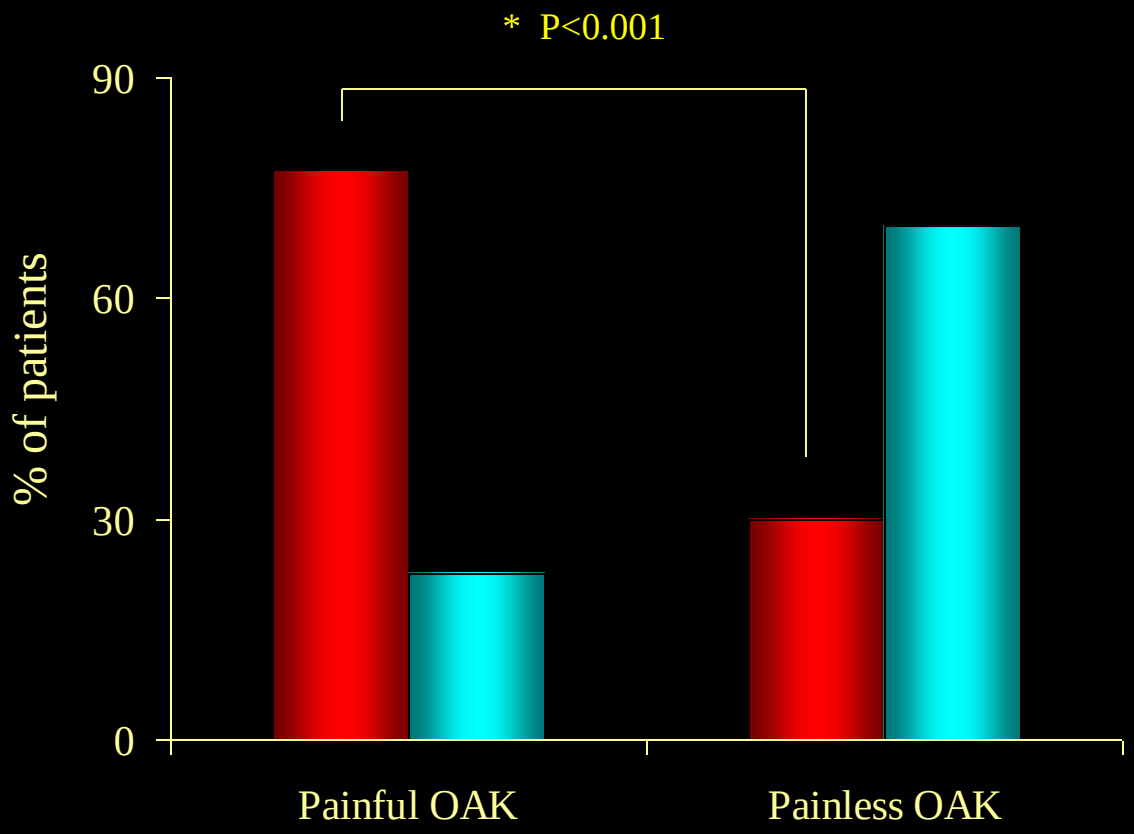
Koo KH et al. *Radiology* 1999

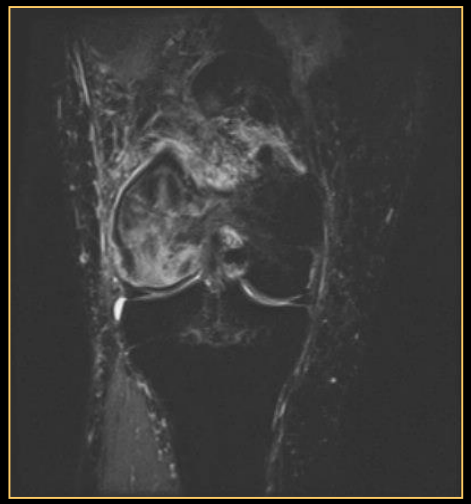




Kim YM et al. *J Bone Joint Surg* 2000

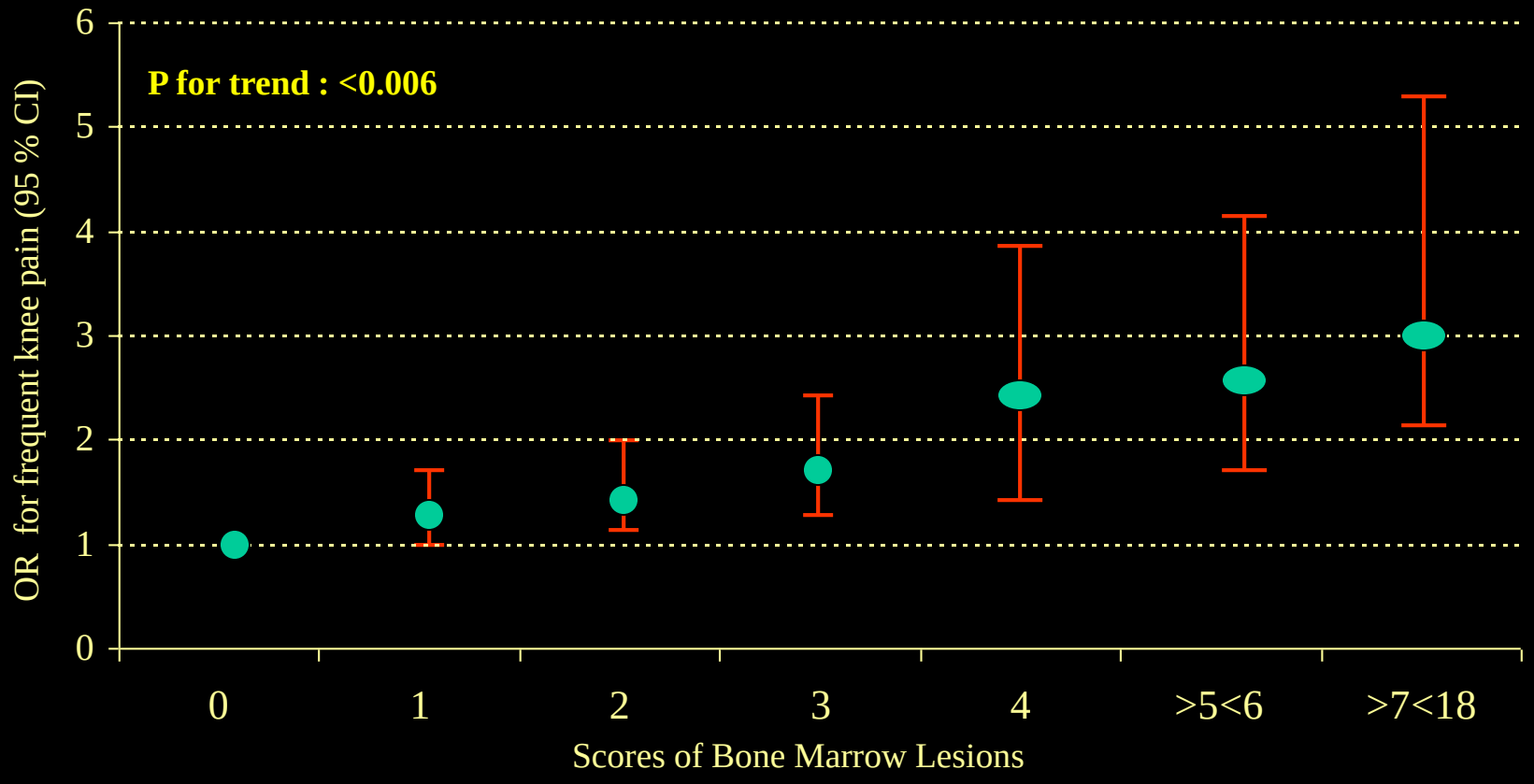
Bone marrow lesions in knee osteoarthritis with and without joint pain





Felson et al. *Ann Intern Med* 2001

Fluctuations of knee pain and changes in Bone Marrow Lesions in patients with Knee OA



Zhang Y et al. *Arthritis Rheum* 2011

EXTENDED REPORT

Increasing synovitis and bone marrow lesions are associated with incident joint tenderness in hand osteoarthritis

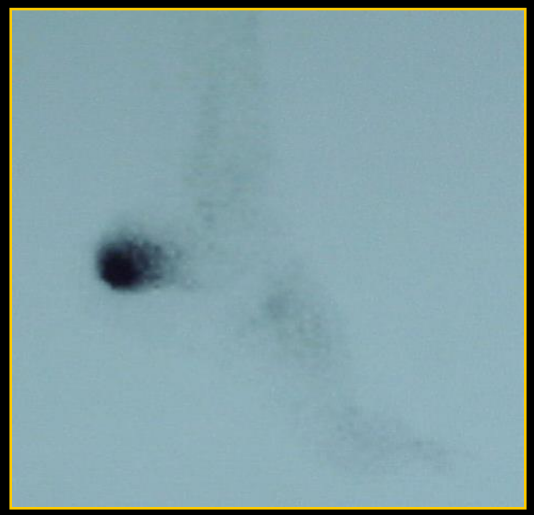
Ida K Haugen,[1] Barbara Slatkowsky Christensen,[1] Pernille Bøyesen,[1] Sølve Sesseng,[2,3] Désirée van der Heijde,[1,4] Tore K Kvien[1]

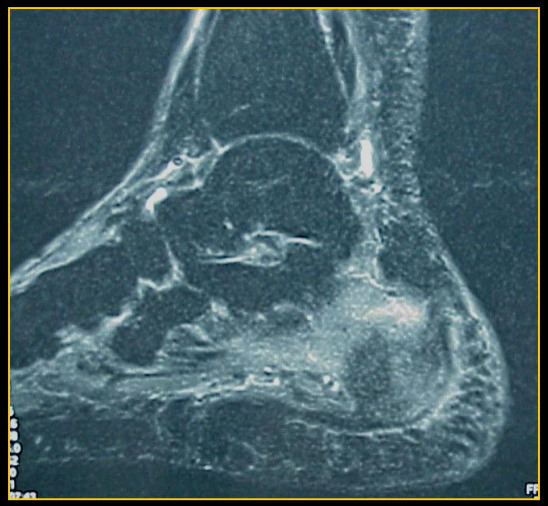
Table 3 The associations between increasing/incident MRI features and incident joint tenderness (in joints without tenderness at baseline)

	Number of (%) joints with incident tenderness	Crude analyses OR (95% CI)	Adjusted analyses OR (95% CI)*	Adjusted analyses OR (95% CI)†
Associations between increasing/incident MRI features and incident joint tenderness				
Synovitis‡				
No change/decrease	46/175 (26.3%)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Increase	23/45 (51.1%)	2.53 (1.39 to 4.61)	2.62 (1.35 to 5.06)	2.66 (1.38 to 5.11)
Bone marrow lesions‡				
No change/decrease	88/265 (33.2%)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Increase	29/47 (61.7%)	2.73 (1.33 to 5.59)	2.84 (1.22 to 6.60)	2.85 (1.23 to 6.58)

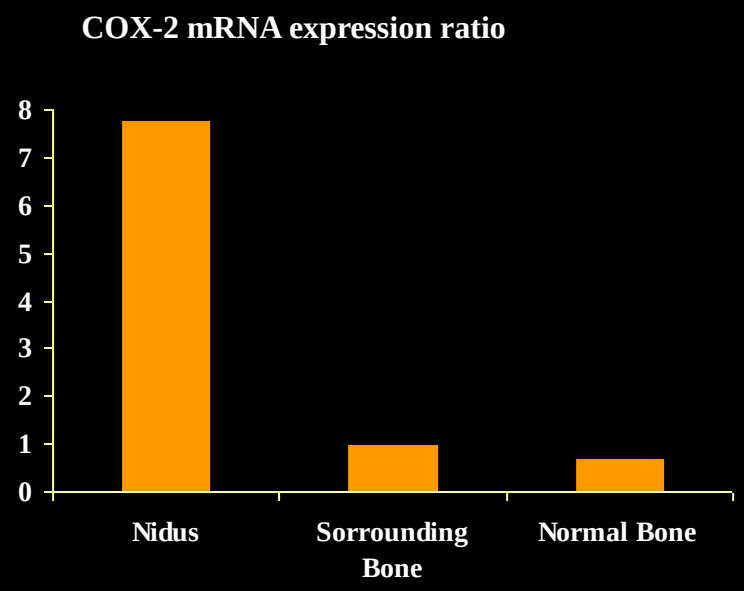
*Adjusted for age, sex, body mass index and follow-up time.
†Adjusted for age, sex, body mass index, follow-up time and change in radiographic osteoarthritis (Kellgren–Lawrence grade).
‡N=302/551 non-tender joints (one missing) from 69 persons were included in analyses on bone marrow lesions, whereas n=220/373 non-tender joints (11 missing) from 48 persons were included in analyses on synovitis.

Haugen IK et al. *Ann Rheum Dis* 2015





Bone edema, inflammation and pain in Osteoid Osteoma



Kawaguchi Y et al. *Pathol Int* 2001

Bone Marrow Edema

- Diagnosis
- Pathophysiology
- Clinical relevance
- **Predictive role**

Extended report

MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA)

M L Hetland,[1] B Ejbjerg,[1,2] K Hørslev-Petersen,[3] S Jacobsen,[4] A Vestergaard,[5] A G Jurik,[6] K Stengaard-Pedersen,[7] P Junker,[8] T Lottenburger,[3] I Hansen,[7] L S Andersen,[3] U Tarp,[7] H Skjødt,[1] J K Pedersen,[3] O Majgaard,[1] A J Svendsen,[3] T Ellingsen,[7] H Lindegaard,[8] A F Christensen,[8] J Vallø,[9] T Torfing,[10] E Narvestad,[5] H S Thomsen,[11] M Østergaard,[3] and the CIMESTRA study group

Ann Rheum Dis **2009**

ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 5, May 2016, pp 1080–1088
DOI 10.1002/art.39550

The Course of Bone Marrow Edema in Early Undifferentiated Arthritis and Rheumatoid Arthritis

A Longitudinal Magnetic Resonance Imaging Study at Bone Level

Wouter P. Nieuwenhuis, Hanna W. van Steenbergen, Wouter Stomp, Theo Stijnen, Tom W. J. Huizinga, Johan L. Bloem, Désirée van der Heijde, Monique Reijnierse, and Annette H. M. van der Helm-van Mil

Ors for development of erosive progression at bone level during the first year, in the presence or absence of local synovitis or bone edema at baseline

	Erosive progression			
	Yes	No	OR (95% CI)	*P*†
All data				
BME present	30	207	9.7 (5.6–16.8)	<0.001
BME absent	25	1,667	Reference	–
Synovitis present	41	783	3.8 (2.1–7.0)	<0.001
Synovitis absent	15	1,098	Reference	–

***Arthritis Rheum* 2016**

Bone marrow edema lesions and their relation to progression before and after adjustment for mechanical alignment

Variable	Adjusted Odds Ratio (95% CI)†	Adjusted Odds Ratio† Including Alignment (95% CI)‡
Medial lesion	8.9 (3.6–21.8)	5.6 (2.1–14.8)
No medial lesion	1 (referent)	1
Lateral lesion	5.9 (1.9–18.1)	2.8 (0.8–10.1)
No lateral lesion	1 (referent)	1

Felson et al. ***Ann Intern Med*** **2003**

Bone marrow lesions predict increase in knee cartilage defects and loss of cartilage volume in middle-aged women without knee pain over 2 years

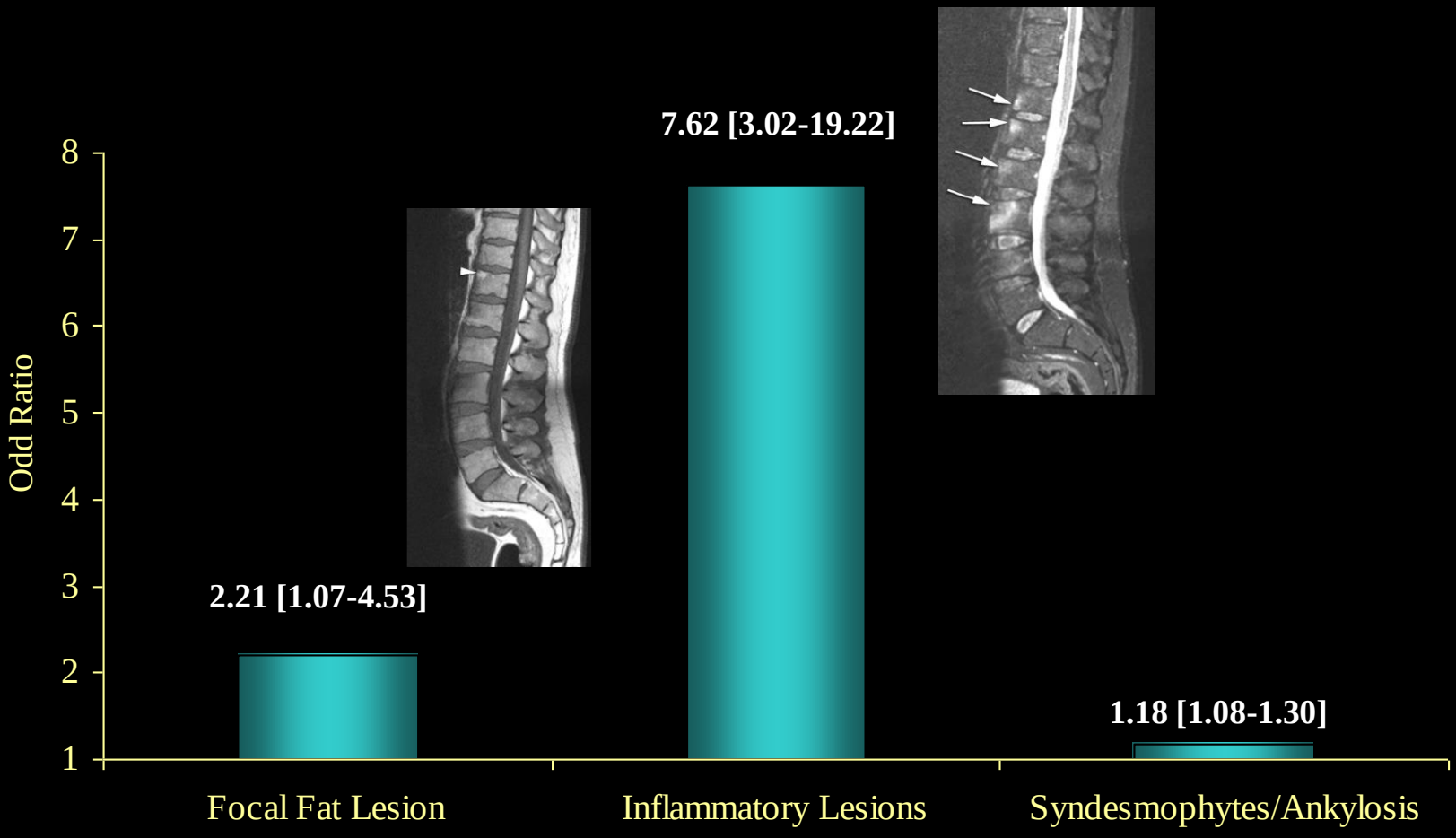
A E Wluka,[1,2] F Hanna,[1,2,3] M Davies-Tuck,[1] Y Wang,[1] R J Bell,[3] S R Davis,[3] J Adams,[3] F M Cicuttini[1]

Odds of progression of tibiofemoral cartilage defect score according to whether a "large" BML or a "very large" BML was present

	Multivariate OR*	95% CI*	p Value
Medial tibiofemoral cartilage defect score			
Large BML	2.25	0.46 to 11.06	0.32
Very large BML	31.4	1.60 to 607	0.02
Lateral tibiofemoral cartilage defect score			
Large BML	1.35	0.30 to 6.20	0.70
Very large BML	2.09	0.30 to 14.75	0.46
Total tibiofemoral cartilage defect score			
Large BML	2.88	0.96 to 8.68	0.06
Very large BML	5.55	1.04 to 29.6	0.045

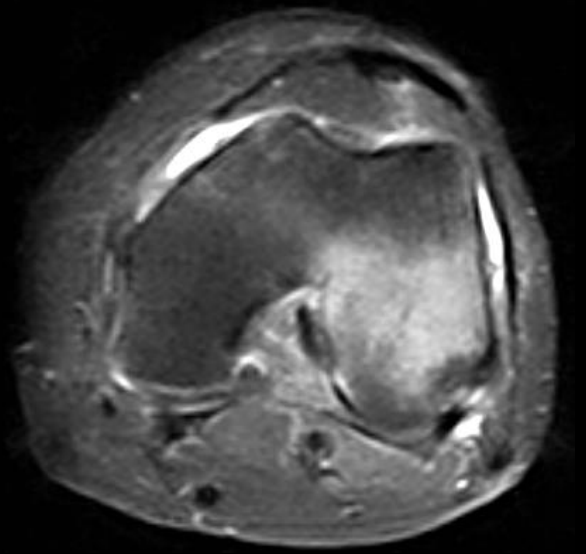
Ann Rheum Dis 2009

Logistic Regression Analysis on predictors of the development of new syndesmophytes after 2 years in 100 patients with AS



Chiowchanwisawakit P et al. *Arthritis Rheum* 2011

Natural History ?



The natural history of BML in community-based adults with no clinical knee OA

- Incident BML in initially BML-free knees : 14 %
- Incident BML associated with incoming knee pain (OR 4.2; 1.2-15.1)
- BML present at baseline : complete resolution in 46 %

Davies-Tuck ML et al. *Ann Rheum Dis* 2009

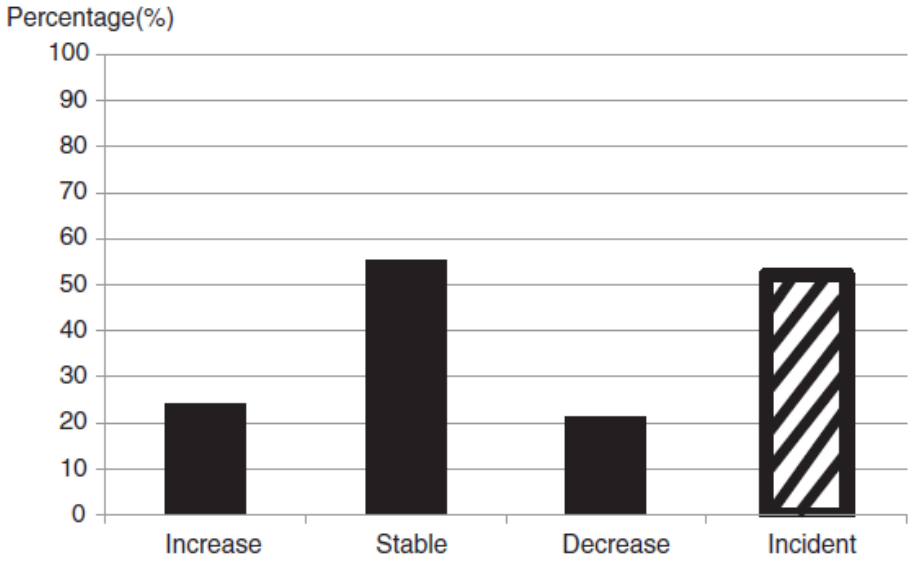
Foong et al. Arthritis Research & Therapy 2014, 16:R149
http://arthritis-research.com/content/16/4/R149

arthritis research&therapy

RESEARCH ARTICLE Open Access

The clinical significance, natural history and predictors of bone marrow lesion change over eight years

Yi Chao Foong[1*†], Hussain Ijaz Khan[1†], Leigh Blizzard[1], Changhai Ding[1,2], Flavia Cicuttini[2], Graeme Jones[1] and Dawn Aitken[1]



Predictors of change in bone marrow lesion size

	Univariable	Multivariable[a]
Body mass index (kg/m^2)	**0.03 (0.00, 0.05)**	**0.03 (0.01, 0.05)**
Strenuous activity (per unit change)	**0.13 (0.03, 0.22)**	**0.14 (0.04, 0.23)**
Current smoker (yes/no)	0.04 (−0.13, 0.20)	–
Ever smoker (yes/no)	0.06 (−0.20, 0.31)	–
Radiographic osteoarthritis (yes/no)	0.28 (−0.06, 0.61)	–
Light activity (per unit change)	0.02 (−0.10, 0.13)	–
Offspring status (yes/no)	0.13 (−0.11, 0.38)	–
Leg strength (kg)	0.00 (0.00, 0.00)	–

Seminars in Arthritis and Rheumatism 43 (2014) 600–612

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Association of obesity and systemic factors with bone marrow lesions at the knee: A systematic review

Yuan Z. Lim, MBBS (Hons)[1,a], Yuanyuan Wang, MBBS, MD, PhD[1,a],
Anita E. Wluka, MBBS, FRACP, PhD[a], Miranda L. Davies-Tuck, B Biomed Sci (Hons), PhD[a],
Fahad Hanna, BSc (Hons), PhD[a,b], Donna M. Urquhart, B Physio (Hons), PhD[a],
Flavia M. Cicuttini, MBBS, FRACP, PhD[a,*]

Risk factors	Level of evidence	Association
Age	Strong	No association between age and BMLs All 4 cohort studies showed no association 1 Cross-sectional study showed an association
Gender	Limited	Being male was associated with increased BMLs 1 Of 3 cohort studies and both cross-sectional studies showed an association
Heritability	Limited	There was a paucity of evidence Only 1 cross-sectional study examined this and showed an association
Obesity	Moderate	Obesity was associated with increased BMLs 2 Of 5 cohort studies and 4 of 5 cross-sectional studies showed an association
Dietary fatty acids	Conflicting	1 Of 2 cohort studies showed an association
Smoking	Limited	Smoking was associated with increased BMLs 1 Cohort study showed an association
Cartilage and bone biomarkers	Limited	CTX-I was associated with increased BMLs 1 Cohort study showed an association
Anti-bone-resorptive treatments	Limited	Anti-bone-resorptive treatment was associated with reduced BMLs 1 RCT showed an association
Serum lipids	Strong	Serum lipids were associated with increased BMLs 2 Cohort studies showed an association.
Licofelone and chondroitin sulfate	Limited	Licofelone and chondroitin sulfate were associated with reduced BMLs 1 RCT showed an association

***Sem Arthritis Rheum* 2014**

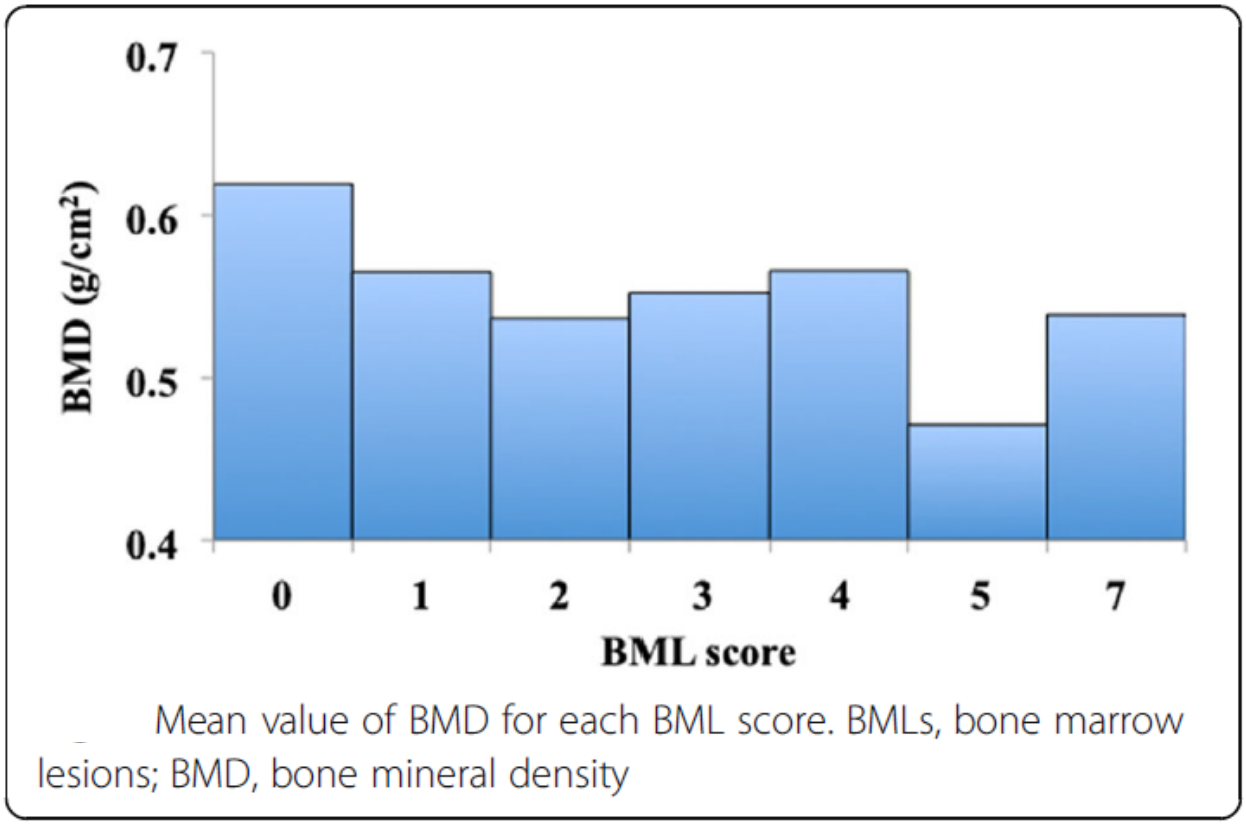
Ota et al. Arthritis Research & Therapy (2019) 21:113
https://doi.org/10.1186/s13075-019-1900-4

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Symptomatic bone marrow lesions induced by reduced bone mineral density in middle-aged women: a cross-sectional Japanese population study

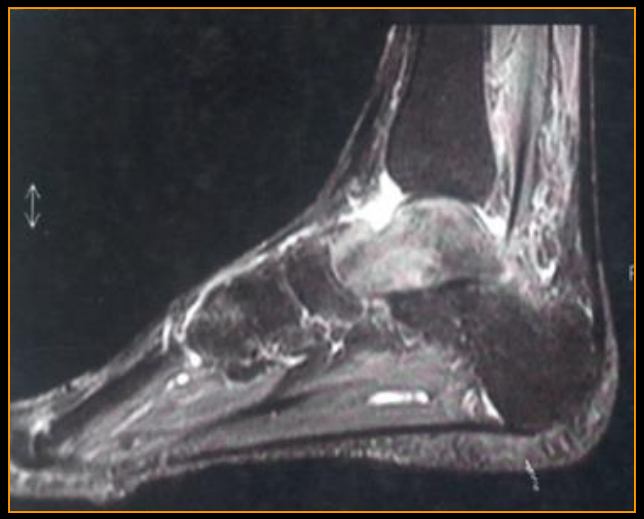
Seiya Ota[1,2*], Daisuke Chiba[1], Eiji Sasaki[1], Gentaro Kumagai[1], Yuji Yamamoto[1], Shigeyuki Nakaji[2], Eiichi Tsuda[3] and Yasuyuki Ishibashi[1]



Mean value of BMD for each BML score. BMLs, bone marrow lesions; BMD, bone mineral density

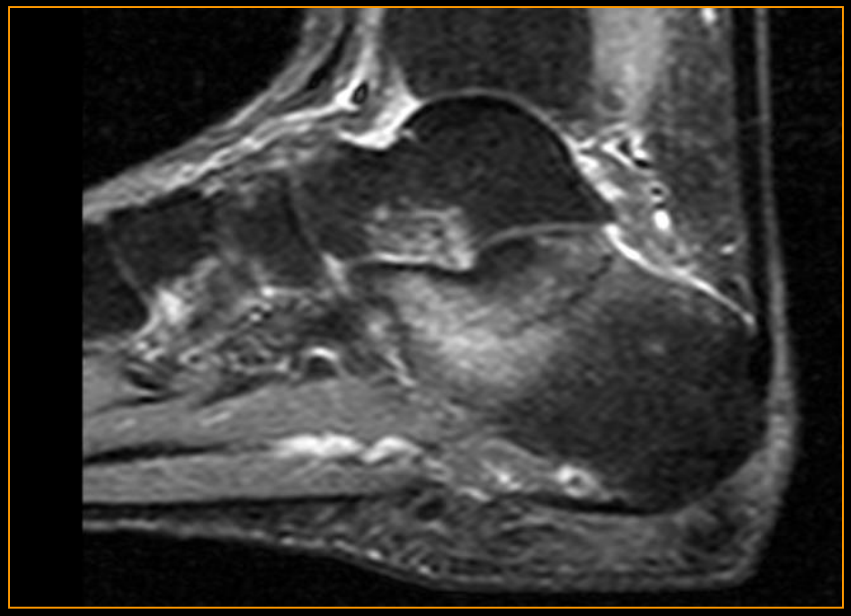
Ota S et al. *Arthritis Res Ther* 2019

Bone edema : a key role for further assessment ?

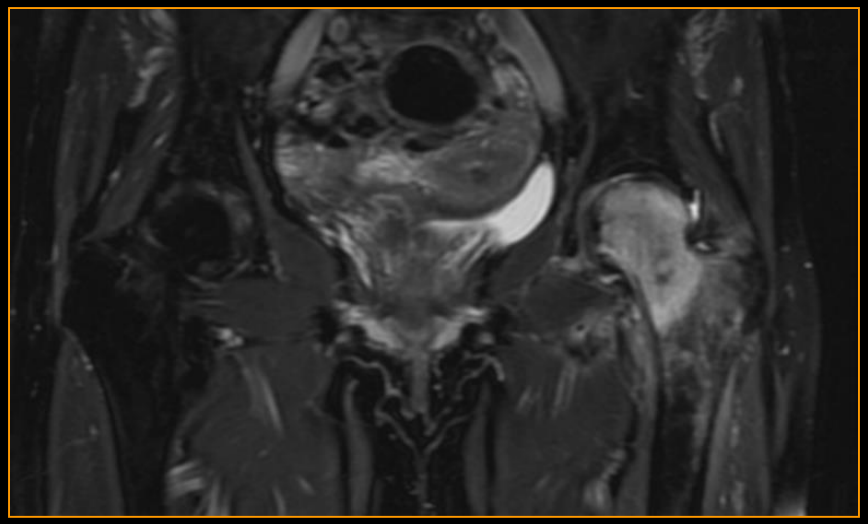


Marzo 2010

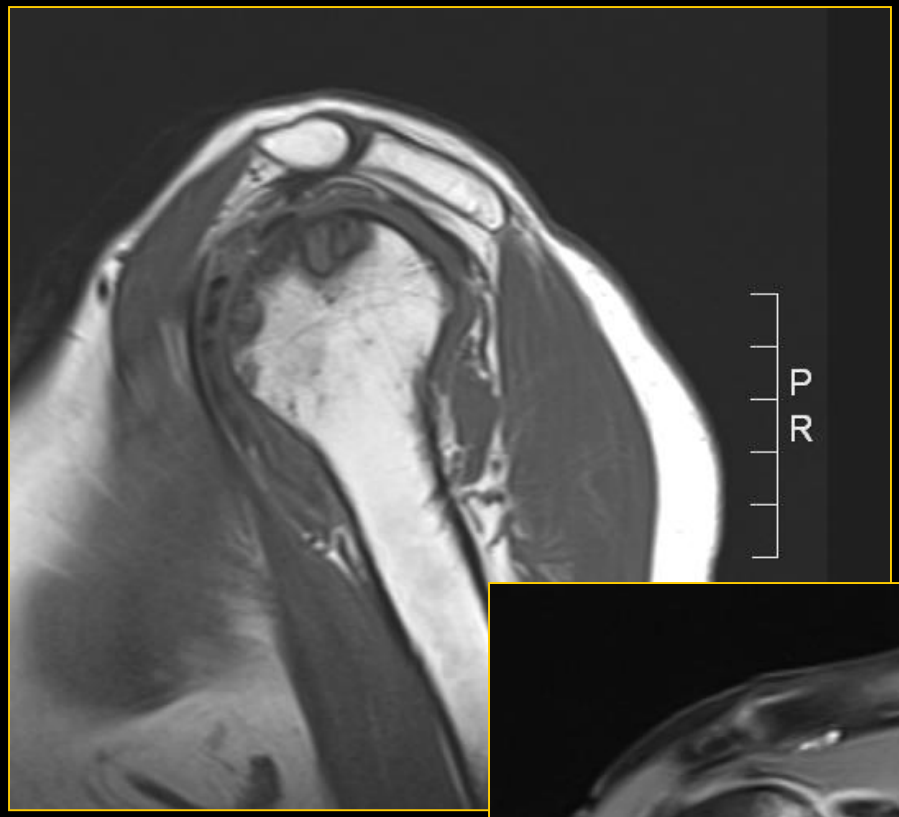
Aprile 2013



Settembre 2013



Febbraio 2014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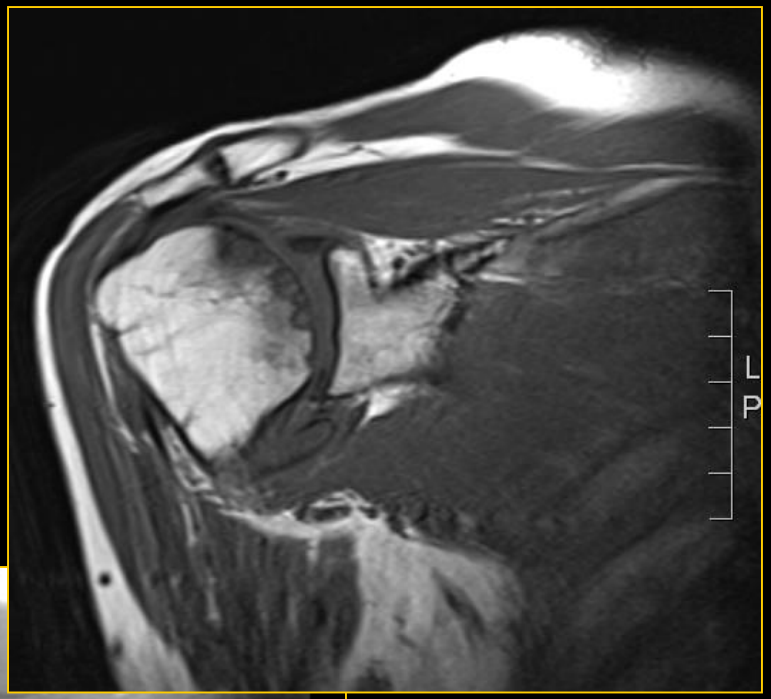
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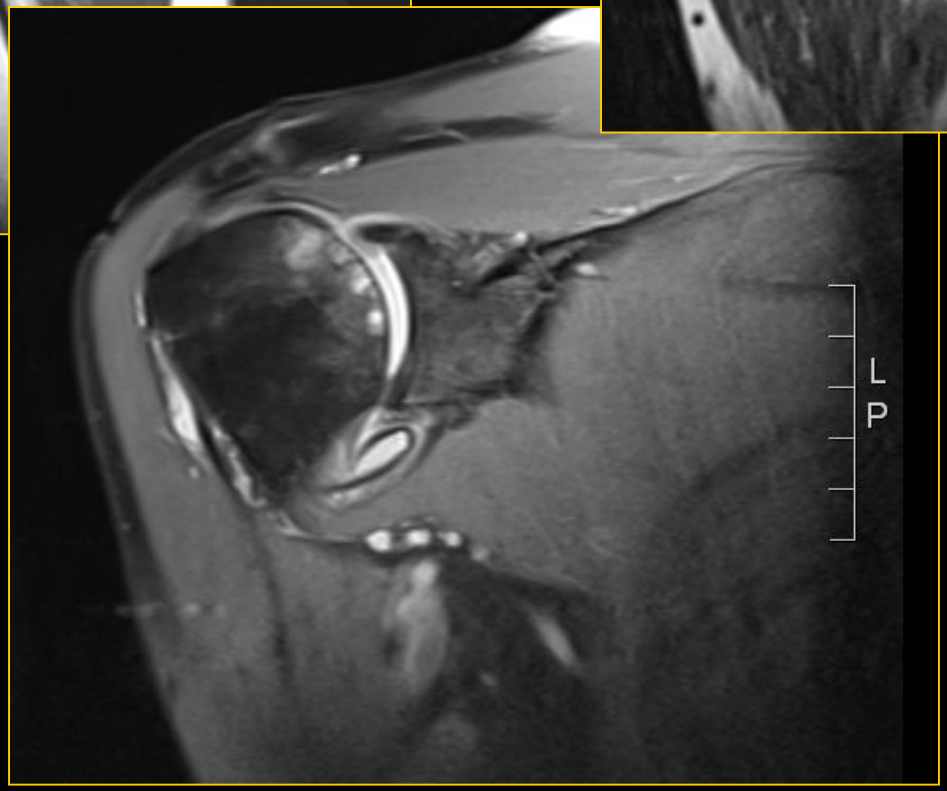
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The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

The Incidentally Discovered Adrenal Mass

William F. Young, Jr., M.D.

Disorder	Symptoms	Signs
Cushing's syndrome	Patient may be asymptomatic if disease is subclinical; symptoms may include weight gain with central obesity, facial rounding and plethora, supraclavicular and dorsocervical fat pads, easy bruising, thin skin, poor wound healing, purple striae, proximal muscle weakness, emotional and cognitive changes (e.g., irritability, spontaneous tearfulness, depression, and restlessness), opportunistic and fungal infections, altered reproductive function, acne, and hirsutism	Hypertension, osteopenia, osteoporosis, fasting hyperglycemia, diabetes mellitus, hypokalemia, hyperlipidemia, and leukocytosis with relative lymphopenia
Pheochromocytoma	Patient may be asymptomatic; episodic symptoms may occur in spells (paroxysms) that can be extremely variable in presentation but typically include forceful heartbeat, pallor, tremor, headache, and diaphoresis; spells may be either spontaneous or precipitated by postural change, anxiety, medications (e.g., metoclopramide, anesthetic agents), and maneuvers that increase intraabdominal pressure (e.g., change in position, lifting, defecation, exercise, colonoscopy, pregnancy, and trauma)	Hypertension (paroxysmal or sustained), orthostatic hypotension, pallor, retinopathy grades 1 to 4, tremor, and fever
Primary aldosteronism	If hypokalemia is present, nocturia, polyuria, muscle cramps, and palpitations may be present	Hypertension, mild or severe; possibly hypokalemia and mild hypernatremia
Adrenocortical carcinoma	Symptoms may include mass effect (e.g., abdominal pain) and symptoms related to adrenal hypersecretion of cortisol (Cushing's syndrome), androgens (hirsutism, acne, amenorrhea or oligomenorrhea, oily skin, and increased libido), estrogens (gynecomastia), or aldosterone (hypokalemia-related symptoms)	Hypertension, osteopenia, osteoporosis, fasting hyperglycemia, diabetes mellitus, hypokalemia, hyperlipidemia, and leukocytosis with relative lymphopenia
Metastatic cancer	History of an extraadrenal cancer	Cancer-specific signs

Young WF *NEJM* 2007

Bone Marrow Oedema = Bone Marrow Lesion

- A final common pathway
- Associated with pain in several clinical conditions
- Possible predictive role (OA, RA, AS)
- Easy to diagnose
- Clinically relevant
- Sometimes a clinical challenge