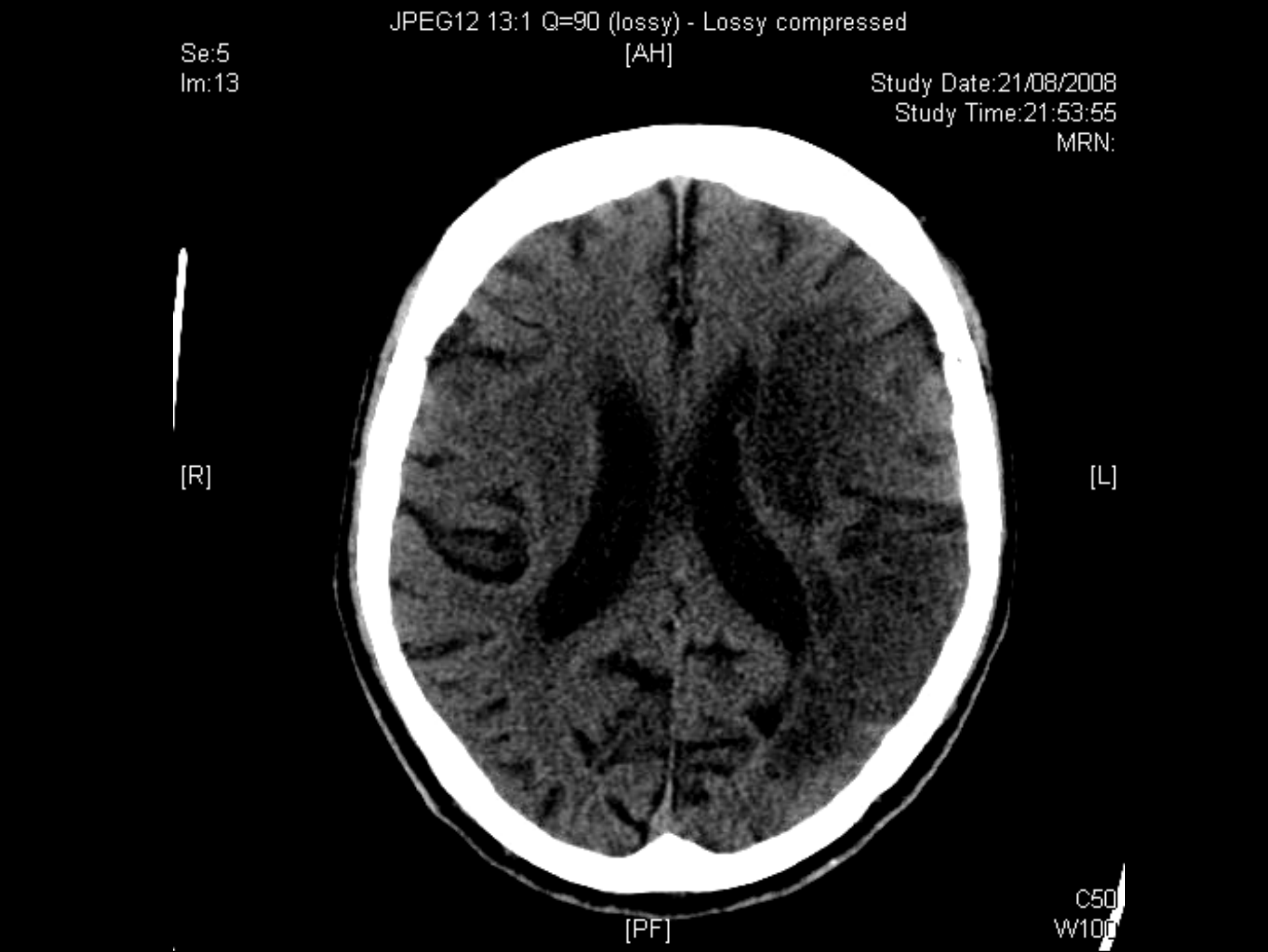
Immobilization Causes Immobilization

Alvin Tam & TK Kwok

Tung Wah Hospital

Mr. LEE

- 86 years old, pre-morbid ADL-I and walks unaided
- PMH: HT, gout, OA knee, CHF (Echo—EF 40%, global systolic dysfunction)
- Admitted to QEH 14 Aug 2008 for sudden onset R sided weakness with global aphasia
- CT brain: L MCA territory infarct


JPEG12 13:1 Q=90 (lossy) - Lossy compressed
Se:5
Im:13
[AH]
Study Date:21/08/2008
Study Time:21:53:55
MRN:
[R]
[L]
[PF]
C50
W100

Progress

- Poor neurological recovery, power 0/5 on r side; required R/T feeding
- ADLs all dependent & bed bound
- Developed multiple complications:
  - nosocomial pneumonia
  - ACEI induced acute on chronic renal failure

- Right LL swelling on 26th Aug 2008
- Doppler USG showed DVT from distal external iliac, common femoral, superficial femoral to popliteal arteries
- Started on Warfarin

Progress

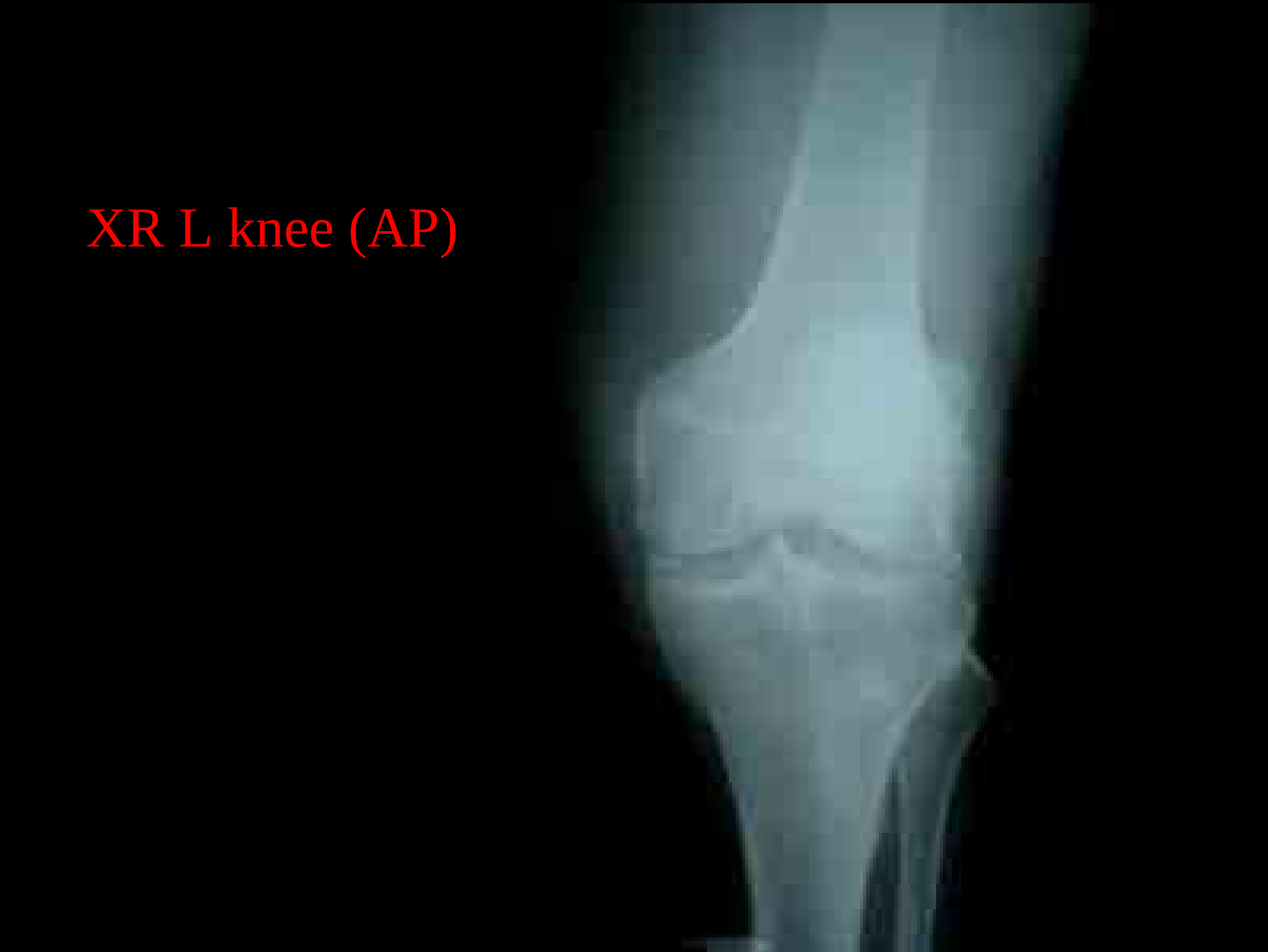
- Transferred to TWH on 9th Oct 2008
- PE:
  - globally aphasic, alert, inconsistent to one-step command
  - Dense right hemiplegia
  - Poor sitting balance, ADL totally dependent
  - Dysphagia require RT feeding
- Noted to have progressive swelling over LEFT (the non-paretic side) thigh in **Nov 2008**

Left thigh

- Temperature normal
- No dilated veins
- No tenderness elicited
- No joint swelling
- L Knee joint markedly reduced **ROM—only 5 degree of flexion** possible

- XR L femur

XR L knee (AP)



Investigation results:

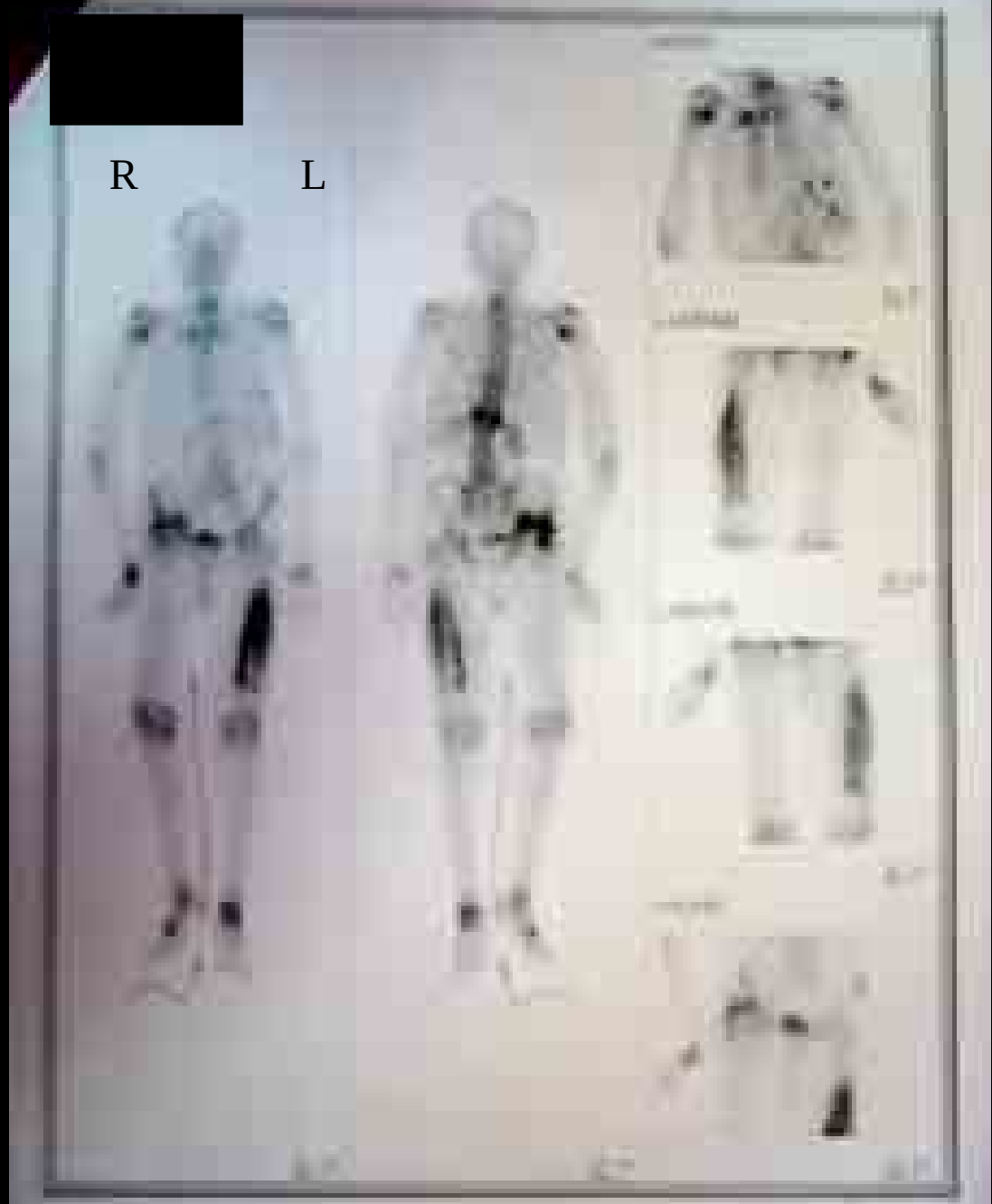
- WCC = 12.96 $x10^9/l$
- ALP 178 u/l, adjusted calcium 2.28 mmol/l
- Doppler ultrasound of L lower limb:
  - no evidence of DVT
  - No definite mass identified
- Skin temp (L/R): 33C/34C

DDx

- Fracture
- Cellulitis/ Superficial thrombophlebitis
- Deep venous thrombosis
- Complex regional pain syndrome
- Hematoma
- Heterotopic ossification

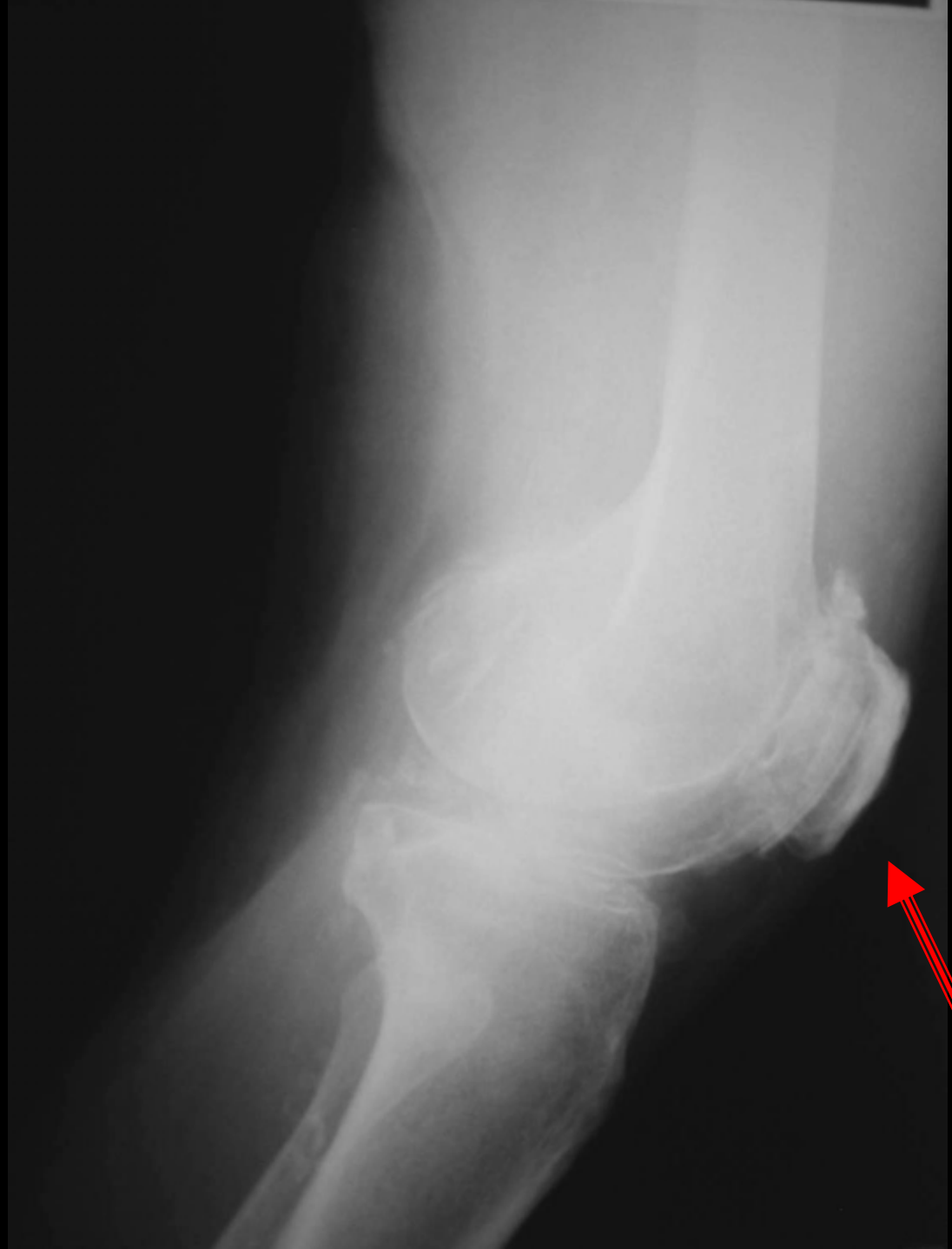
Triple phases Bone scan

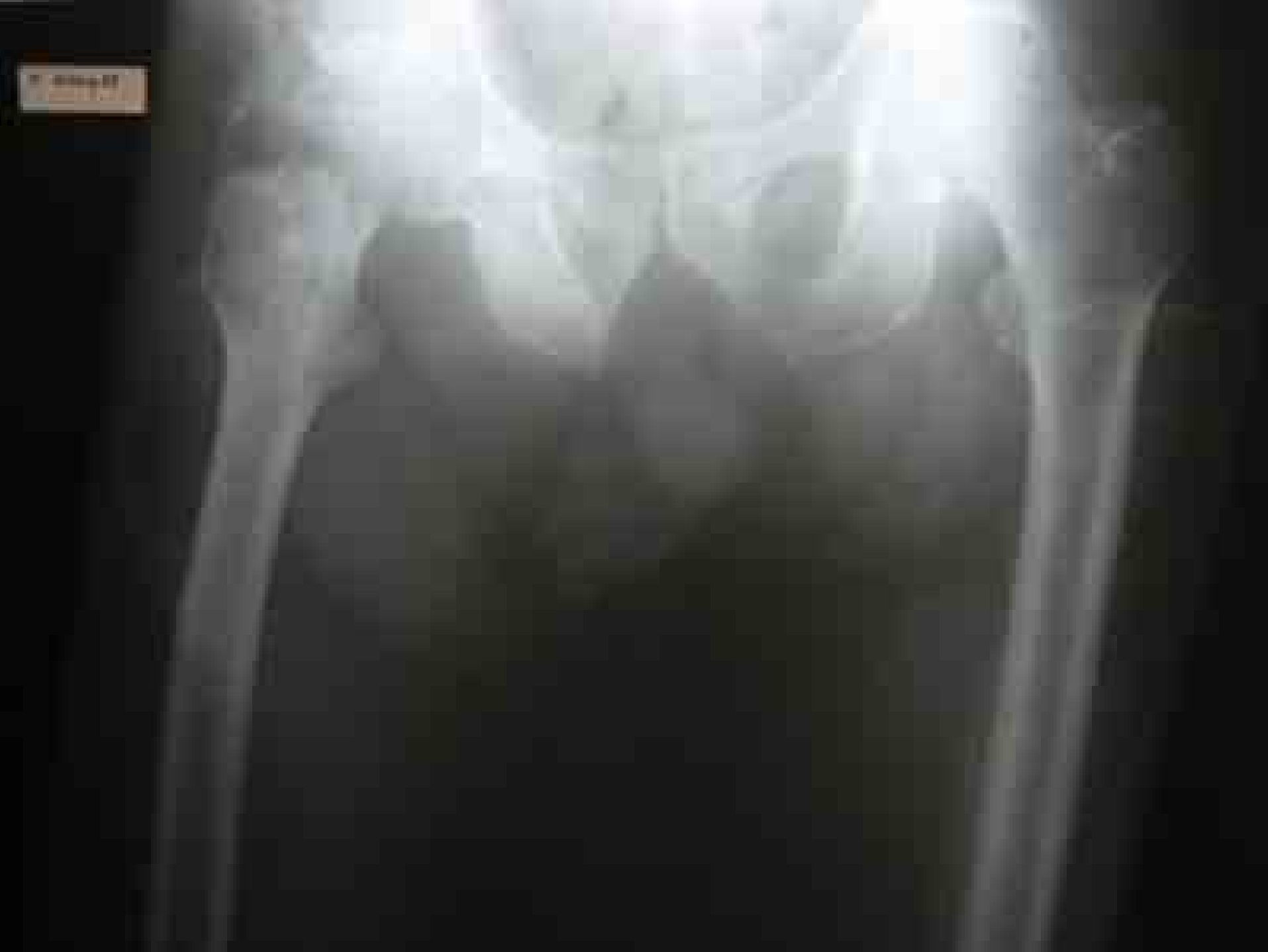
- **intense uptake** in **phase three** over
  - RIGHT hip
  - LEFT thigh


R
L

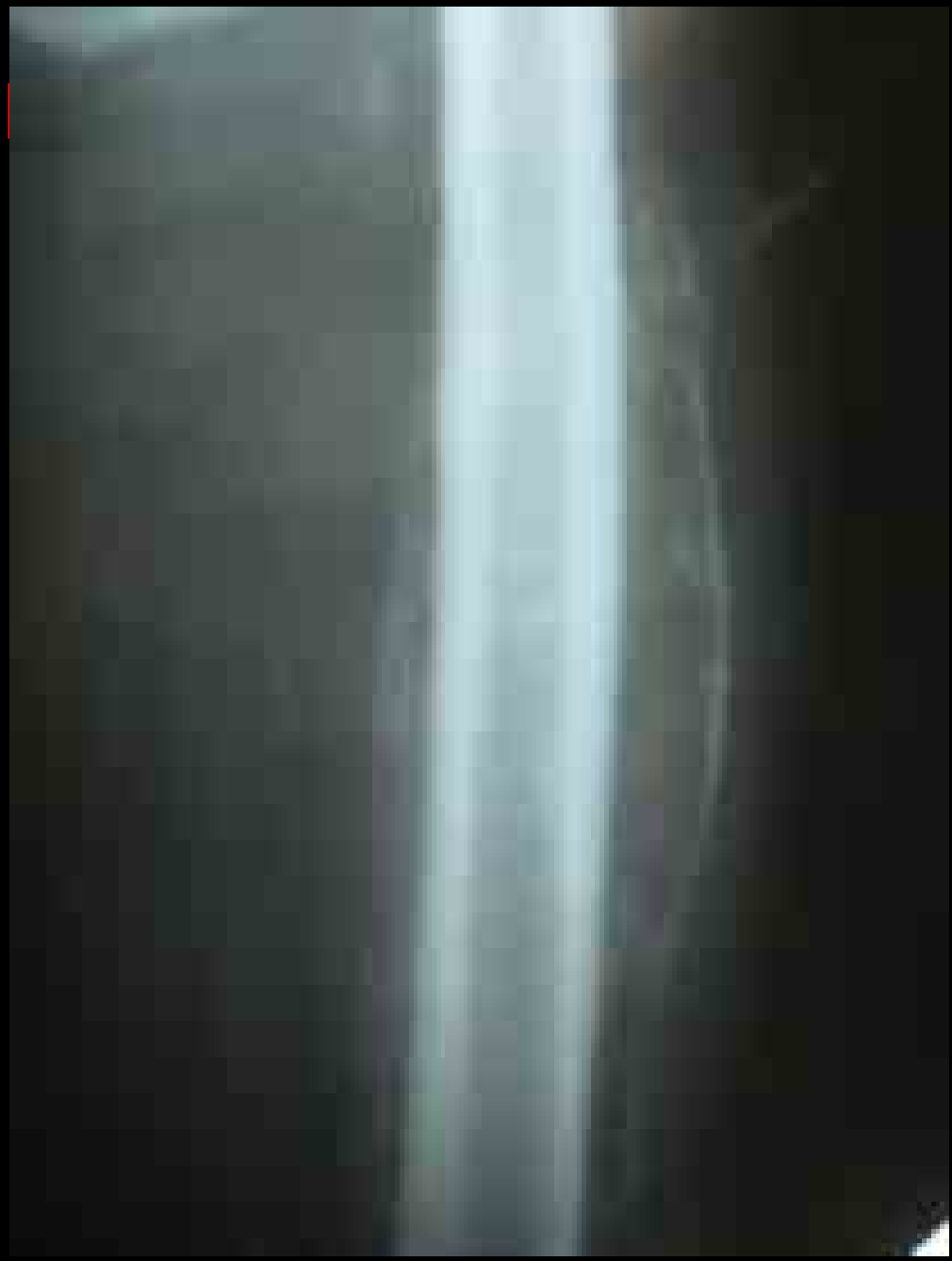
XR L knee

(Lateral)

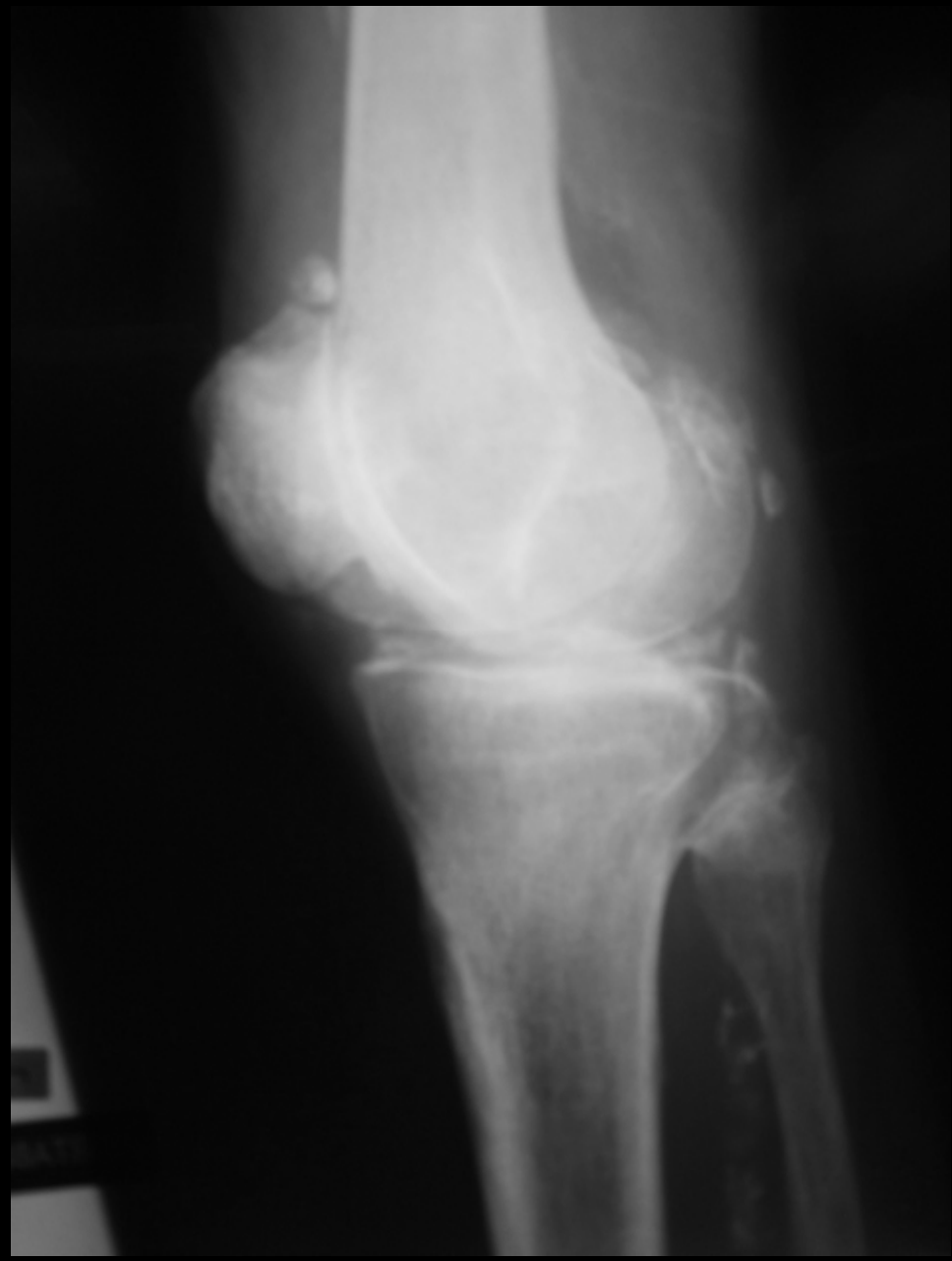




X



XR L knee



Diagnosis

Bilateral heterotopic ossification

HETEROTOPIC OSSIFICATION

What is Heterotopic Ossification?

- The formation of mature, lamellar bone in nonskeletal tissue
- Extraarticular, occurs outside the joint capsule.
- Forms in the connective tissue between the muscle planes and not within the muscle itself
- Generally does not involve the periosteum
- Mature HO shows cancellous bone and mature lamellar bone, vessels, and bone marrow with a minor amount of hematopoiesis

Who will develope HO?

- **Neurogenic**
  - traumatic brain injury, spinal cord injury, CVA
- **Traumatic**
  - burns, fractures, trauma, or muscle injuries and after total joint arthroplasty
- Genetic--Myositis ossificans progressiva (fibrodysplasia ossificans progressiva):
  - Autosomal dominant with variable expression.
  - Recurrent HO
  - congenital malformation of the great toe

How frequent HO happened?

- Spinal cord injury: 3.4% - 47%
- Traumatic brain injury: 11%-76%
- Total hip arthroplasty: 16-53%
- Acetabular fracture 18%-90%
- Burns 1-35% (depends on the severity of burn)
- CVA: 0.5-1.2%
- Other conditions: sickle cell anemia, hemophilia, tetanus, poliomyelitis, GBS, multiple sclerosis, toxic epidermal necrolysis, etc

Where can HO develop?

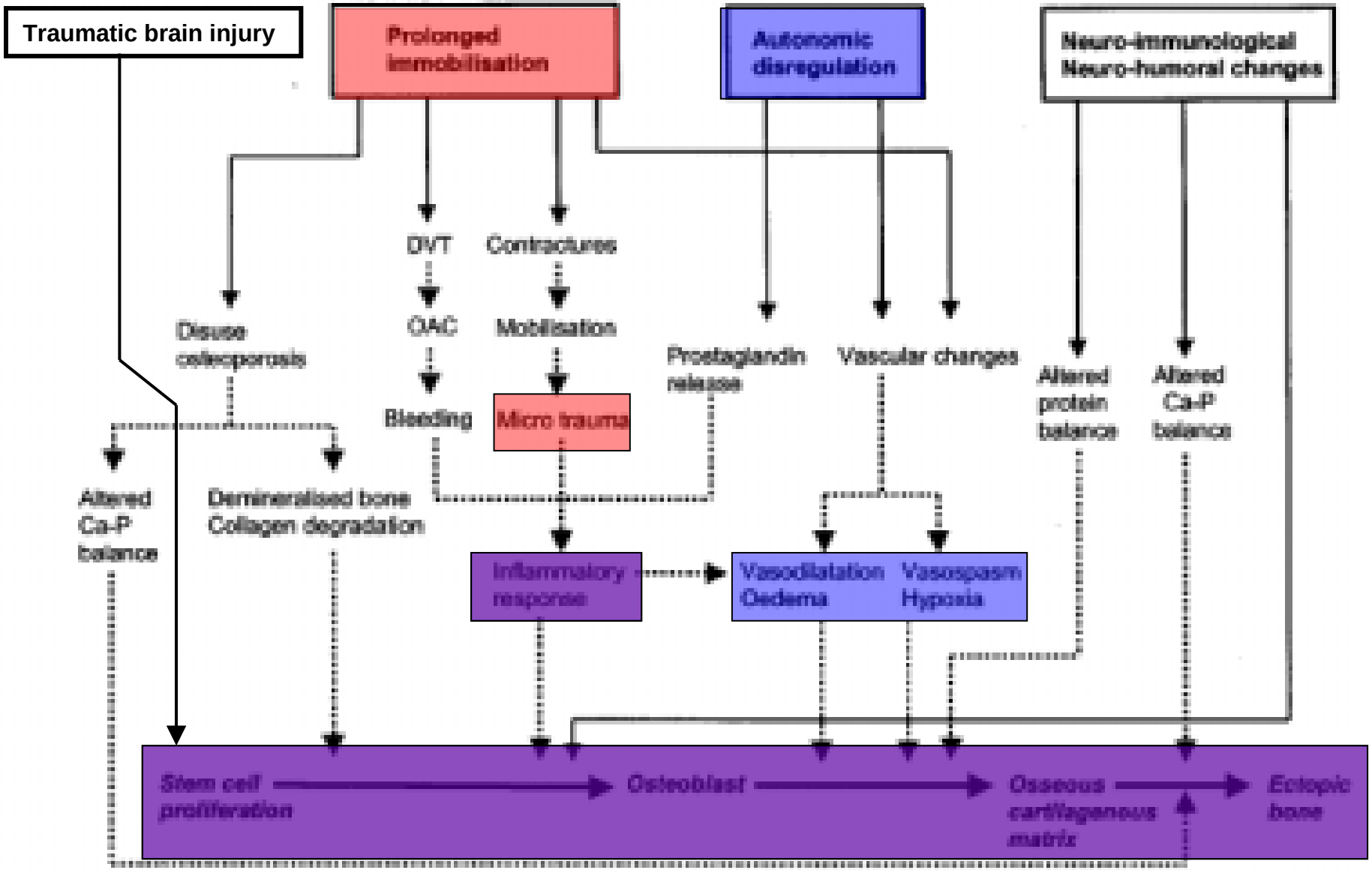
- **Distal joints of the hands and feet are almost never involved**
- Spinal cord injury:
  - always occurs below the level of injury
  - no relation to presence or absence of spasticity
  - the hips are most commonly involved
- Traumatic brain injury
  - almost always occurs on the affected side
  - more frequent in patients with spasticity
  - Common sites affected: hips, followed by the shoulders and elbows; knee uncommon

Where can HO develop?

- CVA
  - Usually develops on the hemiplgic side
  - Common locations include hips, knees and elbows

    Orthop Surg (Tokyo) 1969 (20): 193-201
  - ?due to slower blood flow on the hemiplegic side Arch Phys Med Rehabil 1987 (68): 313-4
- Burns
  - Usually occurs in the burned extremities

Pathogenesis:


Traumatic brain injury
Prolonged immobilisation
Autonomic disregulation
Neuro-immunological Neuro-humoral changes
DVT
Contractures
OAC
Mobilisation
Disuse osteoporosis
Bleeding
Micro trauma
Prostaglandin release
Vascular changes
Altered protein balance
Altered Ca-P balance
Altered Ca-P balance
Demineralised bone Collagen degradation
Inflammatory response
Vasodilatation Oedema
Vasospasm Hypoxia
Stem cell proliferation
Osteoblast
Osseous cartilagenous matrix
Ectopic bone

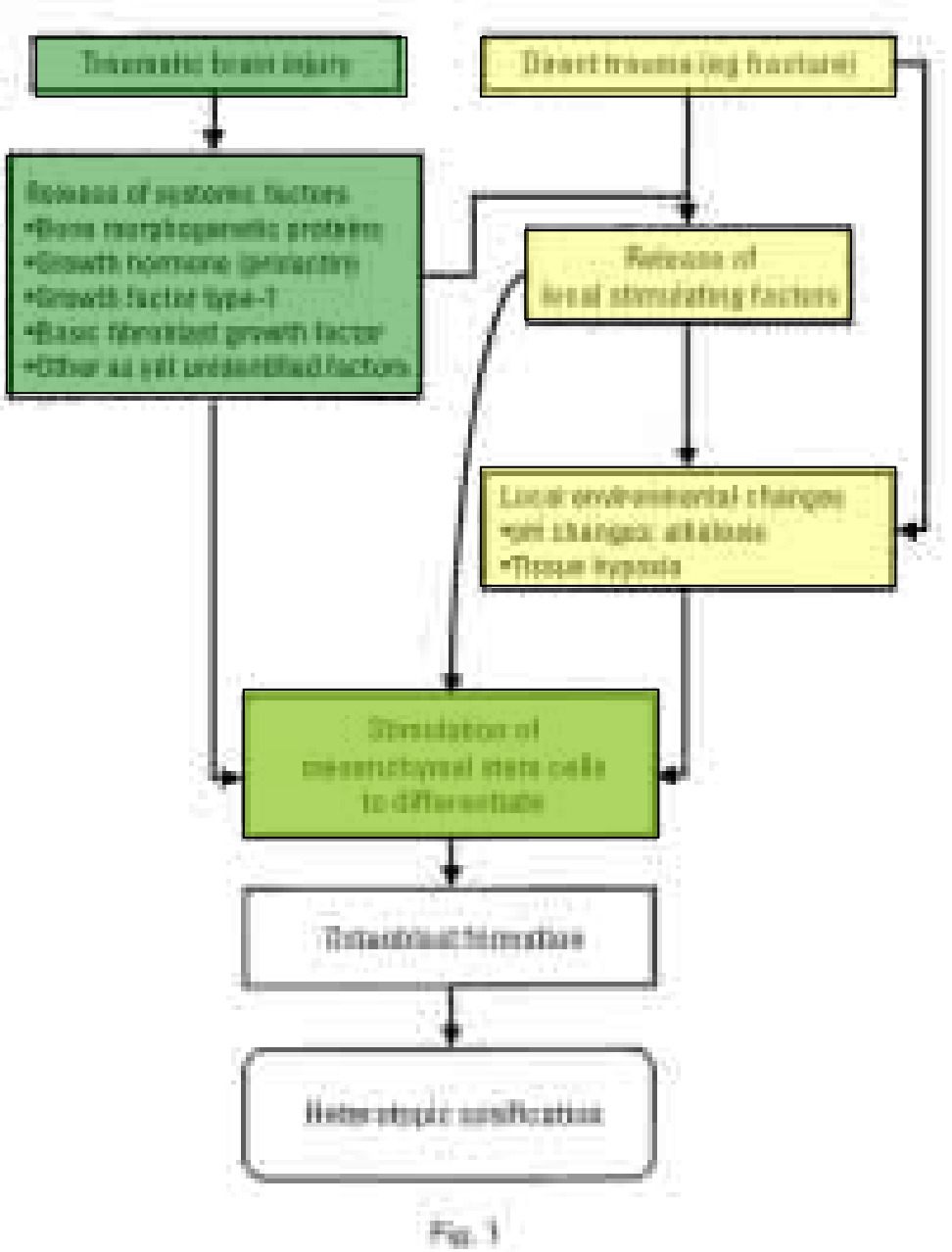


Fig. 1

Diagram demonstrating the potential mechanism for the interaction of systemic and local factors on mesenchymal stem cells resulting in their differentiation into osteoblasts and the formation of heterotopic ossification.

J Bone Joint Surg [Br]
2004;86-B:783-7.

How to make diagnosis?

- Clinical—symptoms and signs
- Imaging—XRs, bone scans, USG etc.
- Laboratory

How to make diagnosis?

- **Clinical—symptoms and signs**
- Imaging—XRs, bone scans, USG etc.
- Laboratory

Symptoms and signs of HO

- Loss of ROM --49%*
- Warmth, erythema, swelling –37%*
- Pain –35%*
- Low-grade fever
- Symptoms of its complications

*- J Nucl Med 1985; 26:125-132

Complications of HO

- Interferes with hygiene, transfers, and ADLs
- Bed sores
- Joint ankylosis (10-16%)
- Nerve entrapment
- DVT
- Lymphedema
- May trigger autonomic dysreflexia in patients with spinal cord injury at or above the T6 level
- Osteoporosis and subsequent pathologic fracture

How to make diagnosis?

- Clinical—symptoms and signs
- **Imaging—XRs, bone scans, USG etc.**
- Laboratory

Plain radiographs

- **Specific**
- Simple and cheap
- HO may not be evident on radiographs until **4 to 6 weeks after** an abnormality is detected on the **bone scan**
- The first radiographic sign is increased density of the periarticular soft tissue (due to edema)

Triple-phase bone scan

- **Sensitive**: possible to discover increased metabolic activity as early as 2 to 4 weeks after injury
- **Not specific**: difficult to differentiate bone tumor, metastasis, or osteomyelitis from heterotopic ossification

What are the three phases?

Phase 1: Dynamic blood flow occurs immediately after injection.

Phase 2: Immediate static scan detects areas of blood flow after injection.

Phase 3: Static phase involves a repeated bone scan after several hours.

Triple phase bone scan

- Phase 1 and 2 will be positive as early as **2.5 weeks** after HO forms
- Phase 3 will be positive 1-4 weeks later
- Returns to normal as the HO matures, usually 6-18 months after the first clinical sign
- The gold standard for determining the **maturity** of HO

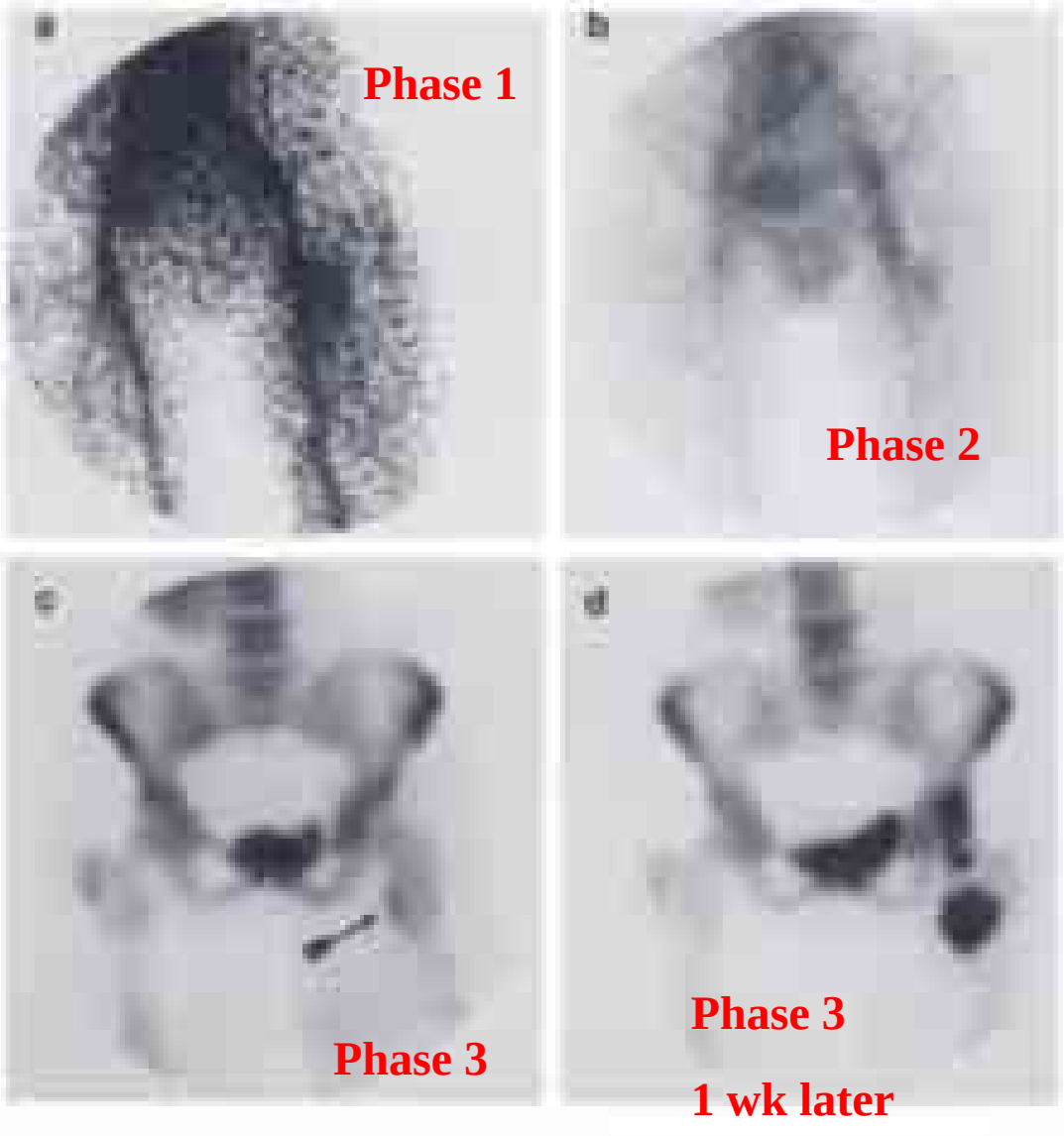


FIGURE 1
Initial three-phase RNBI (a–c) 16 days following acute cord injury with paraplegia demonstrates hyperemia but minimal soft-tissue uptake (arrow). Repeat study (delayed static image only) 1 wk later shows diagnostic soft-tissue uptake (d).

J Nucl Med 26:125–131, 1985

Other imaging

- USG
  - Early diagnosis of ossifications one week after THR in 2/3 of patients

    Unfallchirurg. 2003 Jan;106(1):28-31
  - Sensitive in detecting focal soft tissue abnormalities in SCI patients

    Paraplegia. 1993 Aug;31(8):500-6
- CT/MRI Radiology 1983; 149:775 - 779, Can Assoc Radiol J 1990; 1: 93 - 95
  - Mainly for preoperative assessment/planning
  - No role for the early detection of HO

How to make diagnosis?

- Clinical—symptoms and signs
- Imaging—XRs, bone scans, USG etc.
- **Laboratory**

Alkaline phosphatase (ALP)

- Reflects the activity of the ossification process
- Rise as early as 2 weeks after injury, reaching a peak around 10 weeks
- May be elevated up to 7 weeks before development of clinical symptoms
- ALP level gradually decline back to normal at about 5 months
- **Height of the ALP level DOES NOT correlate with peak activity** in bone formation or the burden of HO lesions
- Of little value in determining the maturity of HO prior to surgical removal

J Nucl Med 26:125–132, 1985

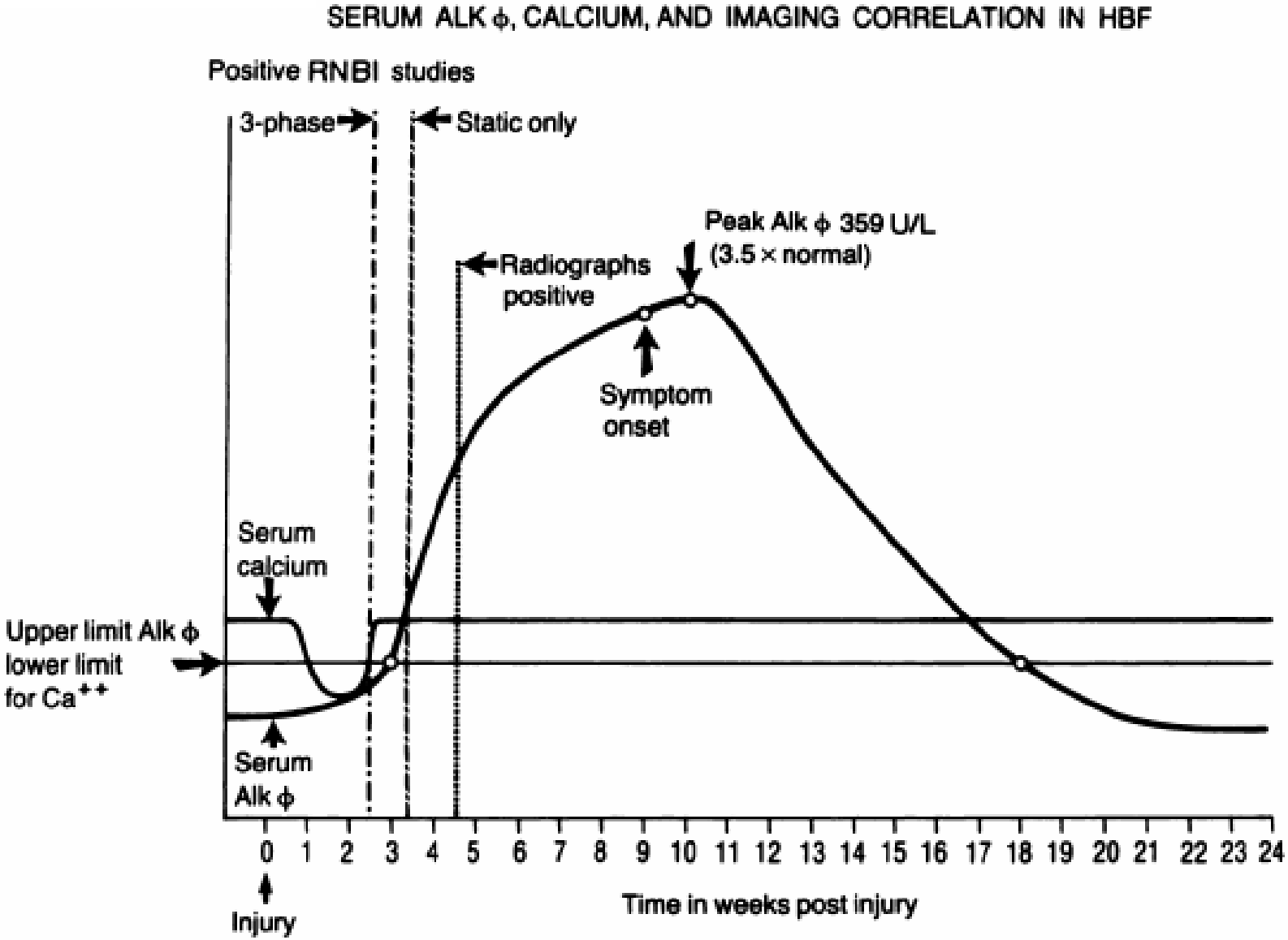


FIGURE 2
SAP and calcium behavior in acute HBF and relationship to RNBI and radiographic studies

Other lab tests

- Creatine kinase (CK)
  - CK were significantly higher in patients with HO and correlated with the severity of HO

    Arch Phys Med Rehab. 2003 Nov;84(11):1584-8
- C-reactive Protein (CRP)
  - higher CRP as a risk factor for HO after total-hip arthroplasty

    Arch Orthop Trauma Surg. 1999;119(3-4):205-7.
- Urine prostaglangin E2
  - increase of 24-hr PGE2 excretion as long as the HO had not reached maturity

    Arch Phys Med Rehabil. 1997 Jul;78(7):687-91

Management of HO

- Physical therapy
- Medications—NSAID, bisphosphonates
- Radiotherapy
- Surgery
- Management of complications/precipitating factors

Management of HO

- **Physical therapy**
- Medications—NSAID, bisphosphonates
- Radiotherapy
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Role of physiotherapy in heterotopic ossification

Pathogenesis of experimental heterotopic bone formation following temporary forcible exercising of immobilized limbs Michelsson JE et al, *Clin Orthop*. 1983; 176: 265-272

- **Heterotopic cartilage and bone formation occurred** in the soft tissues around the joint and in the area of damaged muscle after **repeated passive forcible exercising** of immobilized hip, knee, ankle, or elbow joints in rabbits
- The incidence correlated with the duration of immobilization and the frequency of manipulation.

Heterotopic ossification in spinal cord-injured patients

Stover SL et al. *Arch Phys Med Rehabil*. 1975;56(5):199-204

- 250 SCI patients who had x-ray evidence of early or immature HO or who developed early clinical signs of possible HO were treated with an aggressive program of passive progressive ROM exercises.
- There is **no evidence that exercise increases inflammation with subsequent ossification**

Heterotopic ossification: are range of motion exercises contraindicated? Crawford CM et al. *J Burn Care Rehabil*. 1986 Jul-Aug;7(4):323-7

- Burn patients receiving passive and active-assisted range of motion, especially **beyond the range of pain-free movements**, the ossification **progressed to complete ankylosis**
- Patients who followed a program of **active exercise within the pain-free range gained excellent range of motion**.
- Passive stretching of the periarticular structures during the acute phase of heterotopic bone formation is detrimental to the final outcome

Case Report

Continuous Passive Motion in the Management of Heterotopic Ossification in a Brain Injured Patient

ABSTRACT

Linan E, O'Dell MW, Pierce JM: Continuous passive motion in the management of heterotopic ossification in a brain injured patient. *Am J Phys Med Rehabil* 2001;80:614–617.

We report a man admitted to inpatient rehabilitation 6 wk after traumatic brain injury, who presented with bilateral knee heterotopic ossification. In addition to conventional physical therapy, we applied a continuous passive motion device during 4 wk increasing the range of motion of the knees. On the basis of the limited current literature and this case, we suggest that the use of continuous passive motion devices for heterotopic ossification may be effective and safe and should be the subject of further study.

Role of physiotherapy—conclusion

- No evidence based conclusion!
- Forcible ROM out of pain free range possibly harmful
- **Gentle** ROM in the **pain-free range** maybe helpful

Management of HO

- Physical therapy
- **Medications—NSAID, bisphosphonates**
- Radiotherapy
- Surgery
- Management of complications/precipitating factors

NSAID

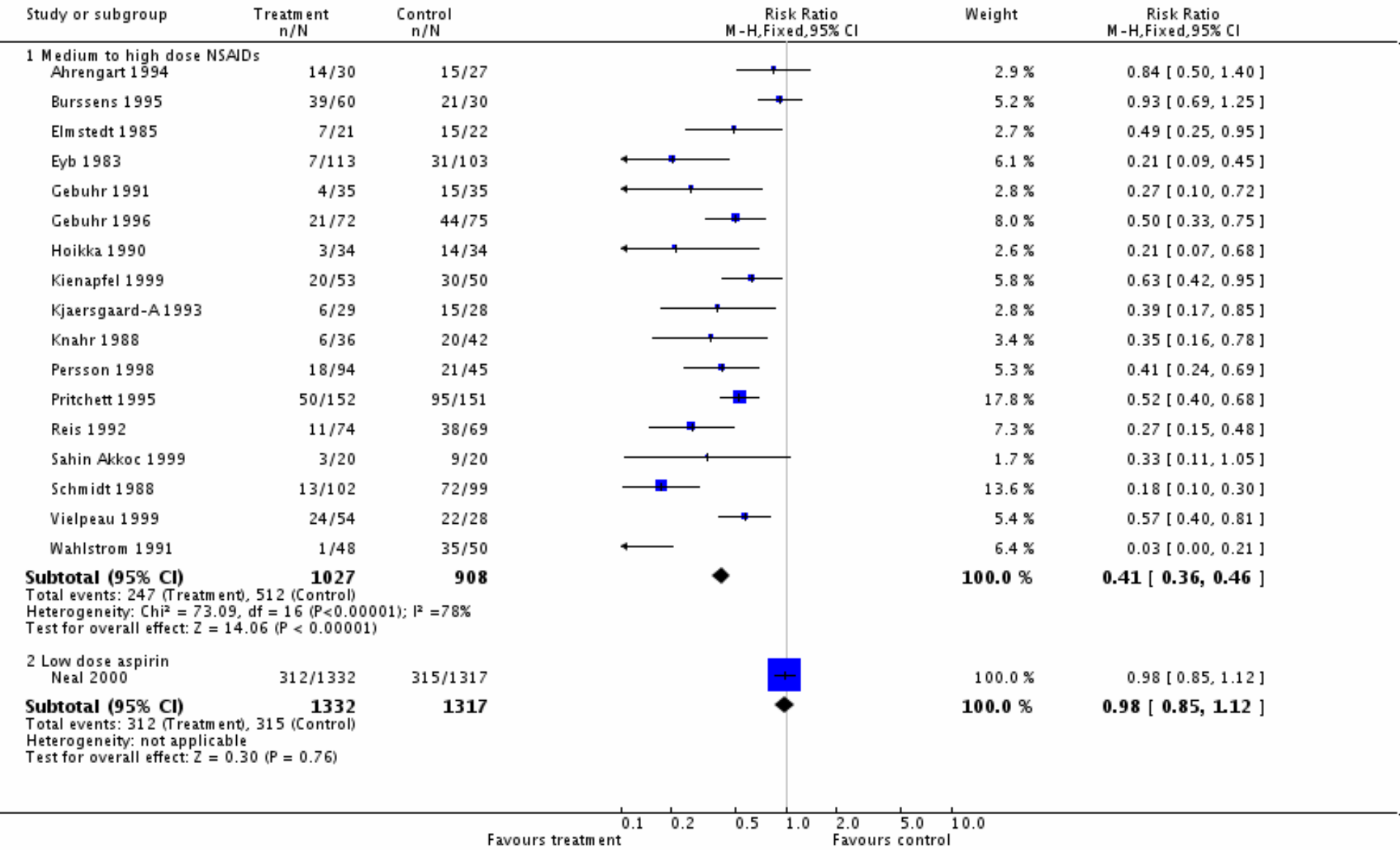
- Mechanism of action
  - Analgesia
  - Anti-inflammatory
  - reduce bone formation by the inhibition of prostaglandin synthetase

***Cochrane Database of Systematic Reviews* 2004, Issue 3**

NSAID for preventing heterotopic bone formation after hip arthroplasty

- Perioperative NSAID (medium to high dose) may be able to **prevent** 15-20 cases of HO among every 100 total hip replacements performed
- There was a non-significant 31% increase (95% CI 0%-71% increase) in the risk of GI side effects among patients assigned NSAIDs

Review: Non-steroidal anti-inflammatory drugs for preventing heterotopic bone formation after hip arthroplasty
Comparison: 1 Treatment versus control
Outcome: 1 Heterotopic bone formation



Prevention of heterotopic ossification after spinal cord injury with indomethacin

Spinal Cord. 2001 Jul;39(7):370-4

- This randomized, prospective, double-blind, placebo-controlled trial (N=33) showed **prophylatic indomethacin SR 75 mg daily for 3 weeks started 21+/-14 days after SCI significantly the lower incidence of HO** diagnosed by bone scan and XRs (25% and 12.5% respectively) when compared with the placebo group (65%; and 41% respectively; P<0.001)

Celecoxib versus indomethacin in the prevention of heterotopic ossification after total hip arthroplasty

J Arthroplasty. 2004 Jan;19(1):14-8

- COX-2 inhibitor (celecoxib) was compared with indomethacin in the prevention of HO after total hip arthroplasty for 20 days after surgery,
- No statistically significant difference between the two arms
- 8.4% patients in the indomethacin group 2.0% in the celecoxib group required treatment discontinuation, because of side effects ($P < .05$).
- Conclusion: Celecoxib shows the same efficacy as indomethacin in the prevention of HO after THR with fewer side effects

Bisphosphonates: mechanism of action

- Delay the aggregation of apatite crystals into large, calcified clusters (delay mineralization)
- Reduces further progression of surrounding cells
- Also has some anti-inflammatory effect
- **DOES NOT** eradicate bone that has already formed

Bisphosphonates

- Etidronate is the bisphosphonate used in most studies
- Dose:
  - SCI: 300 mg IV daily for 3 days followed by 20 mg/kg daily PO for 6 months

    J Spinal Cord Med 2000; 23: 40–44
  - TBI: 20 mg/kg per day PO for 3 months, then reduced to 10 mg/kg per day for 3 months

    Arch Phys Med Rehabil 1983; 64:539-542
  - Lack of evidence for other bisphosphonates

Bisphosphonates

- S/E
  - nausea,
  - diarrhea, osteomalacia, hyper-phosphatemia
- If withdrawn after a short treatment duration, a rebound ossification secondary to prolonged osteoclast inhibition may result

Cochrane Database of Systematic Reviews 2004: Pharmacological interventions for treating acute heterotopic ossification.

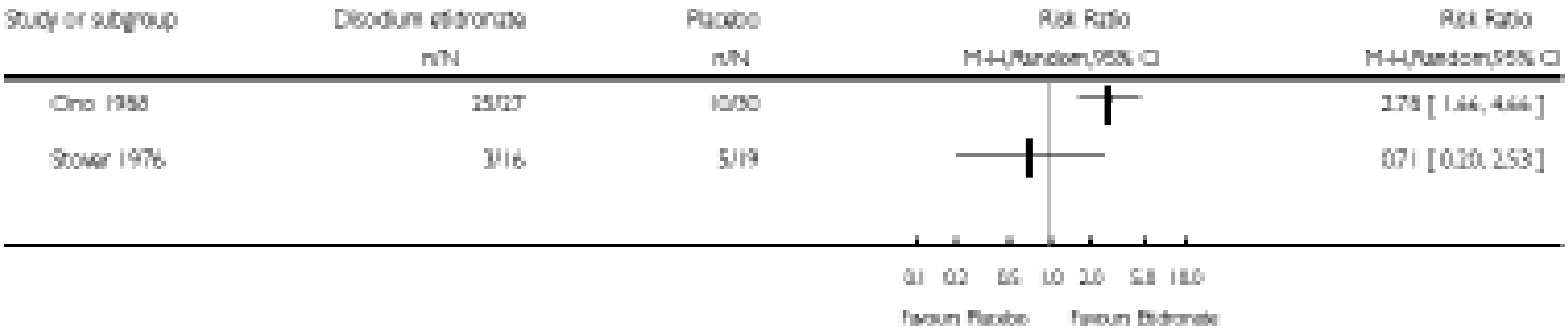
- Evaluated 2 RCTs
- Given the absence of long term radiographic outcomes in the included studies, there is **insufficient evidence** to recommend the use of disodium etidronate **for the treatment** of acute HO.
- Further studies are required to assess all pharmacological treatments for acute HO with sufficient follow-up duration.

Analysis 1.2. Comparison 1 Disodium etidronate versus placebo, Outcome 2 Improvement in HO grade versus no improvement (end of 12 weeks of treatment).

Review: Pharmacological interventions for treating acute heterotopic ossification

Comparison: 1 Disodium etidronate versus placebo

Outcome: 2 Improvement in HO grade versus no improvement (end of 12 weeks of treatment)



Management of HO

- Physical therapy
- Medications—NSAID, bisphosphonates
- **Radiotherapy**
- Surgery
- Management of complications/precipitating factors

Radiotherapy

- Interferes with the differentiation of mesenchymal cells to bone precusor cells
- Has been shown to help **prevent** HO after total hip arthroplasty and after resection of mature HO

J Bone Joint Surg [Br] 1997; 79-B:596-602

Radiotherapy

- Metaanalysis showed that post-op RT is more effective than NSAIDs in preventing HO after major hip procedures, although absolute differences may be small, and its efficacy is dose dependent

  Int J Radiat Oncol Biol Phys. 2004 Nov 1;60(3):888-95

- Not practical in prophylaxis for other conditions of HO

Radiotherapy

- No evidence that it is useful as a form of treatment of HO so far
- Maybe useful for symptomatic control:
  - RT has been used for pain control in a case of HO developed after TBI with pain refractory to NSAID

    Yonsei Med J. 2000 Aug;41(4):536-9

Management

- Physical therapy
- Medications—NSAID, bisphosphonates
- Radiotherapy
- **Surgery**
- Management of complications/precipitating factors

Surgical treatment for HO

- By means of **surgical resection** of HO
- Indications for surgery
  - Significant functional impairment due to joint immobility
  - Complications of HO e.g. peripheral neuropathy
  - Complications due to immobility, e.g. bed sores
- Timing: When the HO **matures** (to lower the rate of recurrence) i.e. when the 1st and 2nd phase of bone scan normalized

Complications of surgery

- Hemorrhage
- Infection
- Bone fracture (due to osteoporosis)
- High recurrence rate:
  - Radiologically the recurrence rate is 82%-100%, and clinically 17–58%

    Spinal Cord (2002) 40, 313 - 326
  - Therefore surgical resection must always be combined with NSAID or postoperative radiation

Prevention of HO

- Better nursing care, positioning
- Early identification and treatment of the precipitating risk factors (urinary tract infections, decubitus ulcers, DVT etc)
- Proper physiotherapy
- ?NSAID for SCI patients
- NSAID/RT for high risk patients after hip replacement

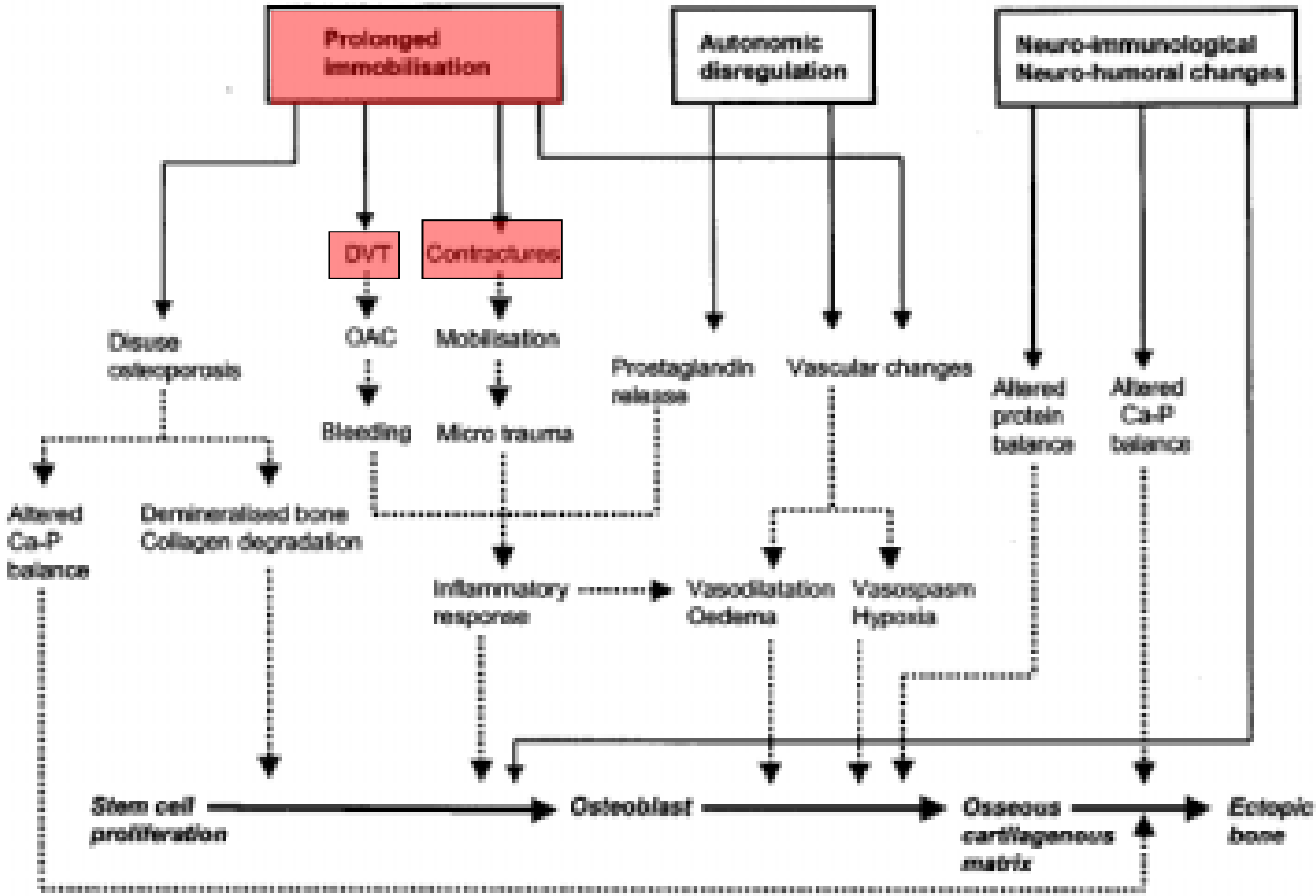
Bilateral HO

Bilateral HOs: case reports from Pubmed

- **Bilateral sciatic nerve entrapment due to heterotopic ossification in a traumatic brain-injured patient.**
  Safaz Iet al. *Am J Phys Med Rehabil*. 2008 Jan;87(1):65-7.
- **Heterotopic ossification in bilateral knee and hip joints after long-term sedation.**
  Sugita A et al. *J Bone Miner Metab*. 2005;23(4):329-32
- **Heterotopic ossification in the knee following encephalitis**: a case report with a 10-year follow-up.
  Saito N et al. *Knee*. 2004 Feb;11(1):63-5
- **A case of bilateral ulnar nerve palsy in a patient with traumatic brain injury and heterotopic ossification.**
  Chua et al. *Singapore Med J*. 1997 Oct;38(10):447-8
- **Postburn heterotopic ossification: insights for management decision making.**
  Peterson SL et al. *J Trauma*. 1989 Mar;29(3):365-9

CVA and bilateral HO

- No case report of CVA + bilateral HO found in literature
- Contributing factors in this case
  - CVA
  - Prolonged immobility due to severity of stroke and the complications (pnemonia, DVT etc)


Prolonged immobilisation
Autonomic disregulation
Neuro-immunological Neuro-humoral changes
DVT
Contractures
Disuse osteoporosis
OAC
Mobilisation
Prostaglandin release
Vascular changes
Altered protein balance
Altered Ca-P balance
Bleeding
Micro trauma
Altered Ca-P balance
Demineralised bone Collagen degradation
Inflammatory response
Vasodilatation Oedema
Vasospasm Hypoxia
Stem cell proliferation
Osteoblast
Osseous cartilaginous matrix
Ectopic bone

Immobilization caused Immobilization!

The patient: progress

- Gentle ROM exercises
- Given Alendronate 40mg Daily PO

Date	18/11/08	2/12/08	10/12/08	23/12/08	12/1/09
ALP	178	161	147	122	100

- Despite effort, poor recovery and gradual downhill cause
- Extensive grade IV sacral sore with sepsis

Conclusion

- HO an uncommon complication of CVA
- Bilateral involvement is extremely rare
- Diagnosis is clinical + radiological
- Bisphosphonate is the classical choice of treatment but not supported by strong evidence

Conclusion

- Surgery is the treatment for suitable cases but recurrence is un-avoidable and not without risks
- Prevention is better than cure, though medical prophylaxis only available for cases of hip replacement

The end