

Heterotopic Ossification-An Update

Heterotopik Ossifikasyon

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ABSTRACT

Heterotopic ossification (HO) is a pathological process of mature, lamellar bone formation in non-osseous tissues. Causes of HO are mainly soft tissue trauma and central nervous system injury, also arthropathies, vasculopathies and inheritance. The initiating event- usually local soft tissue trauma, inflammation, or vasogenic edema- signaling from the injury site (bone morphogenetic analogs, receptors, and inhibitors), local immature cells with the ability to differentiate into osteoblasts and local environment leading to bone formation are necessary components. The varieties of HO are traumatic, non traumatic, hereditary, HO after burns, traumatic brain injury, spinal cord injury, etc. A painful, swollen and warm joint with decreased range of motion (ROM) is a candidate for HO. Complications are ankylosis of the joint, loss of function, pressure ulcers and peripheral nerve entrapment. Clinical findings, laboratory tests, direct radiogram, triple phase bone scan, computed tomography and ultrasonography are helpful for diagnosis. Prophylaxis of HO, including passive ROM exercises and early mobilisation, is quite important. Nonsteroidal anti-inflammatory drugs (NSAIDs) (especially indomethacin) and bisphosphonates(etidronate) are the main medical options for prevention and treatment of HO. NSAIDs inhibit arachidonic acid metabolism, prostaglandin(PG) production so reduces inflammation, and slows bone metabolism. Etidronate is shown to inhibit calcium phosphate precipitation and transformation to hydroxyapatite and delay the aggregation of apatite crystals into large, calcified clusters. Treatment is consisted of exercise, physical therapy, medications, radiotherapy and surgery (surgical resection of the tissue). Bone morphogenic protein(BMP) type 1 receptor inhibition, BMP antagonist(like noggin), nuclear retinoic acid receptor-gamma agonist(RAR-gamma), free radical scavengers, platelet rich plasma injections are under investigation.

Keywords: Ossification, heterotopic, rehabilitation

ÖZET

Heterotopik ossifikasyon(HO), kemik dışı dokularda matür, lamellar kemik oluşumunu içeren patolojik bir süreçtir. Sebepleri arasında yumuşak doku travması, santral sinir sistemi yaralanması, artropatiler, vaskulopatiler ve kalıtım sayılabilir. Bu süreç için gerekli faktörler şunlardır; başlatıcı olay-genellikle lokal yumuşak doku travması, inflamasyon, veya vazojenik ödem- zedelenme bölgesinden sinyal(kemik morfojenik analogları, reseptörleri ve inhibitörleri) gönderimi, osteoblastlara farklılaşma yeteneği olan lokal immatür hücreler ve kemik formasyonuna izin veren lokal çevre. Travmatik HO, non travmatik HO, yanık sonrası HO, travmatik beyin yaralanması ve omurilik yaralanması sonrası oluşan HO, herediter HO gibi sınıflandırılabilir. Azalmış eklem hareket açıklığıyla(EHA) birlikte ağrılı, şiş ve sıcak bir eklem HO'yu düşündürmelidir. Heterotopik ossifikasyon komplikasyonları eklem ankilozu, fonksiyon kaybı, başı yaraları ve periferik sinir tuzaklanmasıdır. Klinik bulgular, serum ve idrar tetkiklerini içeren laboratuvar testleri, direkt grafiler, üç fazlı kemik sintigrafisi, bilgisayarlı tomografi ve ultrasonografi kullanılabilir tanı yöntemleridir. Pasif EHA ve erken mobilizasyon yöntemleri HO'nun önlenmesi açısından önemlidir. Önleme ve tedavide kullanılacak temel ilaçlar non steroidal antiinflamatuvar ilaçlar (NSAİİ) (özellikle indometazin) ve etidronat gibi bifosfonatlar. NSAİİ'ler arachidonic asit metabolizmasını etkileyerek, prostaglandin üretimini ve böylece inflamasyonu azaltır, kemik metabolizmasını yavaşlatır. Etidronat ise kalsiyum fosfat presipitasyonunu ve hidroksiapatite transformasyonunu inhibe eder, apatit kristallerinin agregasyonunu geciktirir. Egzersiz, fizik tedavi modaliteleri, NSAİİ, bifosfonatlar, radyoterapi ve oluşan kemik dokunun cerrahi rezeksiyonu HO'daki temel tedavi seçenekleridir. Kemik morfojenik protein(BMP) tip1 reseptör inhibisyonu, BMP antagonisti(Noggin gibi), nükleer retinoik asit reseptör gama agonisti, serbest radikal temizleyicileri ve plateletten zengin plazma enjeksiyonları gibi yeni tedavi seçeneklerine ait araştırmalar sürmektedir.

Anahtar sözcükler: Ossifikasyon, heterotopik, rehabilitasyon

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Definition

Heterotopic ossification (HO) is a pathological process of mature, lamellar bone formation in non-osseous tissues (muscle and connective tissue) and is a true osteoblastic activity (1). The term HO is translated from its Greek (heteros and topos) and Latin (ossificatio) etymologic origins. HO can be literally defined as "bone formation in another location". According to Potter et al, the first written account belongs to Al-Zahrawi (Albucasis), widely considered the father of surgery, in the year 1000 (2). The old term "myositis ossificans" is not used anymore because primary muscle inflammation is not necessary in this process.

Etiopathogenesis

There are many causes of HO, including mainly soft tissue trauma and central nervous system (CNS) injury, and others like arthropathies, vasculopathies and inheritance. One of the least understood components of HO is the interaction of the peripheral nervous system with the induction of this process. Recent work has shown that, upon traumatic injury, a cascade of events (neurogenic inflammation) is initiated. It involves the release of neuropeptides, that are substance P and calcitonin gene related peptide. Release of these neuropeptides finally leads to the recruitment of activated platelets, neutrophils and mast cells to the injury site. These cells appear to be involved with remodeling of the nerve and potentially recruiting additional cells from the bone marrow to the injury site (migratory stem cells) (3). The initiating event- usually local soft tissue trauma, inflammation, or vasogenic edema- and signaling from the injury site (bone morphogenetic analogs, receptors, and inhibitors), local immature cells with the ability to differentiate into osteoblasts and local environment leading to bone formation are necessary components (4). It is thought that high levels of bone morphogenic proteins (BMP) are playing a key role in this process.

Heterotopic ossification (HO) has been reported after a wide range of CNS lesions, such as spinal cord injury (SCI), cerebrovascular accident, traumatic brain injury (TBI), encephalomyelitis, anoxic encephalomyelitis and encephalopathies, poliomyelitis, tabes dorsalis, brain neoplasm, multiple sclerosis, syringomyelocoele, and arachnoiditis.

The varieties of HO

a) Traumatic HO (Myositis Ossificans Traumatica):

Might occur after blunt injury especially after direct traumas in athletes-hip, elbow, knee fractures, luxations-, after burn and surgery- operations like total hip or knee prosthesis, internal fixation of acetabular fractures.

Type of the surgery can be important. A randomized study comparing types of hip arthroplasties found a significantly higher rate of severe HO in surface replacement arthroplasty than the total hip arthroplasty (THA) group (5).

Heterotopic ossification (HO) after burns is related with time of immobilization of joint, depth of burn, systemic metabolic changes and personal tendency. Incidence is 1-2 %. Heterotopic ossification is mostly seen at the posterior of elbow joints and it may compress ulnar nerve (6). When burn patients have decreased range of motion (ROM) or "locking sign" in their joints, X-ray is indicated to rule out HO (7).

b) Nontraumatic myositis ossificans, has some special names;

Panniculitis ossificans: HO in subcutaneous fat

Rider's bones: in adductor muscles

Shooter's bone: in deltoid muscle

HO after TBI: There is enhanced osteogenesis in these patients. Risk factors are spasticity, immobilization, comatous states, long bone fractures, decreased range of motion. The incidence of HO is 11% to 76 % (8).

HO after SCI: Various possible mechanisms have been proposed, including nerve stimulation, secretion of growth factors and overproduction of prostaglandin E2. Patients with complete lesion, associated spasticity, presence of tracheostomy, urinary tract infection, pneumonia and thoracic trauma have higher risk (9).

HO after stroke: Not common, but risk factors are spasticity, urinary tract infections, deep vein thrombosis and pressure ulcers.

Hereditary HO: Myositis ossificans progressiva (Fibrodysplasia ossificans progressiva, FOP), or Münchmeyer disease, is a rare autosomal dominant disease that results in progressive ossification of, muscles, tendons, ligaments and fascia (10).

There are also very rare foci of HO like mesenter and abdominal scars (11,12).

Classification

In 1973, Brooker classified HO of the hip as:

Class 1: Bone islands within soft tissues about the hip.

Class 2: Bone spurs in pelvis or proximal end of femur, leaving at least 1 cm between the opposing bone surfaces.

Class 3: Bone spurs that extend from the pelvis or the proximal end of the femur, which reduce the space between the opposing bone surfaces to less than 1 cm.

Class 4: Radiographic ankylosis of the hip (13).

A new classification method of neurogenic HO of hip is used according to the anatomical location and neurological injury (14). This new classification is proposed to better manage and evaluate the prognosis.

Type 1: Anterior, at the anterior hip or the proximal end of the femur, with or without ankylosis

Type 2: Posterior, at the posterior hip or the proximal end of the femur, with or without ankylosis

Type 3: Anteromedial, at the anterior and medial hip or the proximal end of the femur, with or without ankylosis

Type 4: Circumferential, around the hip, with or without ankylosis

Subtypes of each type were added on the neurological injury:

a- Spinal cord

b- Brain injury.

Hastings classified HO of elbow as:

Class 1: Radiographic HO without functional limitation.

Class 2A: Limitation in elbow flexion/extension plane.

Class 2B: Limitation in forearm pronation/supination plane.

Class 2C: Limitation in both planes of motion.

Class 3: Ankylosis of forearm, elbow or both (15).

Risk Factors

As mentioned above, after SCI, patients with complete lesion, spasticity, and thoracic trauma, pneumonia, urinary tract infection and presence of tracheostomy have higher risk for developing HO (9).

Delay for surgery or for mobilization of the joint is important. It is showed that risk factors for posttraumatic HO of the elbow include longer time to surgery and longer time to mobilization after surgery (16).

Among patients undergoing primary total hip replacement (THR) surgery, determinants of HO are receiving erythrocyte transfusion, and having general, epidural or spinal anaesthesia. After revision surgery risk

is significantly increased and excessive surgical bleeding is also a risk factor of clinically relevant HO (17). The most common conditions found in conjunction with HO include ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis, hypertrophic osteoarthritis.

Clinical Findings

A painful, swollen and warm joint with decreased ROM is a candidate for HO. Erythema, palpation of a periarticular mass and fever are other findings. The clinical picture of HO may mimic some other pathologies such as cellulitis, thrombophlebitis, osteomyelitis, a tumorous process, deep venous thrombosis, local fracture or trauma.

Complications of HO are ankylosis of the joint, loss of function, pressure ulcers and peripheral nerve entrapment.

Rhabdomyolysis after HO was seen as an unusual complication in patient with SCI (18).

Diagnostic Methods

Clinical findings, laboratory tests, direct radiogram, triple phase bone scan, computed tomography (CT) and ultrasonography (USG) are helpful for diagnosis.

Laboratory tests, serum alkaline phosphatase (ALP) is frequently used in early detection of HO. It has high sensitivity but low specificity. Serum ALP levels can be dependent on renal and hepatic function, so they are not always useful. Especially bone specific ALP is a marker of osteoblastic activity.

Urinary markers, including hydroxyproline, deoxy-pyridinoline, and prostaglandin E₂ have been suggested in detection of HO.

Direct radiography is important in the maturity phase of HO. During the early stage, an x-ray will not be helpful because there is no calcium in the matrix. The typical image is shadow around the affected joint. They are most commonly used due to their low cost and simplicity. Figure 1, X-ray of one of our patients shows formation of HO around right hip. The patient, 52-year-old woman, had traumatic brain injury after a traffic accident. During her treatment, she had pain and limited range of motion of right hip.

Nuclear imaging, triple phase bone scintigraphy can be used in early diagnosis. In the early acute stage it will show bone formation 7 - 10 days earlier than an X-ray. Increase in uptake of Technetium(Tc)-99m is seen in these patients. The examination consists of a

radionuclide angiogram followed by a blood pool image over the suggestive site. A delayed image is obtained 2-3 hours later. This method is the most sensitive and "gold standard" imaging modality for early detection. Figure 2 demonstrates HO around right femur and acetabulum in a patient.

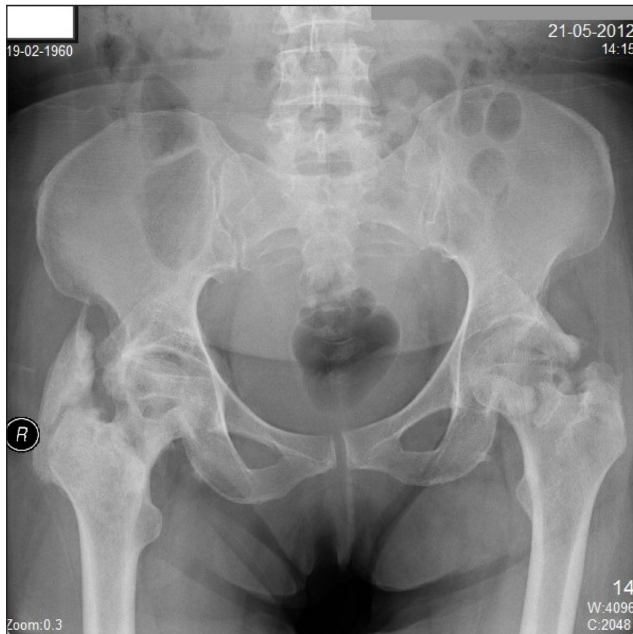


Figure 1. Anteroposterior radiograph of the hip in a patient with TBI, demonstrating HO around right hip.

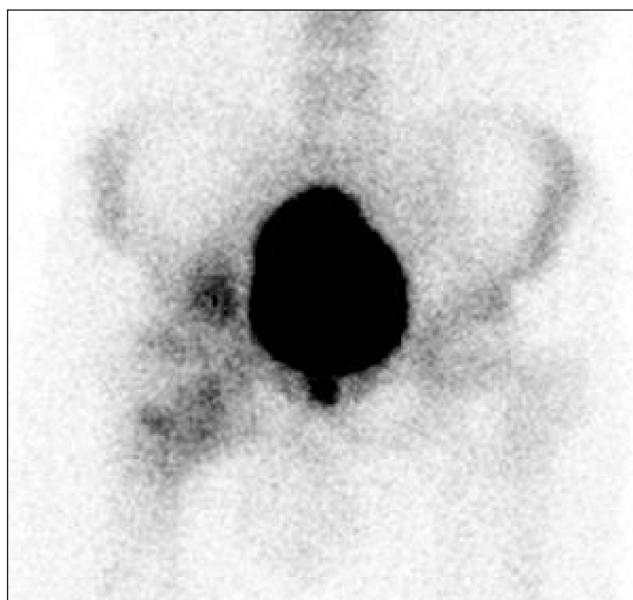


Figure 2. Image from a technetium-99m (99mTc) methylene diphosphonate(MDP) bone scan demonstrates marked soft-tissue uptake of tracer around right femoral head, neck and acetabulum.

CT shows localisation and width of HO. It is especially used in preoperative planning for resection. Both CT and magnetic resonance imaging (MRI) are helpful to establish relationships of bone to surrounding tissues like muscle and neurovascular bundles. Figure 3A,B are MR images of bilateral HO, as diffuse calcifications, in the leg and adductor regions.

USG is used especially for calcifications. It has advantage for earlier detection than conventional radiograph. It is a noninvasive method and may be useful for differential diagnosis from thromboflebitis.

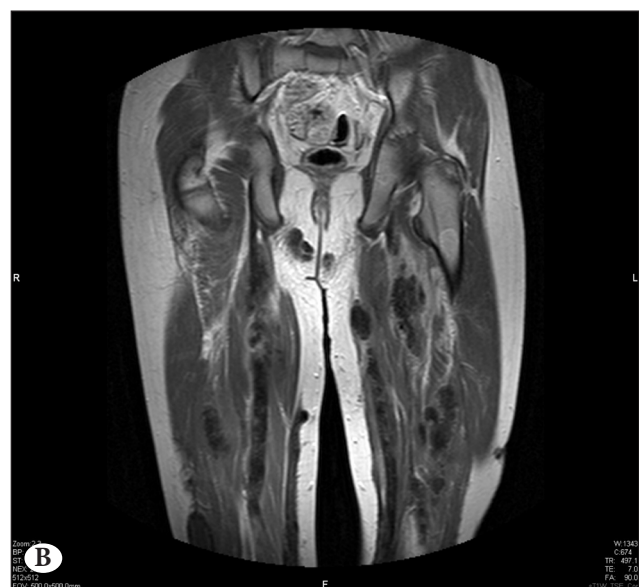
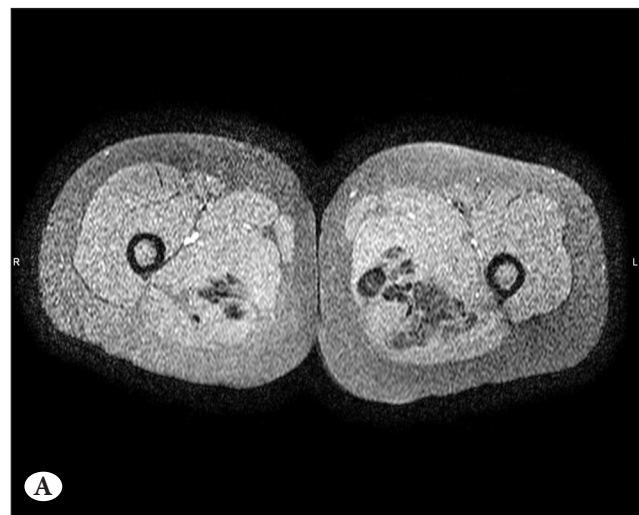


Figure 3. T1-weighted MR images showing HO in a patient with dermatomyositis as hypointense, A) axial plane B)coronal plane

Prophylactic Methods

Prophylaxis of HO, including passive ROM exercises and early mobilisation, is quite important. Nonsteroidal anti-inflammatory drugs (NSAIDs) and bisphosphonates are the main medical options for prevention of HO (19).

Treatment and Medical Rehabilitation

Treatment is consisted of exercise, physical therapy, medications, radiotherapy and surgery (surgical resection of the tissue).

Exercise: ROM exercises (Passive ROM, Active Assistive ROM, Active ROM) and strengthening will help prevent muscle atrophy and preserve joint motion.

Physical therapy: Superficial heat or deep heat like short wave diathermy and ultrasound are physical modalities to be used. Medical rehabilitation is very important, both in prevention and treatment of HO. Careful physiotherapy involving ROM exercises and gentle stretching has benefit but care should be taken not to move the joint beyond its pain-free range of movement because this can exacerbate the condition (20). Exercise which is too aggressive can aggravate the condition and lead to inflammation and increased pain.

Medical treatment: Medical drug options are NSAIDs (especially indomethacin) and etidronate disodium, a bisphosphonate.

NSAIDs 1: Non selective cyclooxygenase (cox) inhibitors: NSAIDs inhibit arachidonic acid metabolism, prostaglandin (PG) production so reduces inflammation, and slows bone metabolism. Indomethacin downregulates cox-1 and inhibits PGE2 and osteoprogenitor cell differentiation to osteoblasts. 25 mg indomethacin three times daily for a period of 6 weeks has been shown effective (21). Due to the side effects (gastrointestinal symptoms, like peptic ulceration), duration may be reduced, but at least 7 days is suggested.

2: Selective cox-2 inhibitors (-coxib) are equally effective as nonselective NSAIDs for the prevention of HO (22). They are more advantageous than conventional NSAIDs regarding side effects (23). However they have potential cardiovascular complications.

Etidronate disodium (ethyl hydroxy diphosphonate, EHDP), is structurally similar to inorganic pyrophosphate and is shown to inhibit calcium phosphate precipitation and transformation to hydroxyapatite and delay the aggregation of apatite crystals into large, calcified clusters. Two randomized controlled trials comparing EHDP

versus placebo were reviewed by Haran and colleagues in Cochrane Reviews, showing that EHDP delays rather than prevents HO mineralization (24). Vasileiadis et al., who studied the use of etidronate 20 mg/kg/day for 12 weeks vs. indomethacin 75 mg/day for 2 weeks for the prevention of HO after THA concluded that both modalities were equally effective, but etidronate therapy was six times more expensive than indomethacin (25).

Aspirin: A non selective and irreversible cox inhibitor, may be used as a dual therapy for both HO and thromboembolic prophylaxis. A retrospective study comparing first-stage bilateral THA patients treated with aspirin versus Coumadin showed significant reduction in prevalence and severity of HO with aspirin (26). In another retrospective study HO incidence and severity was less for the surface replacement arthroplasty (SRA) patients treated with aspirin compared with those treated with warfarin (27).

Radiation therapy (RT): Has been employed since the 1970s for the prevention of HO. A variety of techniques and doses have been used. Generally, radiation therapy should be delivered as close as practical to the time of surgery. A dose of 7-8 Gray in a single fraction has been used successfully. Treatment volumes include the peri-articular region, and can be used for hip, knee, elbow, shoulder and jaw.

When it is compared with NSAID, RT is more expensive than indomethacin. A meta-analysis showed that there is no difference in the effectiveness and safety (complications) of these procedures however the differences in costs are obvious (28). A study conducting a cost-effectiveness analysis of NSAID and radiation in the prophylaxis of HO, the risk difference of HO despite radiation is dominated by NSAID, which is more effective and cheaper (29). Also there are studies that the incidence of HO was significantly lower in patients treated with RT than in patients receiving indomethacin (30). Combined protocol regimens using both RT and indomethacin have shown greater efficacy than use of indomethacin alone (31). The recommended dose of RT is 700 c Gy and duration of indomethacin use is 15 days as a part of combined protocol (32). A retrospective study showed that RT in combination with NSAID use is safe and efficacious in preventing development of clinically significant HO in the elbow as in the hip region (33).

Surgical therapy: Surgical excision of heterotopic bone is seen as a possible option for functional impairment or skin ulcers due to deformity. The main goals of surgical intervention are to alter the position of the affected joint or improve its ROM. Procedure is wedge resection of the ectopic bone. Surgical complications,

which carry a high morbidity and are not uncommon, include hemorrhage, sepsis, wound infection, repeated ankylosis, and heterotopic bone recurrence (20). Once HO occurred, surgical treatment is the unique treatment method, so the emphasis is to prevent heterotopic ossification. In order to reduce the recurrence, surgical treatment should be considered after 12-18 months when the bone tissue has matured and serum ALP level decreased to normal (8, 34).

In the prevention of HO, NSAIDs show the greatest efficacy when administered early after SCI, and bisphosphonates are found to be the most effective treatment strategy. In the TBI population, the most effective treatment is surgical excision (35). Another systematic review about therapeutic interventions for HO following SCI showed that pharmacological treatments of HO post SCI have the highest level of research evidence supporting their use. In prevention of HO, NSAIDs demonstrate greatest efficacy when administered early after SCI, while bisphosphonates are the intervention with strongest supportive evidence once HO developed. Of the nonpharmacological interventions, pulse low-intensity electromagnetic field is supported by the highest level of evidence but more research is needed to understand its role (36).

According to Cochrane Database Systematic Review to determine the efficacy of medications to treat acute HO on radiological, symptomatic, functional impairment, and disability outcomes, given the absence of long term radiographic outcomes in the included studies, there is insufficient evidence to recommend the use of disodium etidronate or other pharmacological agents for the treatment of acute HO (37).

Post-operative rehabilitation has also shown benefit in patients with recent surgical resection of HO. The post-op management of HO is similar to pre-op treatment but much more emphasis is placed on edema control, scar management, and infection prevention.

New therapeutic modalities: Bone morphogenic protein(BMP) type 1 receptor inhibitors (like Noggin), BMP antagonist, nuclear retinoic acid receptor-gamma agonist (RAR-gamma), free radical scavengers are new therapeutic modalities and are under investigation.(38) High levels of BMP are thought to play a key role in HO. Osteogenic differentiation is regulated by BMP type 2 receptors that activate BMP type 1 receptors (activin receptor-like kinase[ALK] 2,3,6). The utility of small molecule BMP inhibition as an experimental probe of BMP function, these studies suggest that pharmacologic BMP inhibition might be useful for the therapeutic modulation of bone mineral density, via an unexpected and paradoxical mechanism (39,40).

RAR pathway is inhibitor of chondrogenesis and HO. Evidence from animal models indicate that RAR gamma agonists cause reduction in BMP signalling, human trials are not yet tested (41).

Free radical(FR) scavengers like the combined allopurinol and N-acetylcysteine (A/A) may prevent HO formation. FRs are thought to induce tissue trauma. Limited in vivo data indicate that A/A is superior to indomethacin and equivalent to methylprednisolone in preventing experimentally induced HO in rodents (42,43).

There are also other novel treatment methods, as local lipopolysaccharide and platelet-rich plasma(PRP) injections (44,45). However the use of PRP does not appear to influence the incidence or severity of HO following THA. Further clinical research is needed to fully understand whether this autologous blood product has a role or not.

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