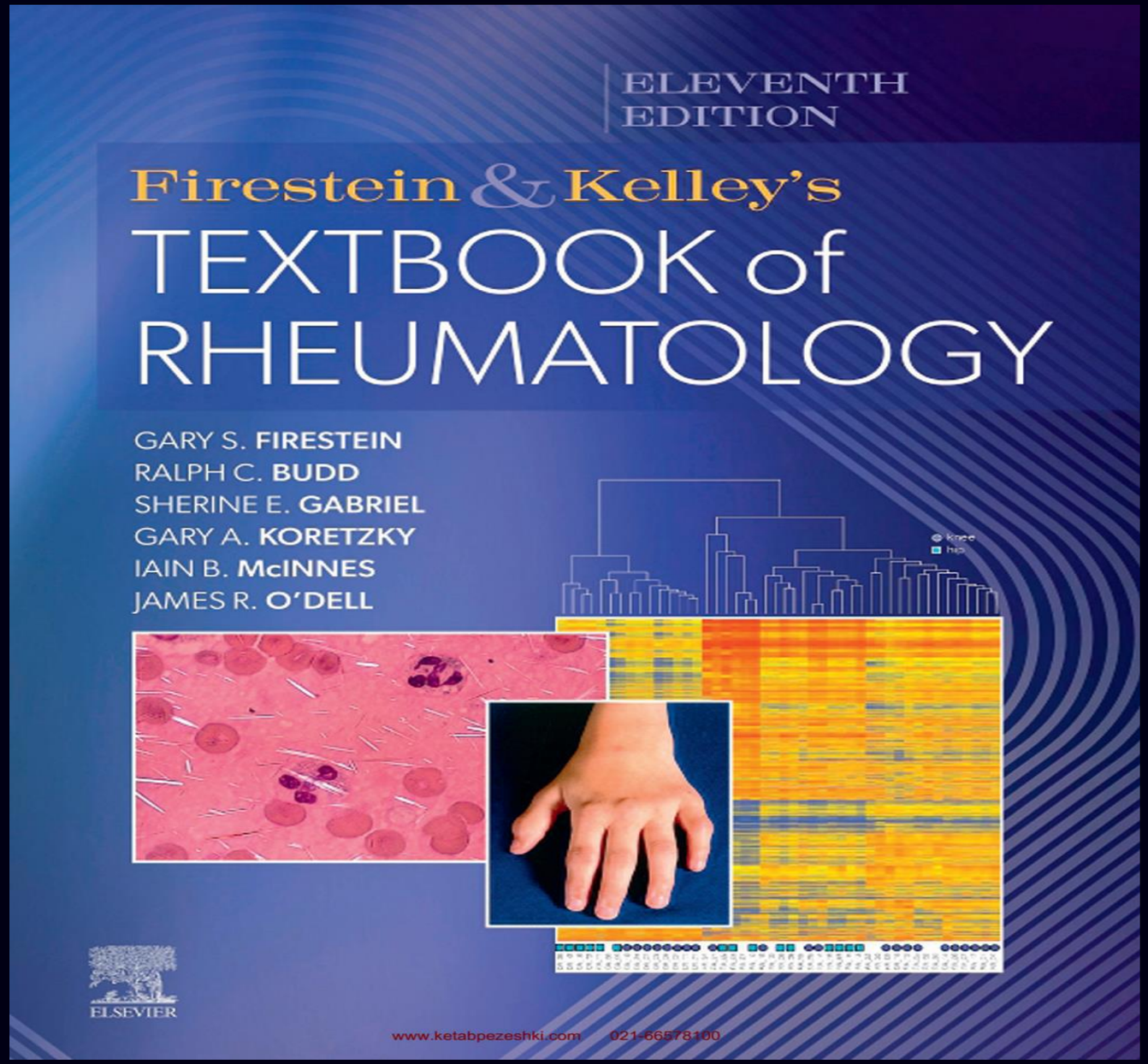
Osteonecrosis

Presentation by :
Dr.sareh basiri
Loghman hospital _ SBMU



Introduction

- Osteonecrosis means “bone death”. Synonyms include avascular necrosis,ischemic necrosis of bone, aseptic necrosis, and subchondral avascular necrosis.

- The first description of the occurrence of bone death in the **absence of infection** was published almost a century later.

- Abnormalities in lipid metabolism, bone homeostasis , regulation of apoptosis, coagulopathies, innate immunity, and oxidative stress may play a role in the pathogenesis of osteonecrosis. The final common pathway in the pathogenesis of osteonecrosis is disruption of blood supply to a segment of bone

Epidemiology

- Osteonecrosis is believed to be the cause of **10% of the hip replacements** performed in the United States each year.
- Osteonecrosis occurs in **15% to 80% of patients with femoral neck fractures**.
- Osteonecrosis primarily affects **men**, except when associated with SLE.
- Osteonecrosis typically occurs in the **third to fifth decade** of life.
- **Osteonecrosis of the jaw (ONJ)** may result from bisphosphonate use. Other drugs and procedures, including dental implants, have also been associated with ONJ.

Etiology

❖ Dietary , Drug , and Environmental Factors

- ✓ Corticosteroids
- ✓ Bisphosphonates
- ✓ Alcoholism
- ✓ Cigarette smoking
- ✓ Dysbaric osteonecrosis
- ✓ Lead poisoning
- ✓ Electric shock

❖ Musculoskeletal Conditions: Compromise in Structural Integrity

- ✓ Trauma
- ✓ Legg-Calvé-Perthes disease
- ✓ Congenital hip dislocation
- ✓ Slipped femoral capital epiphysis

Etiology

❖Metabolic Diseases

- ✓Fat embolism
- ✓Pancreatitis
- ✓Chronic liver disease
- ✓Pregnancy
- ✓Fabry’s disease
- ✓Gaucher’s disease

❖Metabolic Diseases

- ✓Gout
- ✓Hyperparathyroidism
- ✓Hyperlipidemia
- ✓Hypercholesterolemia
- ✓Diabetes

Etiology

❖Hematologic Conditions:

- ✓ Sickle cell anema
- ✓ Hemophilia
- ✓ Hemoglobinopathies
- ✓ Thalassemia
- ✓ DIC
- ✓ Thrombophilia
- ✓ Hypofibrinolysis
- ✓ Marrow infiltrative disorders
- ✓ Thrombophlebitis/venous thrombosis

❖Rheumatologic Conditions

- ✓ APS
- ✓ RA
- ✓ IBD
- ✓ Polymyositis
- ✓ Sarcoidosis
- ✓ MCTD
- ✓ Necrotizing arteritis
- ✓ Mucocutaneous lymph node syndrome

Etiology

❖Infectious Diseases

- ✓ **HIV** infection
- ✓ **SARS**
- ✓ Osteomyelitis
- ✓ Meningococcemia

❖Oncologic Disorders and Their Treatment

- ✓ Organ transplantation (with or without corticosteroid exposure)
- ✓ Radiation exposure
- ✓ Regional deep hyperthermia
- ✓ ALL

Etiology : Steroid-Related Osteonecrosis

- The **most common** cause of nontraumatic osteonecrosis is corticosteroid use
- The **risk factors** for the development of steroid related osteonecrosis are not completely clear, and it is therefore important that steroids be prescribed only when indicated and only for the length of time required
- Although the risk of developing osteonecrosis with corticosteroid use is small, it is imperative that patients be advised of this complication due to its potentially **severe morbidity**

Etiology : Steroid-Related Osteonecrosis

- no conclusions about a **“safe”** dose of corticosteroids can be made
- Nonetheless, corticosteroid-induced osteonecrosis is **dependent on dosage**, and the risk is higher with **long-acting steroids** and with **parenteral usage**
- Additional **host-inherent risk factors** also play a role in susceptibility.

Etiology : Steroid-Related Osteonecrosis

- An ARCO task force set up in 2017 reviewed current literature and provided a consensus regarding glucocorticoids and osteonecrosis. They concluded that the **classification criteria for osteonecrosis** of the femoral head associated with steroids must include :

- ✓ A history of steroid use equivalent to greater than 2 g prednisolone in a 3-month period,

- ✓ a diagnosis of osteonecrosis occurring within 2 years of usage of steroids,

- ✓ there should not be any other cause of the osteonecrosis besides steroid use

Etiology : Alcohol and Smoking

- **Smokers** have a threefold higher relative risk for the development of osteonecrosis, independent of all other factor

- A study : the risk of osteonecrosis also increased with increasing **daily consumption of alcohol**.
- The subjects were divided into three groups on the basis of their alcohol consumption of less than 400 mL/week, 400 to 1000 mL/week, and greater than 1000 mL/week. The relative risk of osteonecrosis for these groups, independent of corticosteroid use or smoking, was **threefold, 10-fold, and 18-fold**, respectively.

- The **liver damage** is not necessary for the development of osteonecrosis in patients who consume alcohol, although elevated liver enzymes may be present.

Etiology : Alcohol and Smoking

- **criteria for alcohol-induced osteonecrosis**

✓ a history of alcohol consumption of greater than 400 mL or 320 g per week of pure alcohol in any form for 6 months,

✓ a diagnosis of osteonecrosis made within a year of alcohol consumption at this dose

✓ no other etiology for the osteonecrosis

Etiology : Transplantation

- An association between solid organ transplantation and osteonecrosis has been reported.
- Many of these cases do occur in the context of **steroid use**. In a study of patients undergoing renal transplantation, the 26 patients in whom osteonecrosis developed had taken a **higher cumulative oral dose** of prednisone after 1 and 3 months
- However, reports in the **absence of steroids** are also found in the literature. In a 2008 paper of 204 patients who underwent cardiac transplantation, six developed osteonecrosis of the hip or knee. There was no correlation with steroid use.
- the mechanism may be more related to a **hypercoagulable state or fibrinolysis.**

Etiology : Dysbaric Osteonecrosis

- Dysbaric osteonecrosis has occurred in construction workers exposed to **high pressure environments**.
- The **prevalence** of dysbaric osteonecrosis is 4.2% in divers and 17% in workers exposed to compressed air.
- Patients with dysbaric osteonecrosis may have **more than one lesion**; in addition to the femoral head, common sites include the tibia and the humeral head and shaft.
- The condition is not related to **decompression sickness** , and decompression procedures have no effect on the development of osteonecrosis, which can occur months or years after the last exposure to high-pressure environments

Etiology : Infection

- Osteonecrosis has also been associated with a number of infectious diseases, including (**SARS**).
- Many patients who contracted SARS in the early 2000s received treatment with corticosteroids, and osteonecrosis subsequently developed in some of these patients.
- The incidence of osteonecrosis appears to be higher in this group of patients than in patients with other conditions who were treated with corticosteroids.

Etiology : Infection

- In a large international cohort of 11,820 patients with **HIV**, there were 619 fractures and 89 cases of osteonecrosis. Risk factors for osteonecrosis :

- ✓ advanced age
- ✓ lower (BMI)
- ✓ Caucasian
- ✓ IV drug use
- ✓ lower baseline CD4
- ✓ prior osteonecrosis of fractures
- ✓ cardiovascular disease
- ✓ non-AIDS cancer
- ✓ coinfection with hepatitis C virus

Etiology : Radiation

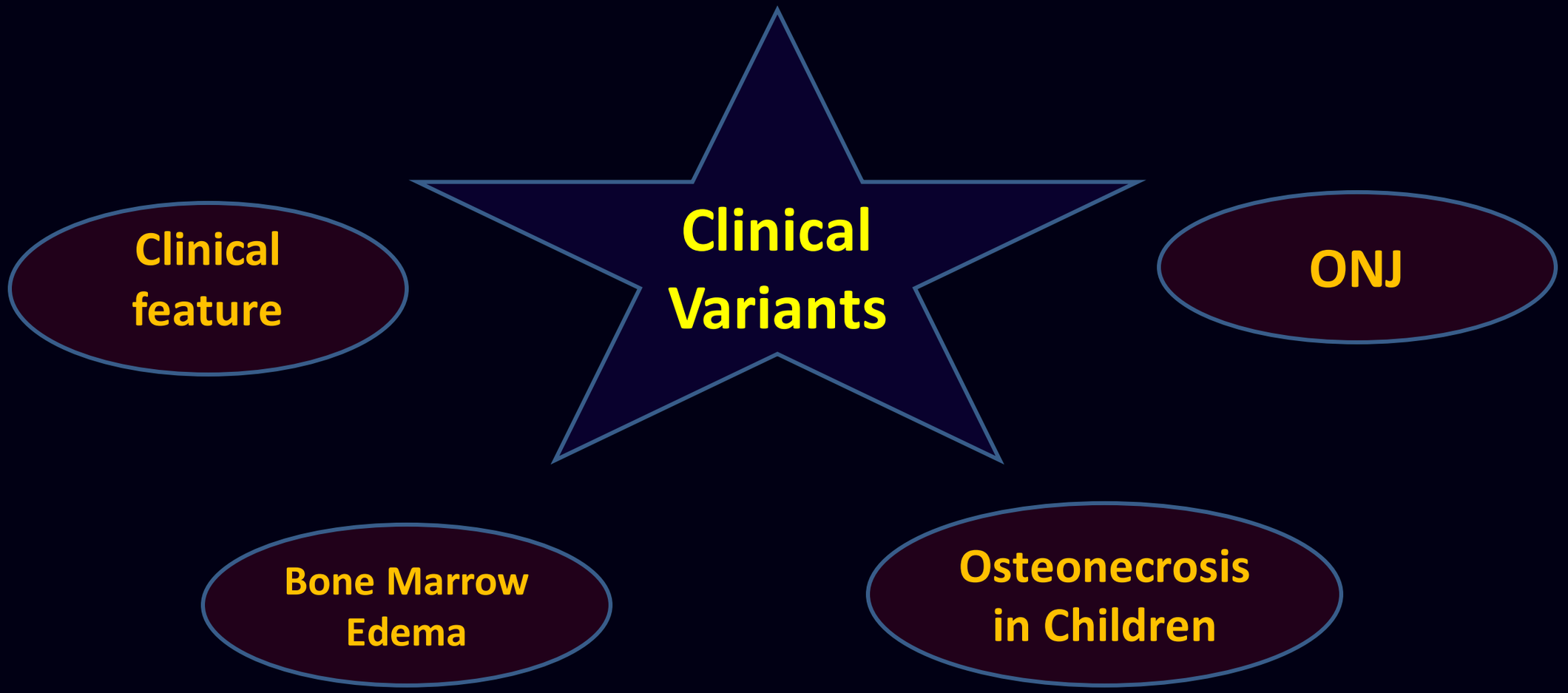
- The earliest reports primarily involved **ONJ** . Most were case reports.
- Exposure to radiation may result in **damage to vascularity of bone** and lead to osteonecrosis in a **dose-dependent manner**.
- In particular, osteonecrosis after radiation for neoplasms is well documented and particularly affects the **femoral head and the mandible**.
- Concomitant administration of **chemotherapy** can accentuate the risk of osteonecrosis in patients who are receiving radiation, particularly elderly women.

Etiology : Radiation

- An animal model of osteonecrosis induced by **high-intensity focused ultrasound (HIFU)** was developed to determine if HIFU could be used to generate osteonecrosis for animal studies.
- possibility of ultrasound-induced osteonecrosis in human
- The proposed mechanism : through **thermal damage** induced by osteocyte damage and vascular thrombosis

Etiology : Coagulopathy

- Hematologic conditions have been associated with osteonecrosis .
- The long-term morbidity of osteonecrosis in patients with **sickle cell anemia** is dismal.
- Osteonecrosis in patients with **hemophilia** has occurred, but no statistically reliable causal link has been established.


Clinical feature
Clinical Variants
ONJ
Bone Marrow Edema
Osteonecrosis in Children

Clinical feature

- The primary presenting symptom in osteonecrosis is **pain**, although many patients may be asymptomatic in the early phases of the disease.

- In osteonecrosis of the **femoral hip**, the pain is located in the hip joint but may radiate to the groin, anterior thigh, or knee.
- The severity of the pain can vary, depending on the **size of the infarct** and whether the **onset of disease** is insidious or sudden
- The pain of osteonecrosis is usually increased with **use of the joint**, but in individuals with advanced disease, the pain can be persistent at rest.
- **Limitation of range of motion** is progressive and is usually a late symptom, except when it results from accompanying pain.
- The risk of developing osteonecrosis of the **contralateral hip** when one side is affected ranges from 31% to 55%.

Clinical feature

- osteonecrosis can affect **other sites** such as the humeral head,femoral condyles and proximal tibia, the wrists and ankles , the bones of the hands and feet, the vertebrae ,the jaw , and bony structures of the face.
- Osteonecrosis of the **humeral head** is the second-most common location; pain is usually present in the shoulder and is associated with reduced ROM and weakness.
- Pain in the ankle is the main presenting symptom in nontraumatic **osteonecrosis of the talus**
- **Kienböck's disease** involves osteonecrosis of the lunate. Patients present with pain in the radiolunate joint, along with weakness and limitation of motion. Kienböck's disease appears to be related to manual labor

Clinical Variants : Bone Marrow Edema

- Bone marrow edema is a **common observation** in people with osteonecrosis and is frequently accompanied by vascular congestion. Bone marrow edema is not specific for osteonecrosis.

Clinical Variants : Bone Marrow Edema

- A specific syndrome known as **bone marrow edema syndrome** was initially thought to be a precursor to osteonecrosis, but it is now believed to be a separate entity.
- Bone marrow edema is a **transitory**, self-limiting condition typically seen in middle-aged men or in women in their third trimester of pregnancy.
- Patients report **pain**, limited range of motion, and an abnormal gait.
- Osteopenia is detected with **radiographs**, and **MRI** confirms this diagnosis .
- The **three phases** : an **initial phase** lasting about 1 month, followed by a **plateau phase** lasting 1 or 2 months, and finally a **regression phase** lasting an additional 4 to 6 months.
- **Subchondral fractures** do not occur.
- One study : None of the cases progressed to osteonecrosis

Clinical Variants : Bone Marrow Edema

- Differentiation between bone marrow edema syndrome and osteonecrosis can be facilitated through **analysis of perfusion patterns** including **mean transit times** (MTTs) and **plasma flow** (PF) based on dynamic contrast-enhanced three-dimensional MRI.

- **Bone marrow edema** joints show a subchondral area with high PF and low MTT surrounding by areas of low PF and long MTT. In contrast, **osteonecrosis joints** show a subchondral area with no PF and MTT surround by a rim of high PF and intermediate MTT

- There have been reports of treatment of bone marrow edema syndrome with bisphosphonates and denosumab with good results.

Clinical Variants : ONJ

- Two forms of bisphosphonates are available, and osteonecrosis appears to occur in association with bisphosphonates that **contain nitrogen**.
- The **mechanism** of bisphosphonate-induced ONJ appears to parallel that of glucocorticoids, with derangement in **lipid metabolism**, **bone homeostasis**, and **apoptosis of bone cells** all playing a role.
- the **jaw bone** appears to be the most vulnerable bone in this disease, as opposed to the femoral head.

- This phenomenon is more common with **repeated intravenous infusions** of bisphosphonates.

  One study : ONJ developed earlier in men than in women. Most of the patients (81%) were taking zoledronate at the onset of ONJ.

Clinical Variants : ONJ

- A case of ONJ was reported in association with the use of **raloxifene**.
- **Denosumab**, has also been implicated in ONJ . In addition to case reports, animal studies also suggest that anti-RANKL interferes with the normal bone resorptive functions of osteoclasts after **dental trauma** ,which may play a role in the pathogenesis of ONJ.

Clinical Variants : ONJ

- Osteonecrosis of the jaw can also occur after head and **neck radiation therapy**.
- **Diagnostic criteria** for this condition is exposed necrotic bone lasting for a minimum of 8 weeks in patients receiving at least 50 Gy of radiation in the absence of bisphosphonate therapy. Persistent or recurrent malignancy must be differentiated from osteonecrosis.

- **Idiopathic** osteonecrosis of the jaw has also occurred

Clinical Variants : ONJ

- Bisphosphonates
- Denosumab
- neck radiation therapy
- Idiopathic

Clinical Variants : Osteonecrosis in Children

- Osteonecrosis can develop in children with **ALL** but this phenomenon may be a result of **steroid use** .An additional risk factor for patients with ALL has been found to be **high BMI**.

- Osteonecrosis can be a complication of **anti-leukemic therapy in children**.
- The highest risk is in adolescents. Severity can range from mild to disabling. Serial MRIs in these patients may be indicated to reduce morbidity.
- SNPs near bone morphogenic protein 7 **(BMP7)** and the glutamate receptor gene **(GRID2)** may present a **genetic risk**.

- Children with **sickle cell disease** are also at risk for osteonecrosis. The mechanism appears to involve vaso-occlusion of the watershed zones that supply nutrients to bone.

Osteonecrosis in Children

➢ **Musculoskeletal conditions** can lead to osteonecrosis in children.

- Femoral head osteonecrosis is a feature of **Legg-Calvé-Perthes (LCP)** and has been linked to trauma, congenital hip dislocation,and transient synovitis.
- Bilateral involvement is common, and associated clinical manifestations include abnormal growth and stature,delayed skeletal maturation,disproportionate skeletal growth, congenital anomalies,and abnormal hormone levels.

➢ steonecrosis can develop **post-surgical repair of LCP**. Because of hardware present after surgery, MRI may not be the ideal mode of monitoring for osteonecrosis, and the authors suggest **radionuclide bone imaging**

Osteonecrosis in Children

- Hematologic condition
  - SCA
  - ALL
- anti-leukemic therapy in children
- Musculoskeletal conditions
- post-surgical repair of LCP

Staging

- Ficat and Arlet method of staging
- Marcus staging
- modified Steinberg staging system

Modified Steinberg Staging Systems for Osteonecrosis

Stage	Radiographic Appearance	Reversible
I	Normal radiographs, but abnormal bone scan or MRI	Yes
II	Lucent and sclerotic changes	Yes
III	Subchondral fracture without flattening	No
IV	Subchondral fracture with flattening or segmental depression of the femoral head	No
V	Joint space narrowing or acetabular changes	No
VI	Advanced degenerative changes	No

Staging

- **criteria for the diagnosis and staging (2001)** of osteonecrosis of the femoral head :

- ✓ (1) **collapse** of the femoral head without joint space narrowing or acetabular abnormality as seen on a plain radiograph,
- ✓ (2) **demarcating sclerosis** in the femoral head without joint space narrowing or acetabular abnormality,
- ✓ (3) **“cold in hot”** areas on bone scans,
- ✓ (4) a low-intensity band on **T1-weighted MRI**,
- ✓ (5) **histologic findings** of trabecular and marrow necrosis.

- If a patient fulfils two of the fie criteria, the diagnosis is established

Pathogenesis

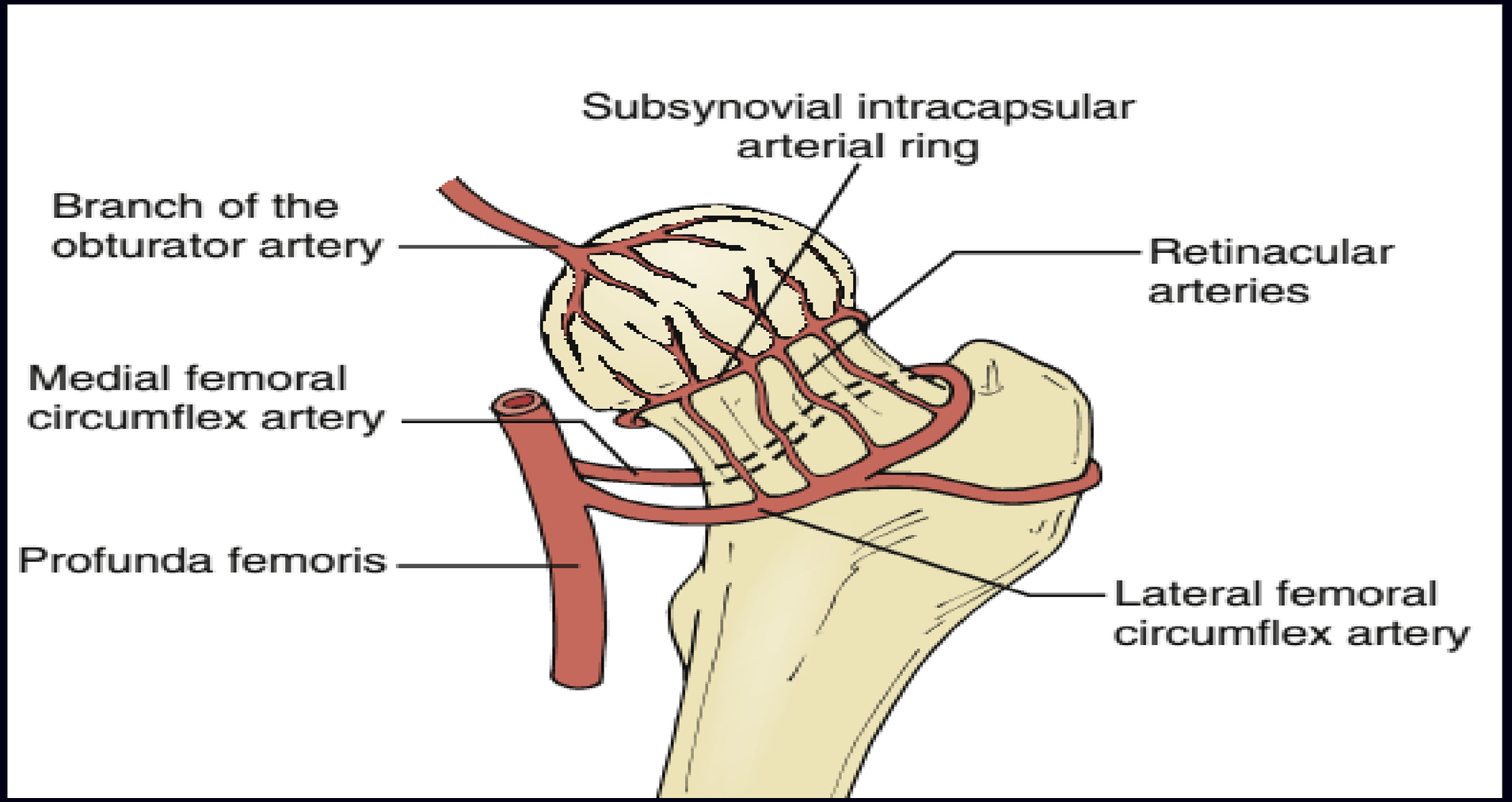
➢ Traumatic Osteonecrosis :

- ✓ Anatomic Considerations

➢ Nontraumatic Osteonecrosis :

- ✓ Vascular and Mechanical Considerations
- ✓ Osteoimmunologic Factors
- ✓ Osteoblast/Osteoclast Balance
- ✓ Apoptosis
- ✓ Role of Lipids
- ✓ Oxidative Stress
- ✓ Nitric Oxide Synthase

Pathogenesis : Traumatic Osteonecrosis



Pathogenesis : Traumatic Osteonecrosis

- Histologically, after an infarct, a **rim of bony thickening or sclerosis** begins to form at the margins of the infarcted area.
- If the necrotic lesion is within the weight-bearing region of the femoral head, **subchondral fractures** occur. With repeated microfractures and continued weight bearing, the original fracture can not heal completely and new fractures appear.
- As time goes on, the femoral head becomes **flattened** and eventually **collapses**.
- A **nonspherical head** articulating with the acetabulum produces friction, erosion, and loss of cartilage. The structure of the joint deteriorates, leading eventually to total joint destruction.

Pathogenesis : nontraumatic Osteonecrosis

- Osteonecrosis secondary to trauma can be easily explained simply based on anatomy, but with nontraumatic osteonecrosis, the pathogenesis is more complex and may involve **immunologic, hormonal, and metabolic factors.**

- Some investigators have likened osteonecrosis to **“coronary disease”** of the hip and propose that the same mechanisms that cause ischemia of the myocardium may also cause ischemia of the femoral head

➢ Nontraumatic Osteonecrosis :

- ✓ Vascular and Mechanical Considerations
- ✓ Osteoimmunologic Factors
- ✓ Osteoblast/Osteoclast Balance
- ✓ Apoptosis
- ✓ Role of Lipids
- ✓ Oxidative Stress
- ✓ Nitric Oxide Synthase

Vascular and Mechanical Considerations

- In **LCP** disease, obstruction to **venous drainage** elevates intraosseous pressure and consequently increases intra-articular pressures

- The pathologic mechanism of **dysbaric osteonecrosis** is unclear. The most intuitive explanation is that formation of **gas bubbles** causes arterial occlusion and ischemia. However, multiple other factors may contribute to the disease, (thromboembolic events such as platelet aggregation, erythrocyte clumping, lipid coalescence,...)
- The **increased vulnerability of bone** to compression disorders has been explained by several factors (relative rigidity of bone, inherent poor vascularization,…)

- Changes in the vasculature through **injury or inflammation** from other diseases may in turn lead to a compromise in blood flow.

Osteoimmunologic Factors

- The factors that regulate **bone homeostasis** include cells of the bone matrix, immune cells, signaling molecules, cytokines and chemokines, and vitamins and hormones.
- Some of these regulatory factors may be present on both bone cells and immune cells, often serving different functions, thereby providing a **link between the immune system and bone.** In fact, osteonecrosis may be a result of such an **imbalance in bone homeostasis**.
- Immune factors may affect **surrounding soft tissue** as well, contributing to the development of osteonecrosis.

Osteoimmunologic Factors

- **Immune factors** involved in bone homeostasis include (RANK) and its ligand (RANKL), IL-1, IL-6, IL-10, TGF- β, TNF, CD80, CD86, CD40, (M-CSF), nuclear factor of activated T cell cytoplasmic (NFATc), and vitamin D

- Many of these factors can be categorized into one of two categories: inducers or inhibitors of **osteoclastogenesis**.

- Because transcription of factors involved in the regulation of bone homeostasis is often influenced by **glucocorticoids** , this mechanism may begin to explain why steroids are associated with osteonecrosis.
- an upregulation in **TLR 4** signaling pathways in animal models of osteonecrosis, leading to activation of osteoclasts (role of the innate immune system)

Osteoimmunologic Factors

- A recent report demonstrated **elevated expression of IL-9** in patients with osteonecrosis and demonstrated that IL-9 is associated with **cartilage degradation** by modulating Jak-Stat signaling.
- **TH17 cells and IL-17** have also been found to be overexpressed in patients with osteonecrosis and have been correlated with the **severity of pain**.
- Reduced levels of **sclerostin** have been observed in nontraumatic osteonecrosis .
- Recently, a role of **IL-33** in osteonecrosis has been proposed, as a biomarker.
- **IL-6** has been found to stimulate revascularization and formation of new bone post-osteonecrosis in mice, suggesting a potential target for treatment

Osteoblast/Osteoclast Balance

- Any disturbance in the normal homeostasis between bone deposition and bone resorption can lead to bone disease.

- Alcohol can affect the ability of **mesenchymal stem cells to differentiate into osteogenic lineages** (reduced ability to differentiate into osteoblasts)

- Alterations in **osteoblast function** may also contribute to the pathogenesis of osteonecrosis.

- One study : although differentiation was not affected, the **proliferation rate** of osteoblastic cells was reduced in patients with osteonecrosis compared with patients who were osteoarthritic.

Apoptosis

- **Osteocyte death** is a feature of osteonecrosis .
- Both alcohol and corticosteroids can induce **osteocyte apoptosis**, possibly via aberrations in lipid metabolism

The Role of Lipids

Fatty liver
Swelling and necrosis of fat cells
Lipid-filled osteocytes
Hyperlipidemia
Adipogenesis of marrow stromal cells
Fatty infiltration of bone marrow
Fat emboli

Lipid-Altering Effects of Steroids and Alcohol

The Role of Coagulopathy in Osteonecrosis

- patients with osteonecrosis had a much higher frequency of having at least one or two **abnormal coagulant levels** compared with normal controls
- both **thrombophilia** and **hypofibrinolysis** have been associated with osteonecrosis.
- Hypofibrinolysis is a mechanism by which **corticosteroids** lead to osteonecrosis .
- coagulation abnormalities may play a significant role in corticosteroid-induced osteonecrosis in patients with **SARS**
- in **alcohol-induced osteonecrosis :** HLP , increased serum FFAs , and increased prostaglandins can trigger vascular inflammation and coagulation

Oxidative Stress

- **Alcohol**
- **corticosteroids**
- The relationship between osteonecrosis and oxidative injury leads one to wonder if corticosteroid-induced osteonecrosis can be prevented or lessened in severity by simultaneous or prophylactic administration of **antioxidants**.

Oxidative Stress

- This was studied in a rabbit model where **intravenous vitamin E** was able to reduce the development of methylprednisolone-induced osteonecrosis from 93% to 0%,accompanied by the preservation of reduced blood glutathione levels.

- A study : **inhibit reactive oxygen species** ⇨ successful treatment of corticosteroid-induced osteonecrosis in rats,

Nitric Oxide Synthase

- Nitric oxide regulates vascular “tension”. Endothelial NOS (eNOS) stimulates the production of nitric oxide
- A defect in this activity can lead to increased vascular resistance and disruption to downstream blood flow, resulting in osteonecrosis.
- **Glucocorticoids** can cause derangements in vascular responsiveness to vasoactive substances such as nitric oxide.

Associated Condition	MECHANISMS OF OSTEONECROSIS							
	Apoptosis	Osteoblast/ Osteoclast Homeostasis	Lipid Abnormalities	Coagulation Abnormalities	Oxidative Stress	Parathyroid/ Calcium Imbalance	Vascular Plugging	Vasoactive Substances
Corticosteroids	X	X	X	X	X			X
Bisphospho-nates	X	X	X					
Alcohol abuse	X	X	X	X	X			
Trauma	X	X						X
Renal trans-plantation	X	X		X		X		
Dialysis						X		
Sickle cell disease							X	

The Multi-hit Theory of Osteonecrosis

➢ concept of cumulative stress

- Corticosteroid-induced osteonecrosis seems to occur with greater frequency in patients who have **significant underlying illness** such as SLE or transplantation and less frequently or never in patients who are not chronically ill but are taking steroids for an acute event such as a head injury.
- Recent observations that corticosteroids induce osteonecrosis in patients with **SARS** further support the notion that more than one insult to the bone or surrounding tissue may be necessary to precipitate osteonecrosis.

- The accumulated cell stress theory suggests that when the **damaging effects of multiple events** are aligned, the involved bone is unable to recover from the chronic stress and osteonecrosis ensues

The Microbiome in Osteonecrosis

- It has been postulated that **infection** is a major risk factor in the development of ONJ

- In one study : predominant species in osteonecrosis lesions in patients with BRONJ included **Streptococcus** (29%), Eubacterium (9%), and Pseudoramibacter (8%) compared with controls, [Parvimonas (17%), Streptococcus (15%), Fusobacterium (15%)]

The Microbiome in Osteonecrosis

- One study also found that in patients with BRONJ, HES revealed that the bacteria were layered and packed into the scalloped edges of BRONJ bone, suggesting the **role of biofilms** as a potential risk factor for the development of BRONJ. They also identified overgrowth of acidophilic species such as **Streptococcus mutans** in the oral microbiome of patients with ONJ.

- Scanning electron microscope images have shown the **presence of biofilms** in BRONJ lesions.

- It should also be noted that bacteria are not the only pathogens found in BRONJ lesions; **fungi**, especially Candida and Actinomyces, have also been found.

Genetics, Epigenetics

- single nucleotide polymorphisms have been noted in a number of genes that may be associated with osteonecrosis .
- polymorphism in the **eNOS gene**

- Forty-one percent of patients with osteonecrosis compared with only 20% of controls were homozygous for the 4G/4G mutation in the **PAI-1 gene.**
- A polymorphism in the PAI-1 gene can also be predictive of osteonecrosis in **children with ALL.**

Genetics, Epigenetics

- Genetic variations in the type and levels of **lipoprotein(A)** have been linked to osteonecrosis.
- Apolipoprotein (A) is involved in lipid metabolism and the coagulation systems
- Apo(A) low-molecular-weight phenotype is associated with an increased risk of osteonecrosis.

- Polymorphisms in the promoter for **(VEGF)** and in the **receptor for IL-23** were associated with osteonecrosis in the Korean population,reflecting the significance of the association of osteonecrosis with vascular disorders and autoimmune diseases, respectively

Genetics, Epigenetics

- **Epigenetic modulation** of gene expression has recently been recognized to affect more than half of all human genes. Several pathways exist for epigenetic transformation (such as microRNAs)

- **microRNA-210** : is upregulated in the cells surrounding osteonecrotic bone (angiogenesis)
- **MicroRNA-17-5p** : expression of this microRNA was lower in patients who had osteonecrosis compared with osteoarthritis

- **Small interfering RNAs** (siRNAs)

Diagnosis : History and Physical Examination

- a **high index of suspicion** for all patients taking oral or parenteral steroids.
- The following information should be elicited:

- ✓ any history of trauma
- ✓ underlying disease
- ✓ alcohol use; tobacco use
- ✓ current medications; past medications
- ✓ history of joint anomalies
- ✓ presence of pain or limitation of motion;
- ✓ involvement in sports, especially high-impact sports
- ✓ occupational history
- ✓ gestational history
- ✓ presence of liver disease or lipid abnormalities

Diagnosis : History and Physical Examination

- For osteonecrosis of the hip, **physical examination** includes palpating the lateral aspect of the hip for tenderness, leg-length discrepancy , the presence of masses, abnormal gait, muscle strength, and range of motion.

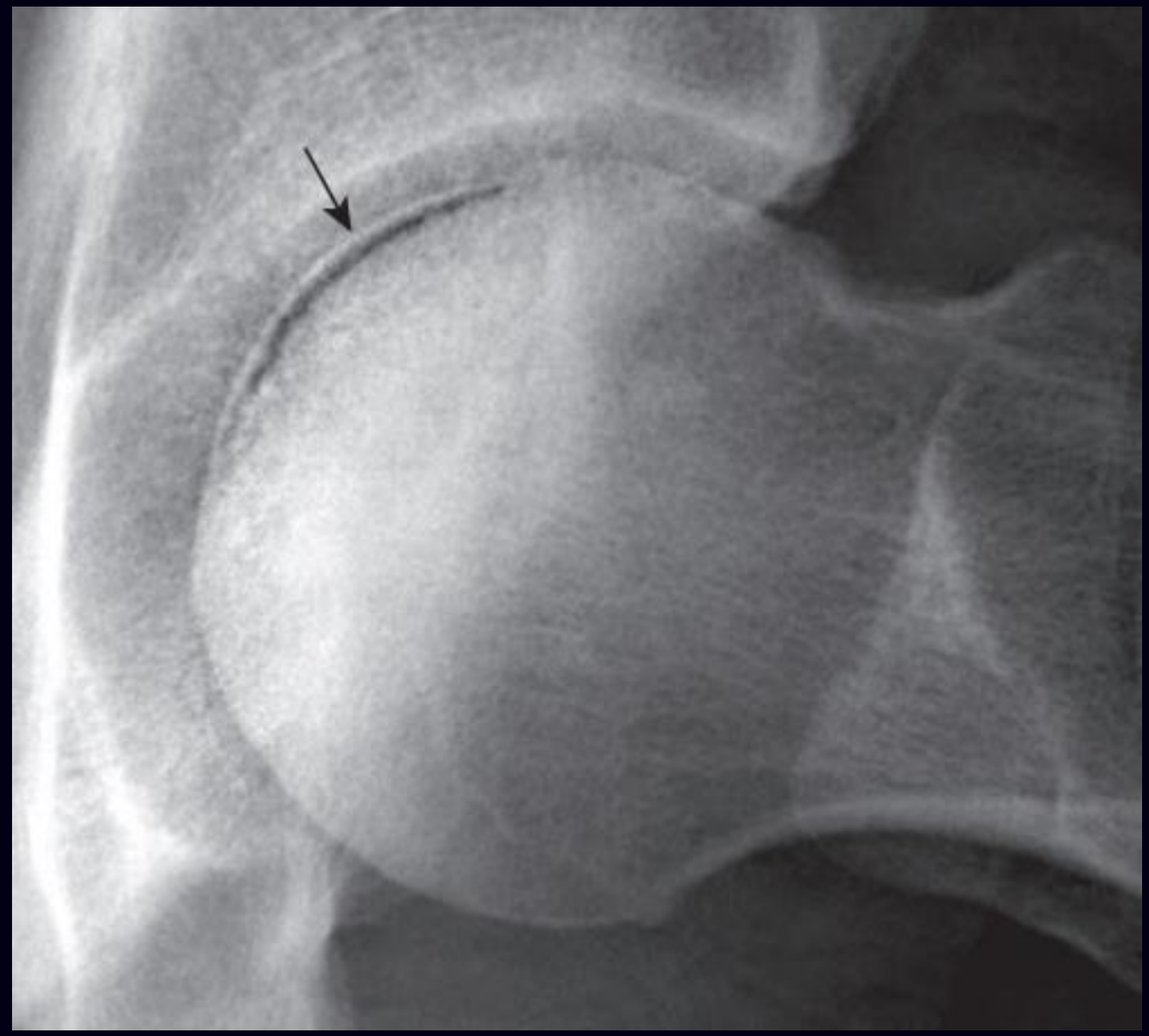
Date of assessment:	Name:		Medical record #:	DOB:
Pain	**Distance walked**	**Activities-shoes, socks**	**Public transportation**	**Limp**
o Totally disabled, crippled, pain in bed, bedridden o Marked pain, serious limitation of activities o Moderate pain, tolerable but makes concessions to pain. Some limitation of ordinary activity or work. May require occasional pain medication stronger than aspirin o Mild pain, no effect on average activities, rarely moderate pain with unusual activity, may take aspirin o Slight pain, occasional, no compromise in activity o None, or ignores it	o Bed and chair only o Two or three blocks o Six blocks o Unlimited	o Unable to fit or tie o With difficulty o With ease	o Unable to use o Able to use	o Severe or unable to walk o Moderate o Slight o None
Support	**Stairs**	**Sitting**	**Limb-length discrepancy**	
o Two crutches or not able to walk o Two canes o One crutch o Cane most of the time o Cane for long walks o None	o Unable to do stairs in any manner o Normally using a railing o Normally without using a railing	o Unable to sit comfortably on any chair o On a high chair for 30 minutes o Comfortably, ordinary chair for one hour	_____cm	**Comments:**
Physician name: _____ Evaluator name: _____	**Motions**			
	Hip flexion: _____ Hip extension: _____	Abduction: _____ Adduction: _____	Internal rotation: _____ External rotation: _____	

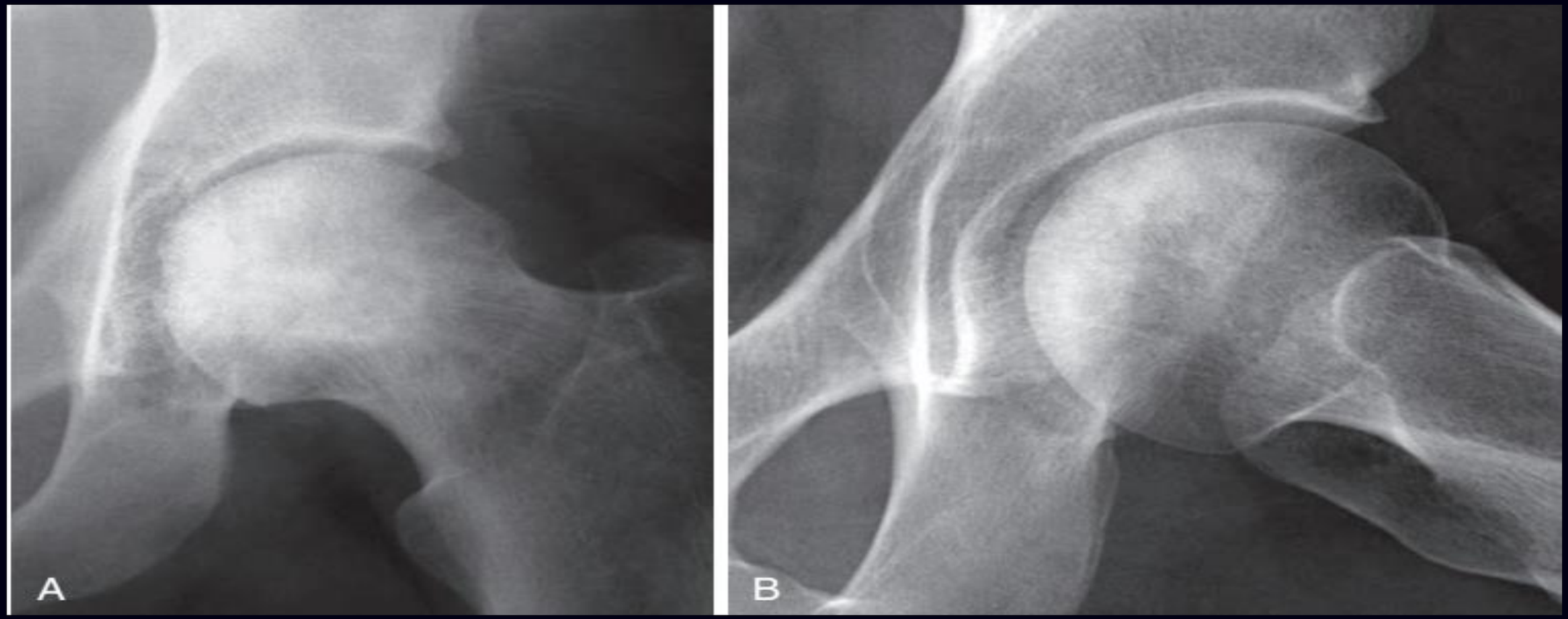
Harris hip score

Diagnosis : imaging

- Radiography
- MRI
- CT scan
- Skeletal scintigraphy

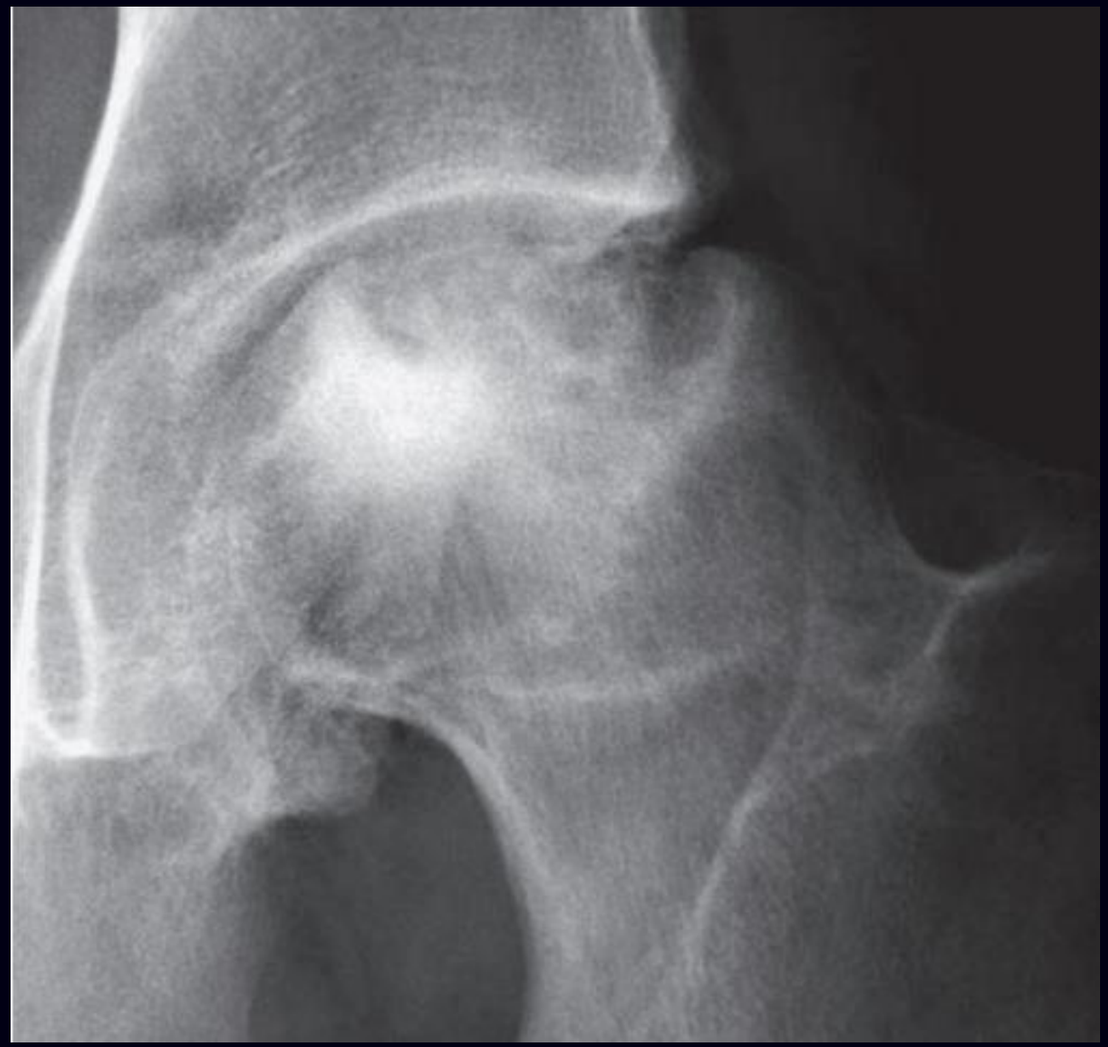
- A radiolucent **crescent** in the subchondral region of the left femoral head is an early radiographic sign of osteonecrosis





- Anteroposterior (A) and frog-leg lateral (B) views of the left hip show **sclerotic changes** of the femoral head typical of advanced osteonecrosis.

- **Increased density** of the femoral head (**creeping substitution**)
- loss of the normal spherical shape
- flattening of the superior aspect

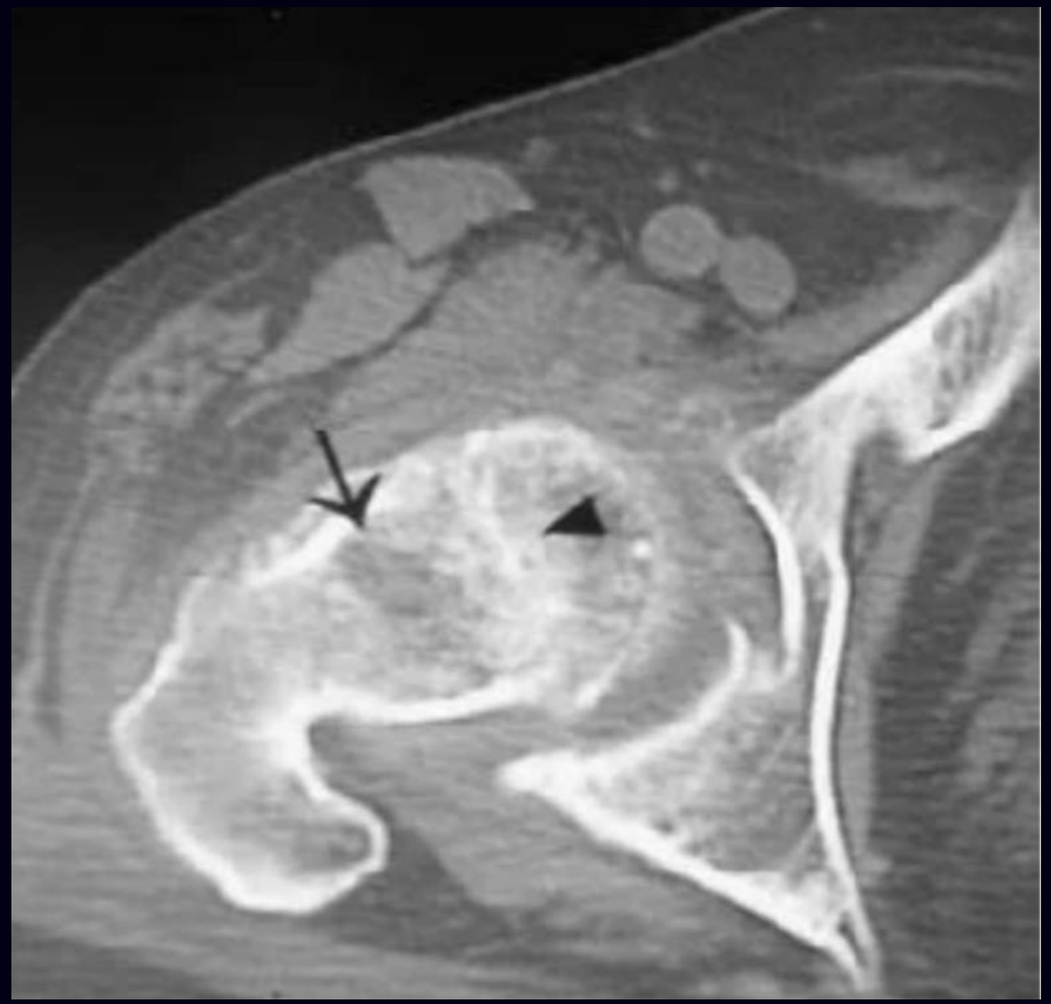


Diagnosis : imaging

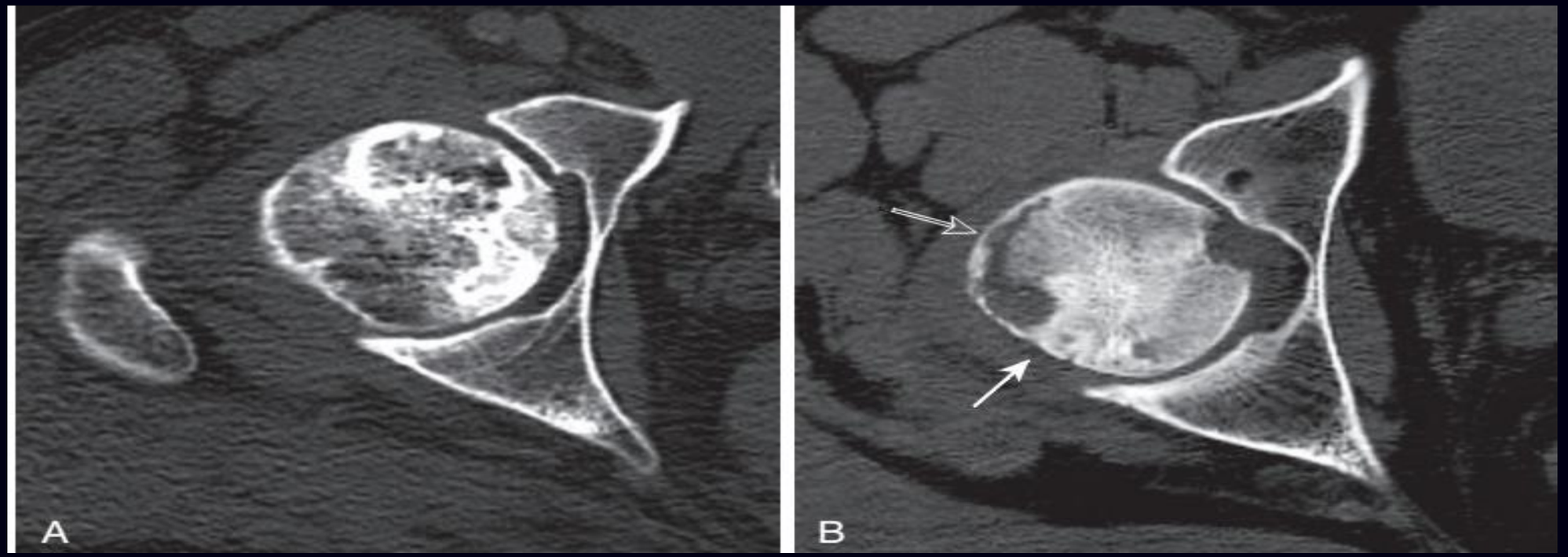
➢ **CT scan** provides for detailed examination of the femoral head.

- A star-shaped structure, formed by weight-bearing bone trabeculae, gives the appearance of an asterisk on a CT scan (the **asterisk sign**).
- At a later stage, the **collapse** of necrotic bone can be well visualized
-

- CT scan shows : clumping and distortion of the central trabeculae representing the **asterisk sign** (arrow head) and an adjacent low density region (arrow) is representing the reparative zone



Diagnosis : imaging

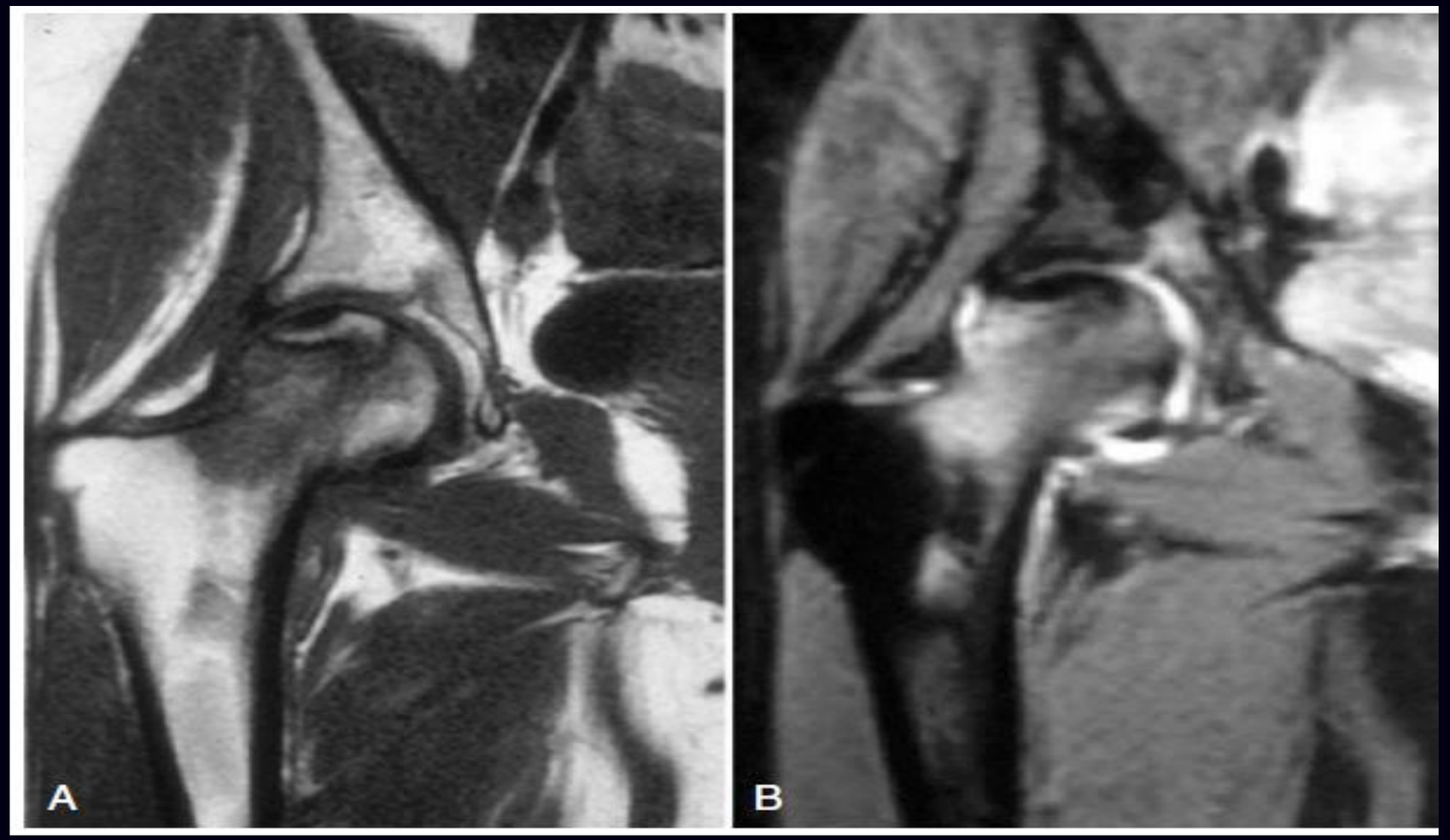


- A CT scan shows osteonecrosis of the femoral head. Although **several sclerotic foci** are present within the trabecular bone, the integrity of the osseous structures is preserved and the femoral head exhibits a normal spherical shape.

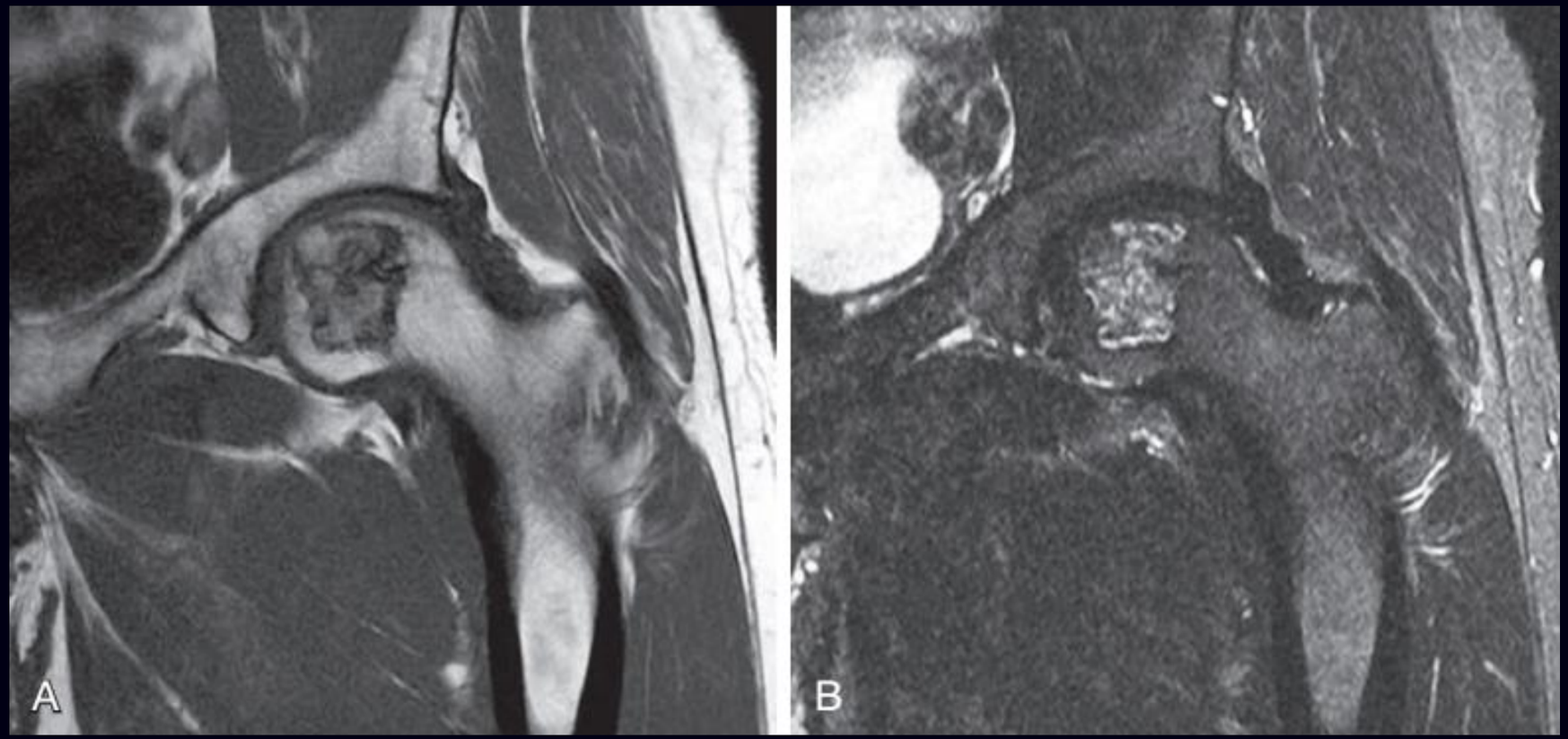
- (B) In a more advanced stage of osteonecrosis of the femoral head, note **increased sclerosis** in the posterior aspect (solid arrow) and **subchondral collapse** of necrotic bone anterolaterally (open arrow).

Diagnosis : imaging

- **MRI** is the **gold standard** for imaging of osteonecrosis. Most of the staging systems for osteonecrosis are now based on MRI appearance
- MRI can detect **bone marrow edema**
- The **typical MRI findings** in osteonecrosis are intermediate or low signal intensity on T1-weighted images and high signal intensity on T2-weighted and other water-sensitive sequences
- As the disease progresses : **“double-line” sign**
- In **advanced osteonecrosis**, the necrotic segment exhibits low signal intensity on both T1-weighted and T2-weighted images
- MRI signal of the necrotic area is often **very heterogeneous.**
- The low signal intensity band in the periphery of the osteonecrotic area correlates with a sclerotic band seen on radiographs and CT and often has **a serpiginous appearance**.



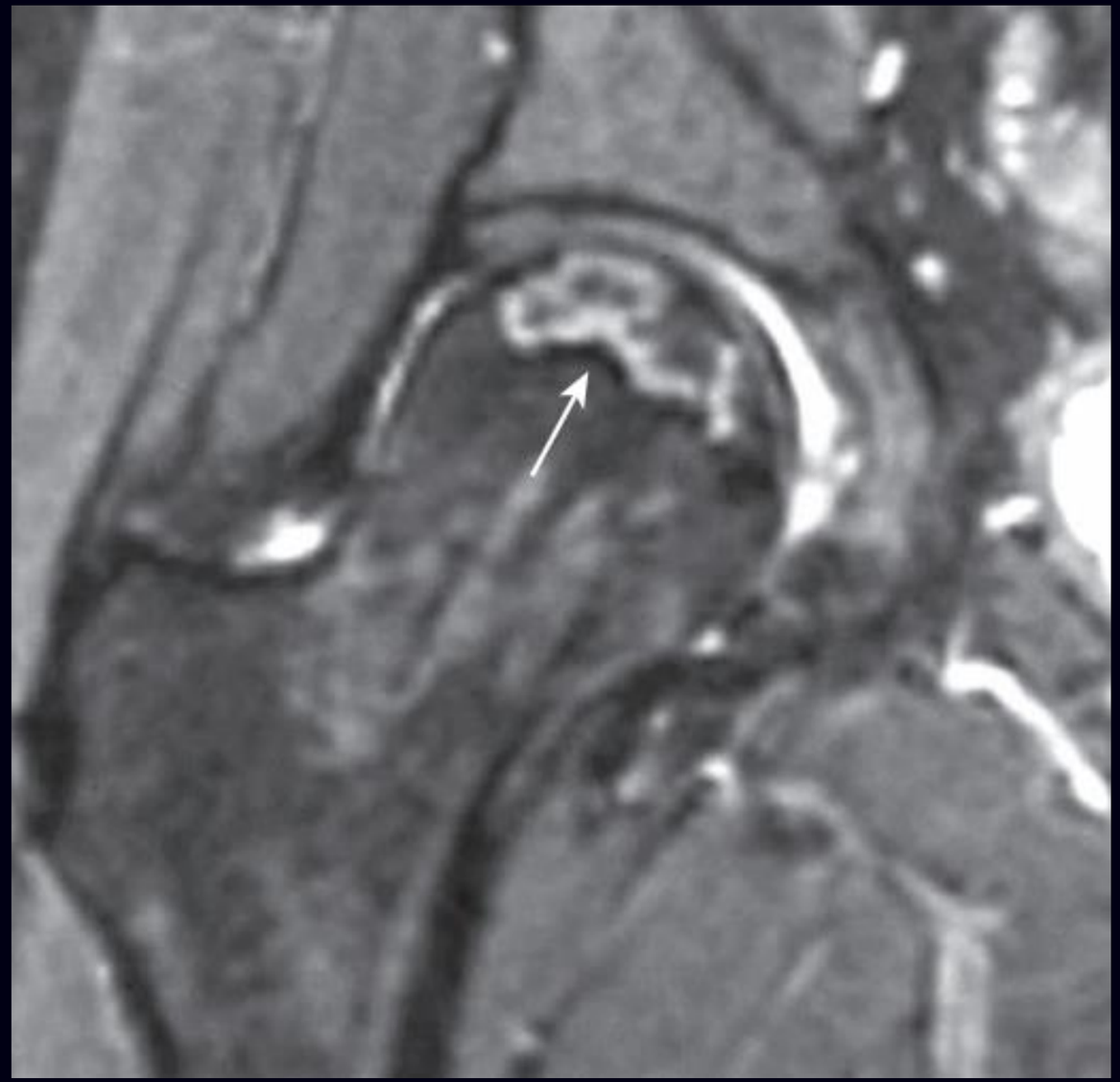
bone marrow edema

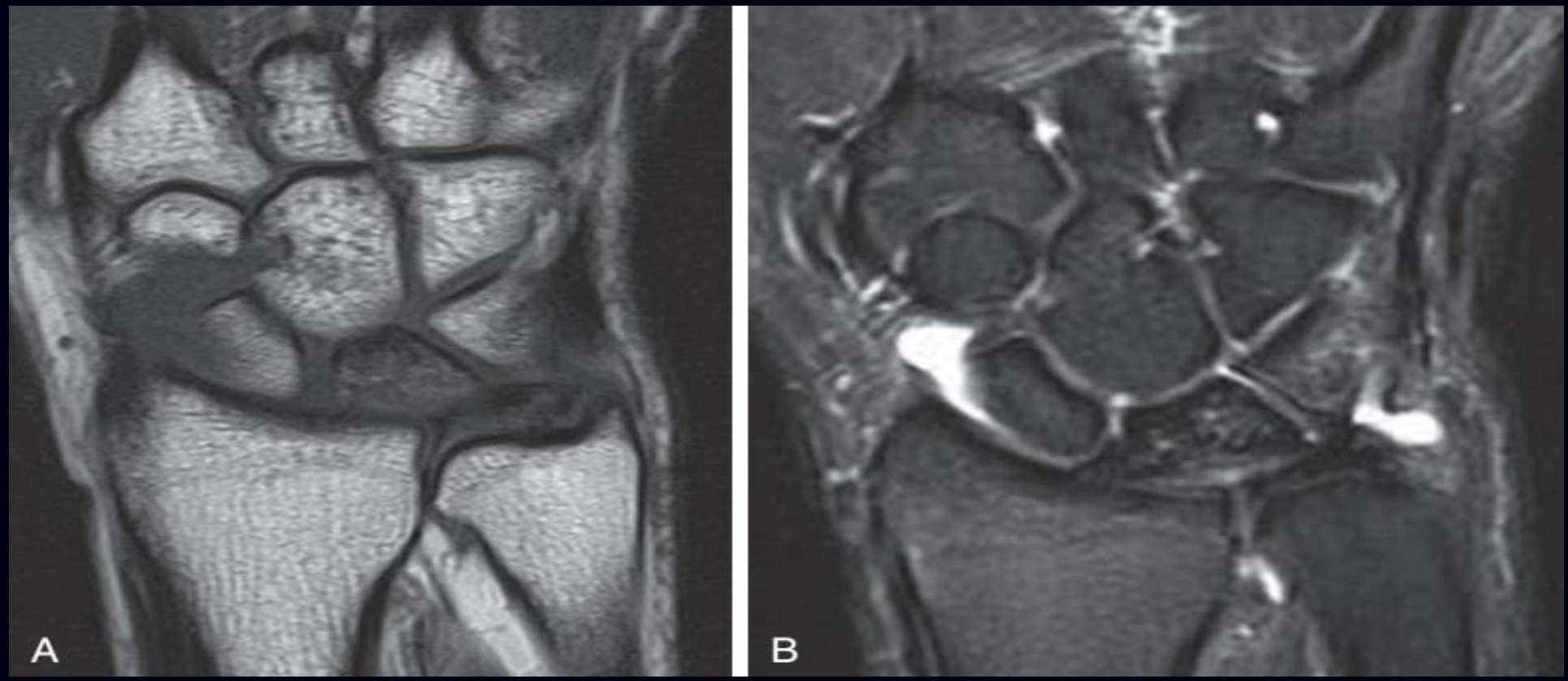


- A) On a T1-weighted MRI, the osteonecrotic segment in the subchondral portion of the femoral head shows low signal intensity (B) On a T2-weighted image, the necrotic bone exhibits high signal intensity, surrounded by a sclerotic low signal rim.
- The low signal intensity rim surrounds a high signal intensity rim, representing the **double-line** sign
- Note that the signal intensity of the necrotic area is **heterogeneous** in both the T1- and T2-weighted sequences.

- A coronal T2-weighted MRI scan of the right femoral head shows the **double-line sign** (arrow), which is characteristic for osteonecrosis:

- low signal at the periphery of the lesion and a high signal band located more centrally.



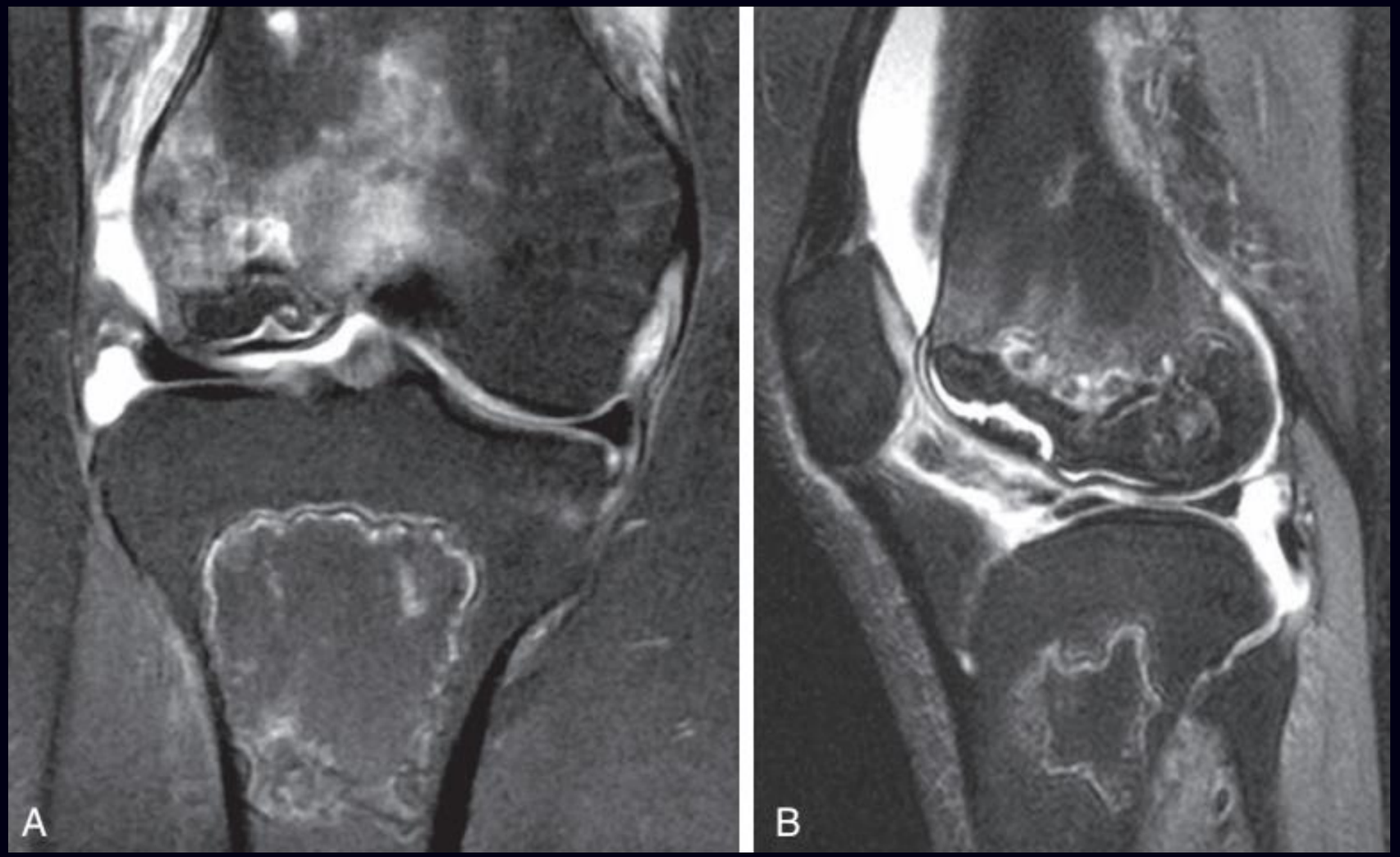


- T1-weighted (A) and T2-weighted (B) MRI of the wrist of a patient with **Kienböck's disease**.
- Note the low signal intensity of the lunate in both pulse sequences without bone collapse, indicating the intermediate stage of osteonecrosis of the lunate.

- Coronal (A) and sagittal (B) T2-weighted MRI demonstrate multiple areas of osteonecrosis of the distal femur and proximal tibia.

- Note the characteristic **double-line sign** in the proximal tibial lesion.

- Note also the **partial collapse** of the medial femoral condyle as a result of the presence of a **subchondral fracture** (high signal intensity line in the subchondral bone in A and B).



Diagnosis : imaging

- MRI employs three techniques to determine the **extent of femoral head involvement**.
- The **first** is estimating head involvement , and is defined by the appearance of abnormal signals on T1-weighted images. The degree of head involvement is classified into three categories: less than 15%, 15% to 30%, and greater than 30%.
- The **second** parameter is the index of necrotic extent of subchondral involvement, which is estimated using a “necrotic arc angle,” defined by the angle of the arc of the necrotic segment from the center of the femoral head.
- The **third** technique is a variation of the second, in which the angle is identified not on midcoronal or midsagittal images but on the image that shows the maximum lesion size in the sagittal and coronal planes.

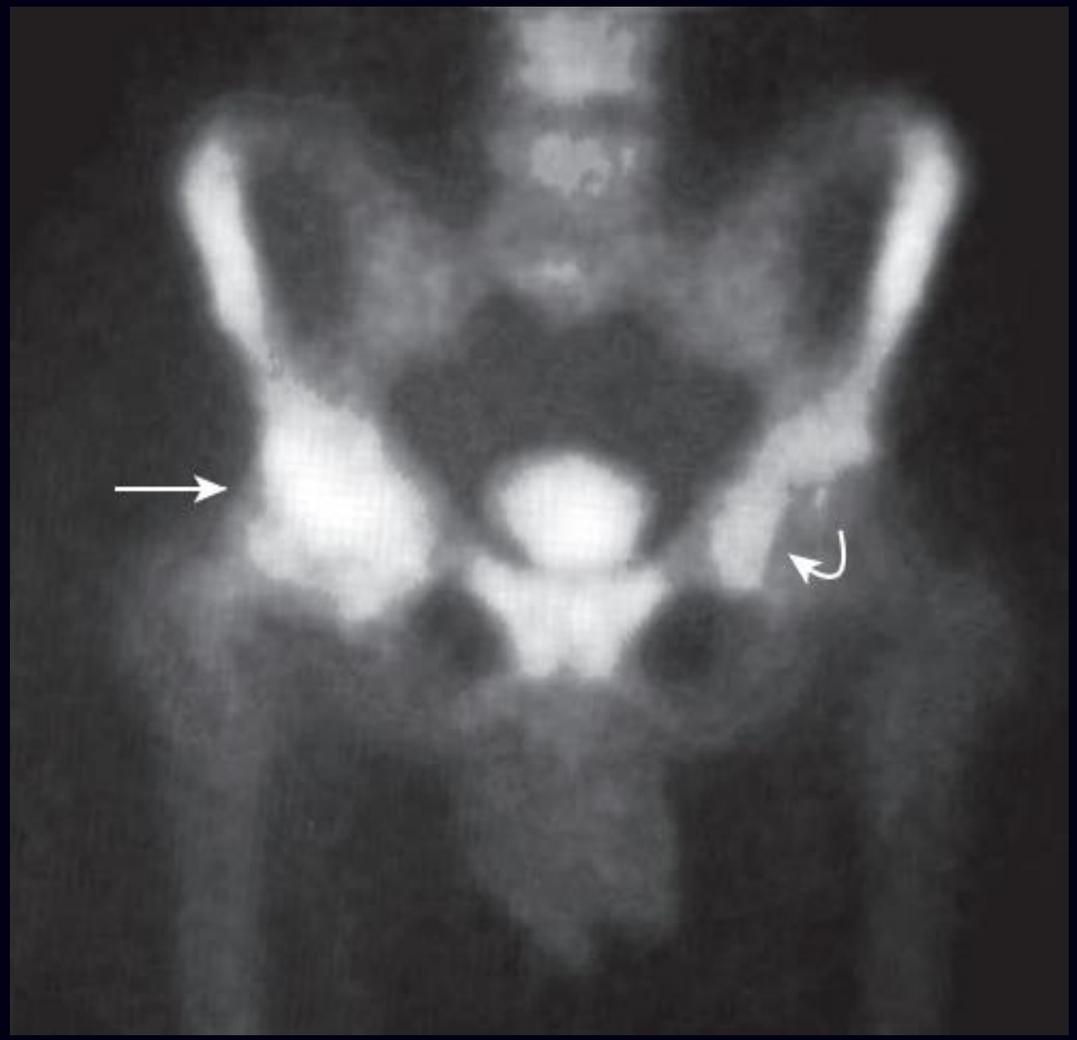
Diagnosis : imaging

➢ **Bone scintigraphy**

- Decreased uptake in subchondral distribution (“cold spot”) : Osteonecrosis
- Increased uptake in subchondral distribution (“hot spot”) : Creeping substitution

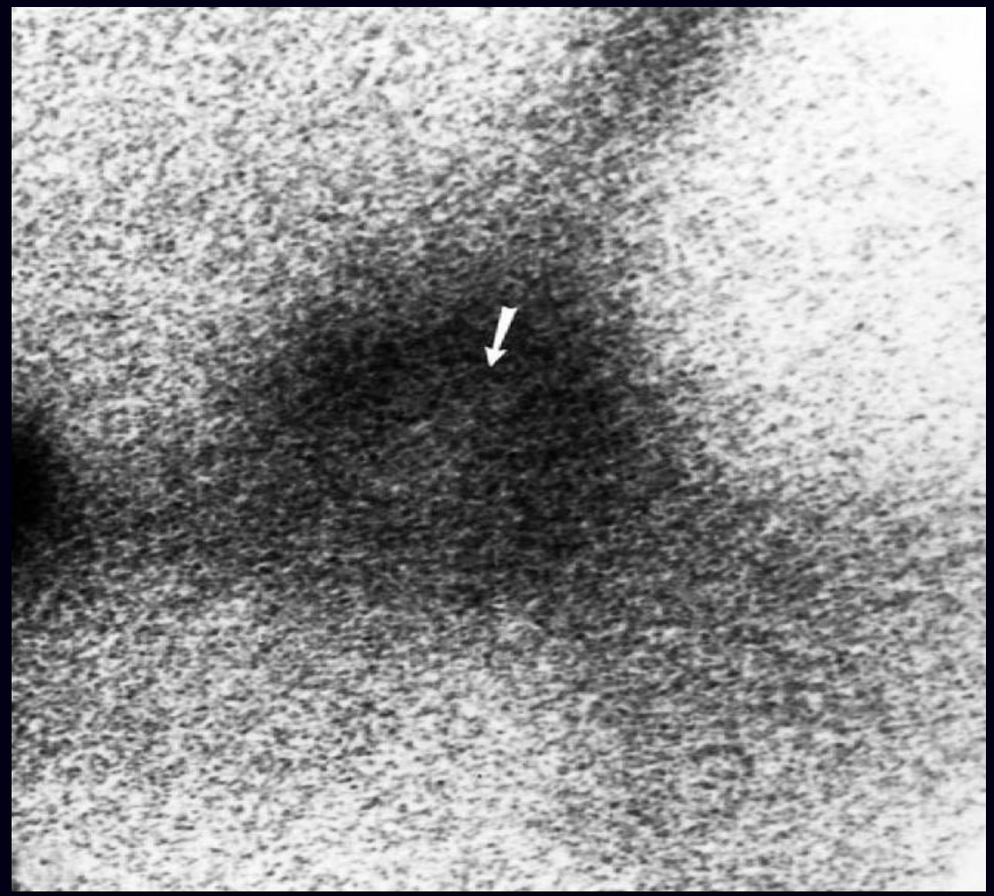
➢ Bone scintigraphy

- Moderate uptake at the site of the osteonecrotic segment in the right femoral head and markedly increased uptake at the site of bone repair (straight arrow).
- The left femoral head (curved arrow) exhibits early-stage disease.



Bone scintigraphy :

a central area of diminished uptake surrounded by a zone of augmented activity



Diagnosis : imaging

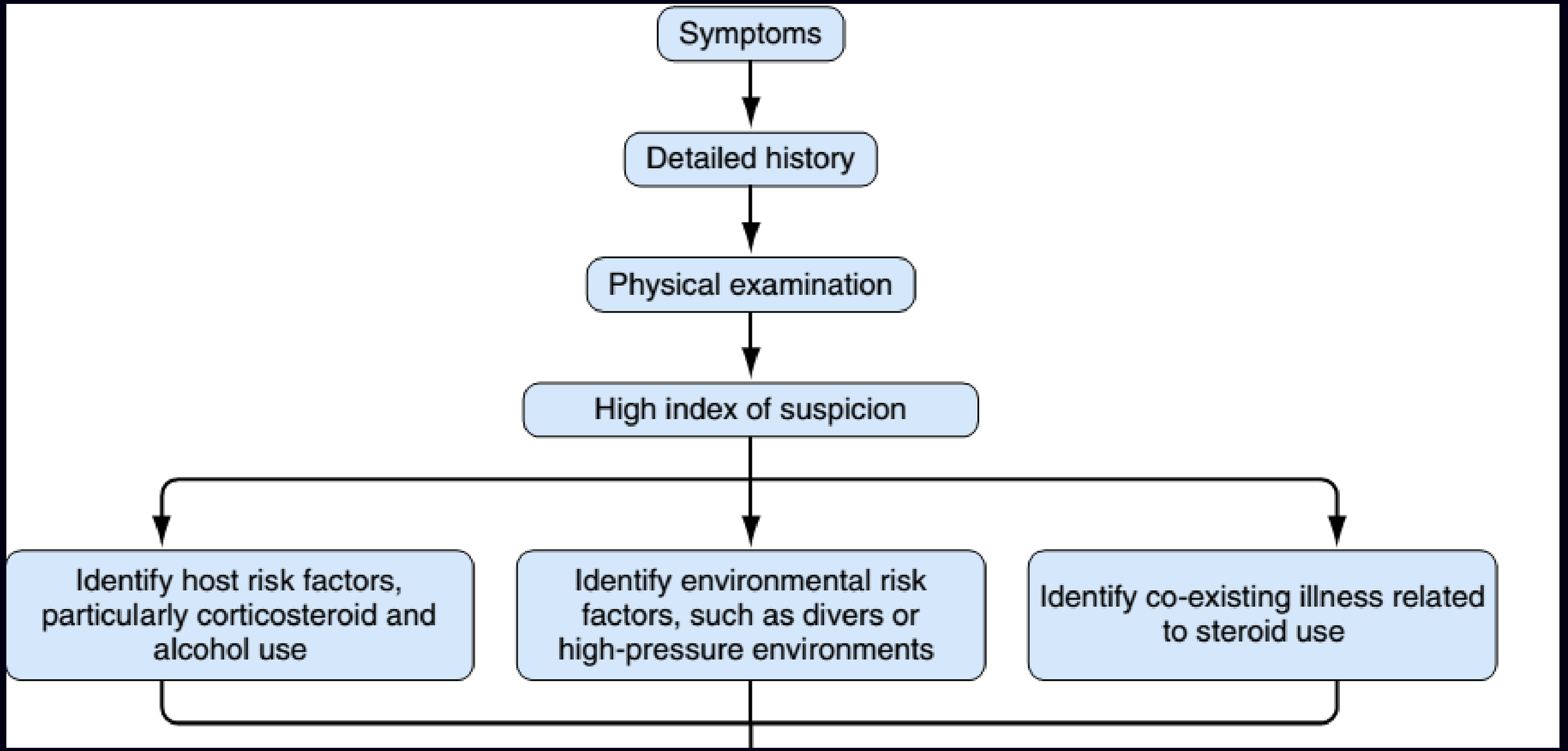
- Hip **arthroscopy** is also used in the staging of osteonecrosis.

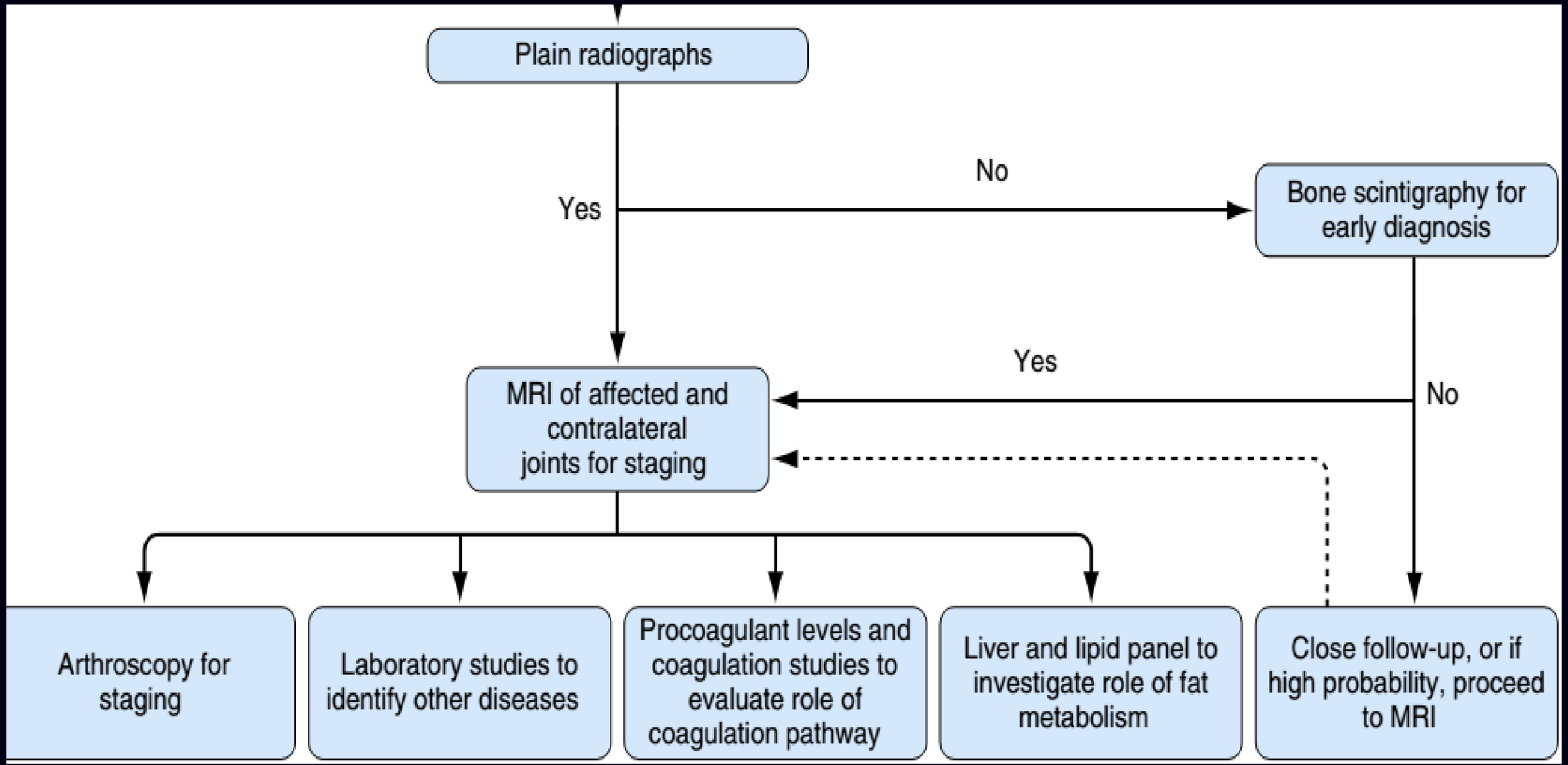
- Arthroscopy was able to detect **osteochondral degeneration** that was not detected by radiography or MRI in 36% of collapsed heads.

Diagnosis : imaging

- A study comparing conventional radiography, MRI, CT, and a Tc 99m MDP three-phase bone scan in diagnosing BRONJ showed that CT and MRI best defined the **extent of the disease** but that a bone scan best identified disease at an **early stage**.

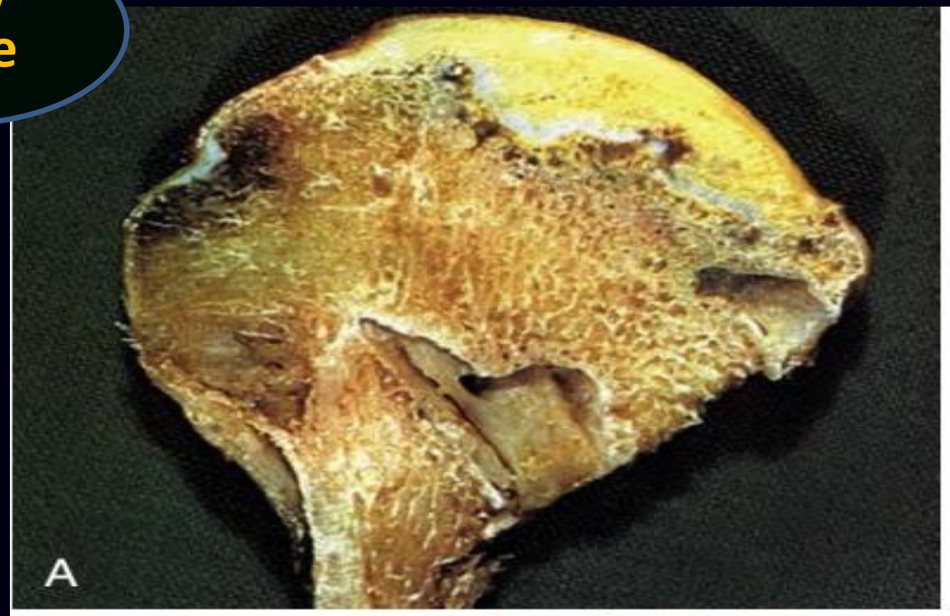
- A bone scan can be an excellent **screening tool** for the diagnosis of osteonecrosis before further characterization of the lesions using CT or MRI.

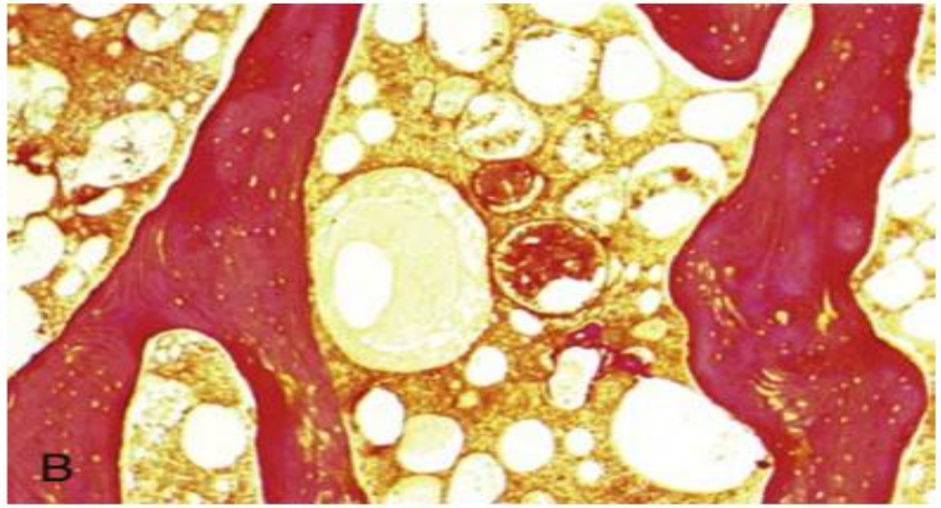

Symptoms
Detailed history
Physical examination
High index of suspicion
Identify host risk factors, particularly corticosteroid and alcohol use
Identify environmental risk factors, such as divers or high-pressure environments
Identify co-existing illness related to steroid use

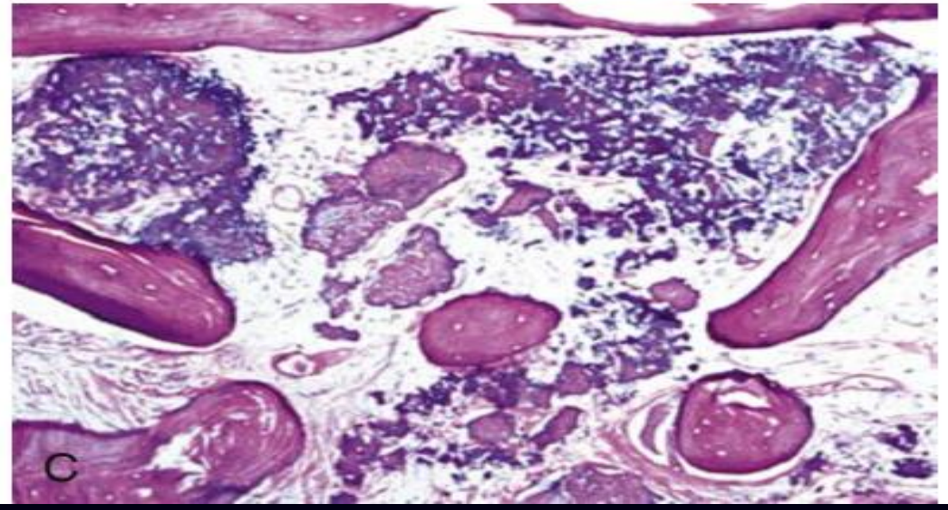

Plain radiographs
Yes
No
Bone scintigraphy for early diagnosis
Yes
No
MRI of affected and contralateral joints for staging
Arthroscopy for staging
Laboratory studies to identify other diseases
Procoagulant levels and coagulation studies to evaluate role of coagulation pathway
Liver and lipid panel to investigate role of fat metabolism
Close follow-up, or if high probability, proceed to MRI

Pathology

early stage

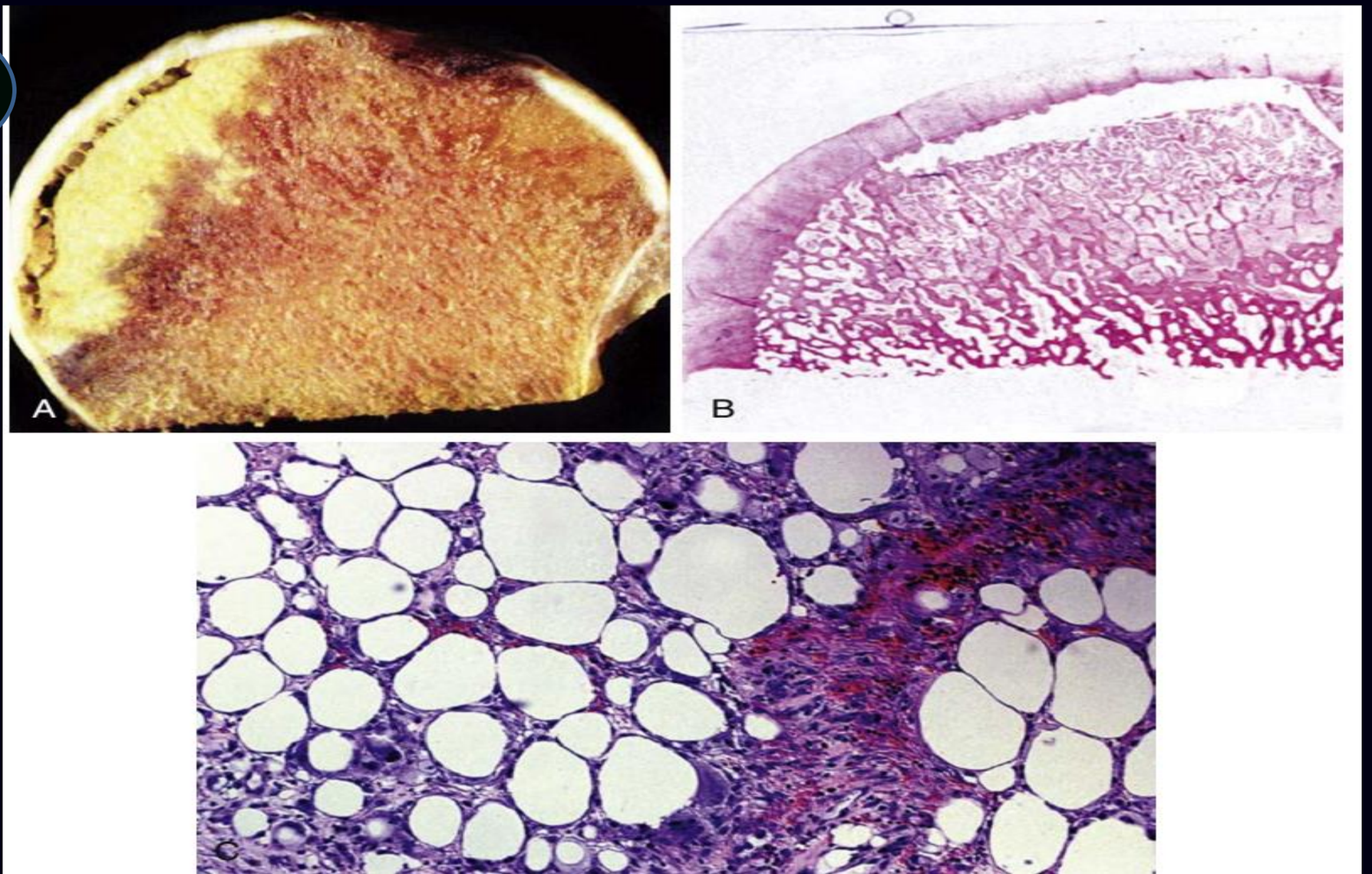






Pathology

More advanced stage



Biomarkers of Disease

- The measurement of serum and urine (**CTX-1**), a marker of bone resorption, has been proposed as a method of **evaluating the risk of ONJ** as a result of bisphosphonate usage, although it is not specific for osteonecrosis, and should not be used solely to determine treatment.

- A serum **osteocalcin** level is another marker for bisphosphonate-related **ONJ** that has been suggested as a risk predictor because levels were significantly lower in the osteonecrosis group compared with a control group.

The Natural History of Osteonecrosis

- The natural history of osteonecrosis depends on the **size** of the infarcted segment, the **site** of occurrence, and the clinical and radiologic **staging** of the disease.
- In the early stages of the disease, when it is still reversible, patients may be asymptomatic. Many patients therefore present with advanced disease.
- Although **spontaneous resolution** of femoral head osteonecrosis can occur, it is rare and occurs only when the lesion size is small.

treatment

- ✓ surgical Approaches
- ✓ Nonsurgical Approaches

Surgical Procedure	Rationale	Stages of Osteonecrosis	Outcome	Comments
Core decompression	Reduction of intraosseous and intramedullary pressure	Early stages	37% radiographic success, 48% clinical success	Success rate depends on disease stage
Structural bone grafting	Provide support to overlying subchondral bone	1 or 2	Poor in advanced disease	100% failure rate in stages 3 and 4
Vascularized fibula grafting	Increase blood flow to graft	2 to 4	96% success in stage 2, 90% in stage 3, and 57% in stage 4	
Osteotomy	Shifting position of osteonecrotic segment out of weight-bearing region	2 and 3	Not available	

Resurfacing arthroplasty	Preservation of bone and joint mechanics with a metallic or ceramic shell over the femoral head	Later stages	Mean 7-year success rate is 90%	An alternative to total hip arthroscopy in later stages of disease
Hemiarthroplasty	Replacement of the femoral head, preservation of the anatomic acetabulum	Later stages	The failure rate for unilateral hemiarthroplasties is 50%-60% at 3 years; for bilateral hemiarthroplasties, the failure rate is 44%	Various techniques are available, some with a better outcome
Total hip replacement	Complete replacement of the hip joint	Late stages	17.4% required revision after 10 years	Eventually most patients will require several hip replacements

Treatment : surgical Approaches

- **Arthroscopy** is a valuable tool used in the treatment of osteonecrosis.
- It has been used to determine the position of the **core decompression** tract to the necrotic part of the femoral or humeral head.
- **arthroscopic debridement** has been used in the treatment of osteonecrosis of the capitellum of the humerus in adolescents, and in individuals with Kienböck's disease and osteonecrosis of the scaphoid

Treatment : surgical Approaches

- **In individuals with ONJ**, the most common surgical procedure is **resection of the affected bone**.
- A larger extent of surgical excision and a higher number of surgical debridements were associated with a lower recurrence rate
- **Conservative treatment** has also been used but has a higher recurrence rate.
- **Nonsurgical treatments**, including hyperbaric oxygen therapy and low-intensity laser therapy, are controversial but have been used to treat ONJ

Treatment :Nonsurgical Approaches

- The key to the successful treatment of osteonecrosis is **early detection**.

- The **choice** of conservative nonsurgical versus more aggressive surgical options depends on the clinical and pathologic staging of the disease.

- Nonsurgical treatment of osteonecrosis of the femoral head includes

✓ **refraining from weight bearing on the affected joint**
✓ **use of analgesic and anti-inflammatory medications**
✓ **physiotherapy**

Treatment :Nonsurgical Approaches

- **Electrical stimulation** has been used in the treatment of osteonecrosis, in conjunction with **core decompression**.
- Electrical stimulation enhances **osteogenesis** and **neovascularization**.
- It also alters **the balance between osteoblast and osteoclast activity**, resulting in increased bone deposition and decreased bone resorption.
- The success of electrical stimulation in the treatment of osteonecrosis has been rather **mediocre**.

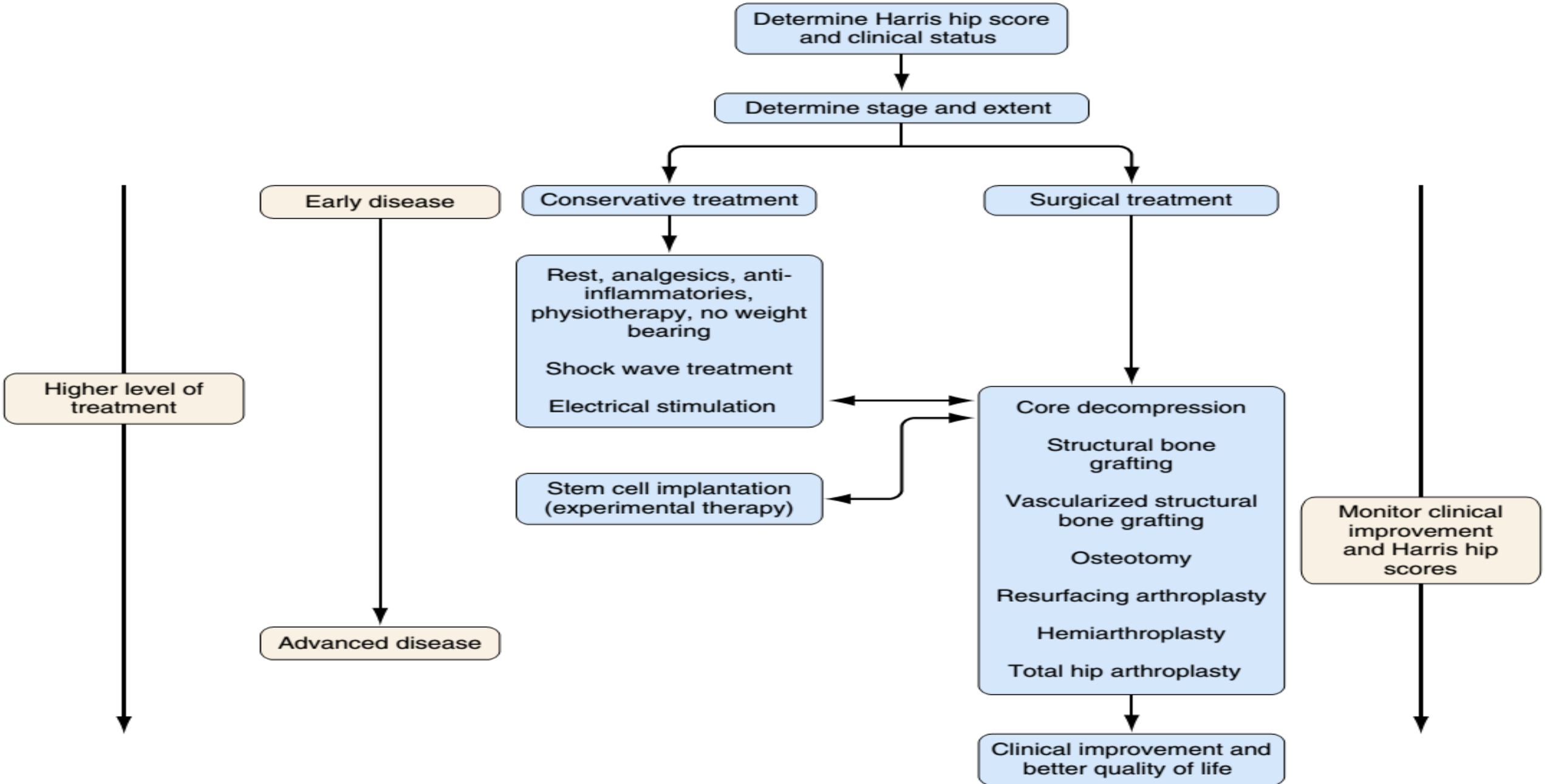
Treatment :Nonsurgical Approaches

- **Extracorporeal shock wave therapy** has been used in the treatment of osteonecrosis of the femoral head.
- A study : the use of shock wave therapy led to improvements in serum **nitric oxide** levels, **angiogenic factors** such as VEGF, and **osteogenic factors** such as (BMP)-2 and osteocalcin . Levels of **inflammatory markers** were reduced.
- It is interesting to note that although these changes did not persist beyond several months, the **clinical and radiographic improvement**, present in 83% of hips, was present after 12 months.

Treatment :Nonsurgical Approaches

- Conservative treatment of osteonecrosis of the **talus** is not promising, and the affected ankles generally continue to progress, requiring either core decompression or arthrodesis.

- Conservative treatment of **BRONJ** includes cessation of bisphosphonate usage or surgical debridement.
- Good oral hygiene, regular dental assessment, and avoidance of dental procedures during bisphosphonate usage can prevent the onset of osteonecrosis


Determine Harris hip score and clinical status
Determine stage and extent
Early disease
Conservative treatment
Surgical treatment
Higher level of treatment
Rest, analgesics, anti-inflammatories, physiotherapy, no weight bearing
Shock wave treatment
Electrical stimulation
Stem cell implantation (experimental therapy)
Core decompression
Structural bone grafting
Vascularized structural bone grafting
Osteotomy
Resurfacing arthroplasty
Hemiarthroplasty
Total hip arthroplasty
Advanced disease
Monitor clinical improvement and Harris hip scores
Clinical improvement and better quality of life

Prevention Versus Treatment

- A recent study evaluated the role of **antioxidants** in the treatment of osteonecrosis.
- The finding suggests that oxidative stress may play a role in the pathogenesis of osteonecrosis and that a role may exist for antioxidants such as **vitamin E**.

- A group of researchers studied the use of **(ACTH)** in rabbits to prevent corticosteroid-induced osteonecrosis and found that if ACTH is administered along with depot methylprednisolone acetate osteonecrosis is reduced.
- The authors of this study believe that ACTH enhances **osteoblast support** and stimulates the **production of VEGF**, which stimulates the generation of new blood vessels.

Stem Cell Transplantation

- The balance between **adipogenesis and osteogenesis** has been targeted as a potential site for the treatment of osteonecrosis.
- Multipotential mesenchymal stem cells from femoral bone marrow near osteonecrosis sites are able to express messenger RNA aggrecan and type II collagen.
- The mesenchymal stem cells can be differentiated into osteocytic lineage in vitro

- In 2014, investigators reviewed the literature and published a report in which they concluded that using core decompression in conjunction with mesenchymal stem cell infusion in the form of bone marrow leads to **improved pain and functionality** and **halts progression of osteonecrosis** of the femoral head, potentially obviating the need for future invasive procedures such as total hip replacement

Stem Cell Transplantation

- An increasing utilization of stem cell therapy for the treatment of osteonecrosis has demonstrated **few safety issues**, and the results of one study show that bone marrow mesenchymal stem cell transplantation with core decompression showed a lowering of total hip replacement arthroplasty conversion rate compared with core decompression alone, although there was no impact on ARCO stage progression


Thank you for
your attention