Current Review of Heterotopic Ossification

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Expert Commentary

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Heterotopic ossification, the abnormal development of bone in areas of the body other than skeletal tissue, commonly occurs in association with traumatic brain injury and spinal cord injury. The prevalence of heterotopic ossification in those sustaining extremity combat injuries has also been highlighted with the recent rise in the number of overseas combat injuries. This ectopic bone formation can have profound effects on the rehabilitation and care of these patients. This clinical entity is still an enigma among scientists and clinicians, and current preclinical work has made slow but steady progress in our understanding of the etiology and pathophysiology behind heterotopic bone formation. This article briefly reviews the most recent concepts regarding the pathophysiology, epidemiology, and treatment of heterotopic ossification.

Heterotopic ossification is a condition in which lamellar bone is formed in non-ossified soft tissue. It was first illustrated by Reidel in 1883 and subsequently described by Dejerne and Ceiller during the First World War, when patients sustaining spinal cord injuries were observed to form heterotopic new bone[1]. This was followed by one of the landmark discoveries in orthopaedic research, when Marshall Urist described the osteoinductive properties of bone morphogenetic protein (BMP) in ectopic areas such as muscle[2, 3]. Since Urist's initial discovery, multiple BMPs have adopted clinical orthopaedic uses, yet our understanding into the formation of new bone in non-skeletal tissue has not progressed as rapidly.

Clinically, heterotopic ossification can have a profound effect on a wide range of patients with predisposing factors such as neurologic injury, major joint surgery, local extremity trauma, and severe burns. Heterotopic bone can limit the range of motion of a number of different joints, most commonly the hip, knee, shoulder, and elbow (Figure 1). It can also develop concomitant with soft tissue contractures which results in greatly limited joint mobility. In addition, certain populations, particularly those that suffer from neurogenic heterotopic ossification, are impacted by the inability to maintain personal hygiene, and skin maceration, pressure ulcers, and intractable pain can develop. Limitations in joint range of motion can lead to further complications such as disuse osteoporosis and eventual fractures during transfers or falls.

This article aims to review the most recent advances in our understanding of the pathophysiology behind ectopic bone formation. Recent data on the epidemiology, clinical evaluation, and treatment of heterotopic ossification is also discussed.

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Pathophyioslogy

The precise pathophysiology behind heterotopic ossification is still unclear but is thought to be related to both local and systemic factors causing osteoblastic differentiation of pluripotent mesenchymal stem cells. The most recent work has focused on BMP signaling and identification of progenitor cells responsible for ectopic bone formation.

Much of our understanding has come from the work of Drs. Eileen Shore and Frederick Kaplan investigating fibrodysplasia ossificans progressiva, a rare genetic disease characterized by heterotopic bone formation. Patients with this congenital disorder have a mutation in the ACVR1 gene that causes constitutive activation of BMP type-I receptor activity and formation of ectopic bone[4]. Inhibition of transcriptional activity of BMP type-I receptors with antagonists such as noggin and chordin has been shown to disrupt the osteoblast differentiation signaling pathway[5,6]. Mice lacking noggin show overactivity of BMP and display exuberant orthotopic and heterotopic ossification. The role of BMP signaling as an important regulator of ectopic bone formation, along with other mediators such as platelet-derived growth factor (PDGF), insulin-like growth factor 1 (IGF-1), and transforming growth factor β-1 (TGF β-1), continues to be the focus of research attempting to elucidate key initiators and regulators in this cellular process.

Trauma and soft tissue injury is a consistent feature of heterotopic ossification, and many investigators have sought to elucidate the cellular and molecular mechanisms that link traumatized soft tissue to ectopic bone formation. Jackson et al recently identified and isolated a population of multilineage mesenchymal progenitor cells with osteogenic potential that were localized primarily in traumatized tissue[7]. Subsequent studies have shown that these mesenchymal progenitor cells isolated from traumatized muscle had the potential to serve as osteoprogenitor cells in the formation of ectopic bone after injury[8]. Lounev et al suggested that cells responsible for heterotopic ossification are from the endothelium of the local vasculature[9]. By using two mouse models of dysregulated

BMP signaling and heterotopic ossification, they were able to identify progenitor cells that contribute to different stages of the heterotopic endochondral anlagen. Progenitor cells with markers consistent with endothelial precursors were present in all stages of the endochondral anlagen, whereas skeletal and smooth muscle progenitors had minimal to no contribution at any stage[9]. Results of this study suggest that, in a setting of chronically stimulated BMP activity, muscle injury and associated inflammation sufficiently triggers heterotopic bone formation and that cells of vascular origin are essential to construction of ectopic bone. This cell lineage, along with stimulating factors such as BMP that create the correct environment for bone formation, could be targets for the development of therapeutic interventions to treat heterotopic ossification.

Prevalence and Risk Factors

These recent advances in our understanding of ectopic bone formation are timely, as multiple studies have recently reported on the high incidence of heterotopic ossification in soldiers sustaining extremity war injuries. Increased use of explosive weaponry has resulted in a rising number of blast type injuries. Furthermore, advancements in resuscitative medical care, hemostatic measures, and damage control surgery have resulted in increased survival from otherwise deadly injuries[10]. A recent retrospective study by Forsberg et al out of the National Naval Medical Center showed that the majority of patients (65%) who sustained extremity war injuries had developed radiographically apparent heterotopic ossification[11]. Associated risk factors for development of heterotopic ossification included lower extremity trauma, amputated limb, and multiple extremity injuries. These results are in concordance with a recent study by Potter et al[12], which supported the role of heterotopic ossification as a cause of pain in the residual limbs of military amputees (Figure 2). This group reported a similar prevalence of heterotopic ossification (63%) as Forsberg et al. Seven percent of amputees required operative excision of bone at an average of 8.2 months after the initial injury. These results highlight the increased prevalence of heterotopic ossification in war-wounded patients when compared to the civilian population and further support the need for research identifying and targeting signals that stimulate ectopic bone formation after local soft tissue trauma.

Historically, heterotopic ossification is more often known to affect patients sustaining traumatic brain injury and spinal cord injury[13]. The rates of heterotopic ossification are reported to be approximately 11% in TBI and 20% in SCI[14, 15] and most often develops in the spastic limbs of these patients. Similar to those patients with fibrodysplasia ossificans progressiva, neurologically impaired patients have a greatly increased rate of heterotopic ossification when they sustain local trauma or with forcible passive movement[16]. Post-traumatic fractures and dislocations are often complicated by heterotopic bone, and the incidence of heterotopic ossification after surgical treatment of acetabular fractures has been reported to be about 25%[17]. It is also one of the most frequent complications following total hip arthroplasty, although ectopic bone in this setting is not always of clinically significance[18].

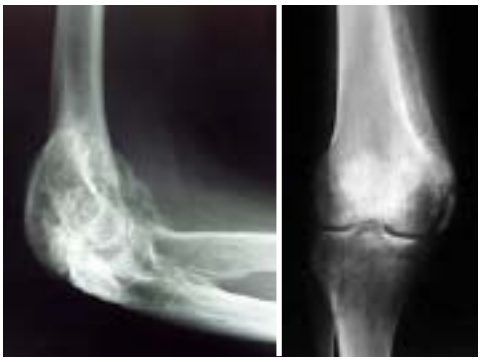


Figure 1. Heterotopic ossification of the posterior elbow (A) and medial knee (B).

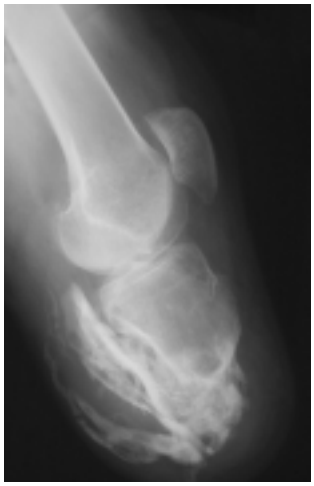


Figure 2. Extensive heterotopic ossification in a residual lower limb.

Patient Evaluation

Early identification of patients with heterotopic ossification can be difficult. The natural history of heterotopic bone formation is not well defined and depends largely on etiology. Usually, heterotopic bone will begin limiting joint range of motion in the first two months after injury or surgery but can also first present over a year after original insult. The most common clinical signs are fairly nonspecific, such as pain, erythema, swelling, and warmth of the affected joint. Because many of these patients have suffered neurologic insult, their cognition may be impaired, further obscuring the clinical diagnosis. In patients with impaired levels of consciousness, the clinician is often obligated to rule out other diagnoses such as infection, deep vein thrombosis, and osteomyelitis. Nonetheless, the diagnosis of heterotopic ossification should be considered in those patients with known risk factors for development.

Radiographically, plain films taken at the time of onset of symptoms are seldom useful, as the maturation of ectopic bone does not become evident until weeks after onset of clinical symptoms. Three-phase bone scintigraphy is a useful imaging modality for early diagnosis, and MRI has been shown

to detect formation of ectopic bone weeks before evidence on x-ray. Laboratory studies such as serum alkaline phosphatase level may potentially be the only helpful objective measure in making the diagnosis in these patients during this initial phase. Although sensitive, it is not specific, and alterations in serum levels can be dependent on hepatic and renal function. Because of the lack of simple objective measures in detecting heterotopic bone formation, the diagnosis is often missed in the early stages, leading to delays in treatment.

As ectopic bone matures and appears on plain films, the effect of substantial joint contractures and range of motion limitations will become more evident. Patients with ankylosed joints or neurologic sequelae due to ectopic bone may be considered surgical candidates. In certain cases, a CT scan can be a helpful adjunct to plain films in defining the presence of intra-articular lesions as well as the extent of ossification and disuse osteopenia (Figure 3). These factors can be predictive of complications such as intra-operative fracture and loss of range of motion[19].

Treatment Strategies

Medical Management and Radiotherapy

With a constellation of appropriate clinical signs in a patient and an appropriate workup to rule out DVT or infection, early diagnosis of heterotopic ossification can be made and is often key to starting appropriate therapy. Early initiation of these various therapies may improve clinical outcomes and preserve joint mobility. Heterotopic ossification identified in the early phases can be addressed with early physiotherapy and medically with bisphosphonates or nonsteroidal anti-inflammatories (NSAIDs). Treatment often begins with gentle physiotherapy and terminal resistance training through a pain-free range of motion. NSAIDs, particularly indomethacin, have shown to be of benefit, but treatment cannot be used in certain patient populations due to associated renal, gastrointestinal, and bleeding complications. Bisphosphonates, such as etidtronate, bind to hydroxyapatite crystals and may inhibit mineralization and calcification of soft tissue. However, clinical evidence supporting the use of bisphosphonates is limited. Radiation therapy has shown value in the prevention of further formation and maturation of ectopic bone. This modality, however, is limited by logistical difficulties, and often it is difficult to predict the eventual site of heterotopic bone formation, particularly in patients sustaining head injuries.

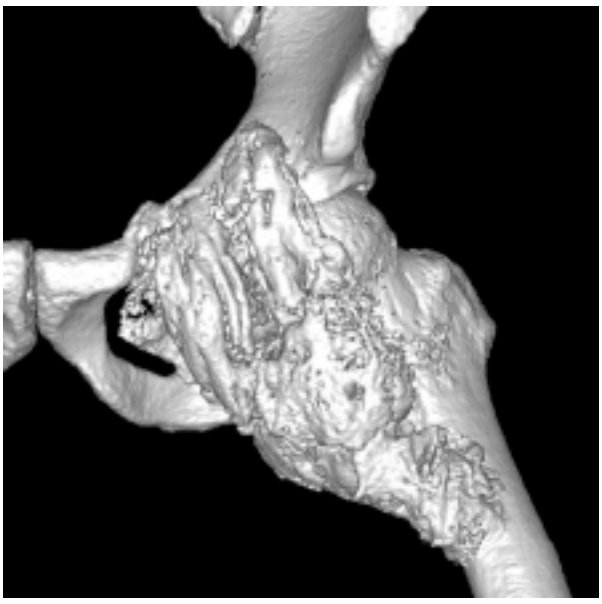
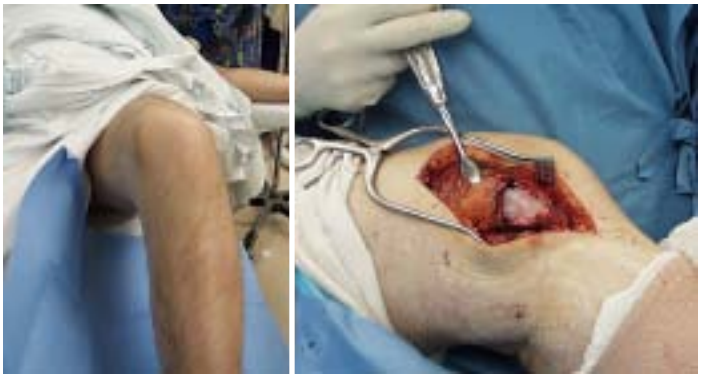


Figure 3. 3D CT reconstruction demonstrating heterotopic ossification of the hip.

The optimal prophylactic treatment for preventing or minimizing ectopic bone formation is controversial. Most of the literature has been related to prophylaxis after total hip arthroplasty and post-traumatic heterotopic ossification, such as post-fixation of acetabular fractures[20]. Evidence comparing the role of NSAIDs and radiation therapy is limited regarding neurogenic heterotopic ossification and non-existent regarding the treatment of trauma-related amputations. Most studies have concluded no difference in recurrence or in complications with either treatment modality[21], while other studies have supported a synergestic effect of both modalities used simultaneously. Unfortunately, the majority of studies in the literature are retrospective in nature and lack control groups. The primary benefit of NSAIDs over radiation is cost, with recent studies using Medicare data reporting the average cost of NSAID treatment ($20) as being 45 times less than that of radiation treatment ($899)[22]. However, administering NSAIDs to all patients at risk for heterotopic ossification is difficult to rationalize when considering the complications associated with its use.

The use of radiation therapy in the prevention of heterotopic ossification stems largely from the total hip literature. A dose of 700 to 800 cGy of local radiation in the first four post-operative days is commonly used to prevent HO formation in high-risk total hip patients. A study by Schaeffer and Sosner utilized a total dose of 20Gy in 10 fractions to two patients with increasing serum alkaline phosphatase associated with clinical signs of heterotopic bone formation[23]. Both patients had complete pain relief and improvement in joint range of motion. More recent studies employing a larger number of patients have failed to show the same results. Cipriano et al showed that the standard single 700cGy dose of local radiation within the first four post-operative days after ectopic bone excision was not effective in patients with neurogenic heterotopic ossification[24]. Further studies with higher doses of radiation therapy may be warranted.

Because of the side effects and logistical problems associated with current prophylactic options, other more selective agents are being studied. Shimono et al report the use of selective retinoic acid receptor agonist in the inhibition of ectopic bone formation, suggesting its possible role in the treatment of heterotopic ossification[25]. Isotretinoin, a nonselective retinoic acid receptor agonist, was previously tested as a treatment in patients with fibrodysplasia ossificans progressiva, and although a decreased incidence of HO was observed compared to controls, a number of significant side effects were noted[26].



A B

Figure 4. (A) Heterotopic ossification of the medial knee causing a knee flexion contracture. (B) Excision of ectopic bone from the medial knee.

Surgical Intervention

Surgical excision is often necessary in the treatment of severe heterotopic ossification limiting mobility or causing neurologic problems and can significantly improve range of motion and quality of life. Controversy over early versus late resection exists, especially regarding excision of neurogenic heterotopic ossification. Some experts believe that ossification is less likely to recur after a prolonged observation period, which allows for resolution of the acute inflammatory phase and maturation of bone. Others have suggested that early excision allows for increased range of motion, the prevention of soft-tissue contracture and muscle atrophy, and prevention of intra-articular ankylosis[27]. Optimal timing of surgery may be dependent on etiology – for example, the formation of heterotopic bone can occur later in traumatic brain injury than in spinal cord injury[28]. The current literature does not support the theory that early excision triggers later recurrence[29].

Many studies have investigated timing of excision of heterotopic bone from the elbow, and for the most part, have supported early excision[30,31]. Most retrospective case series have reported good results after excision of heterotopic ossification of the knee[32, 33] (Figure 4), and excision of heterotopic bone after traumatic amputation has been shown to have low recurrence and complication rates[12]. Heterotopic ossification of the hip, however, can be associated with numerous peri-operative complications, especially iatrogenic femoral neck fractures and infection. Recent studies on excision of hip heterotopic ossification have identified risk factors associated with complications, and association between delayed excision and peri-operative complications have been established[19]. Patients in which excision was delayed until joint ankylosis have higher rates of intra-operative iatrogenic fracture, likely secondary to severely decreased bone density. Intra-articular pathology and osteoporosis, which develop more commonly in patients in which excision is delayed, are associated with a higher chance of iatrogenic femoral neck fracture. In addition, delay in surgery often results in inferior functional outcomes in terms of joint range of motion.

Conclusion

Numerous risk factors are known to be associated with the formation of ectopic bone, but the mechanisms behind which these changes occur are poorly understood. Current preclinical work has made slow but steady progress in our understanding of the etiology and pathophysiology behind heterotopic bone formation. Identification of patients in the early phases of heterotopic ossification can be difficult but is important in timely initiation of various forms of prophylactic therapy. Surgical excision can often provide symptomatic relief and improved mobility, but optimal timing of surgery can be difficult to establish. Hopefully, current laboratory and clinical investigations will help us understand this puzzling clinical entity, and lead to new preventative and therapeutic measures in the management of this debilitating problem.

Ask the Expert

Mary Ann Keenan, MD
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What parameters and patient factors do you prioritize in deciding when to perform surgical excision of heterotopic ossification?

I excise the heterotopic ossification when there is a clear cortex visible on plain radiographs. This indicates that there is sufficient maturity to localize the extent of the heterotopic ossification during surgery. It also decreases the more extensive bleeding that occurs when attempting to excise actively growing heterotopic bone with its associated intense inflammatory response. The ectopic bone becomes well-defined radiographically within a few months. This allows the patient to be mobilized fairly quickly following the inciting injury. Prolonged joint immobilization also causes atrophy of the articular cartilage. To my knowledge there is no clear evidence that the rate of recurrent heterotopic ossification is related to the maturity of the process.

What is your current preference for prophylaxis?

There are no clear studies showing that prophylaxis after surgical excision of heterotopic ossification has any effect on recurrence. Use of NSAIDs is often not possible because of bleeding concerns or gastrointestinal side effects. We recently completed a retrospective study showing that 700 gy of radiation given on the first post-operative day was not effective in preventing recurrence. That being said, I no longer use radiation but I do use Indocin when there are no contra-indications. Using treatments for the prevention of heterotopic ossification after trauma is less well-studied.

Approximately 20% of brain injury or spinal cord injured patients develop heterotopic ossification. The problem has always been that we have no way to know which patients are at risk for heterotopic ossification. It doesn't seem reasonable to treat everyone prophylactically, especially when the long term effects of low dose radiation are unknown and the risk of NSAIDs can be clinically significant.

Do you ever recommend bisphosphonate medical therapy for patients with established HO?

No. The only studies I am aware of are in spinal cord injured patients. If the patient has clinical evidence of HO formation with a hot bone scan and negative radiographs, then immediate IV Didronel seemed to help. Once there were any calcifications seen on radiographs, no effect of Didronel was noted. It is almost impossible to catch a patient at the correct time.

Are there any treatment or rehabilitation strategies for amputees in whom prosthetic use is limited by the development of heterotopic ossification?

Occasionally the heterotopic ossification in the residual limb does not interfere with prosthetic fitting. Most times, heterotopic ossification limits the use of a prosthesis since all prosthetic designs for lower extremity amputees require end weight bearing.When there is extensive skin scarring or split thickness skin grafts of the residual limb, then the patient cannot tolerate any heterotopic ossification. I have also had to remove heterotopic ossification from the posterior knee of through-knee amputees to allow for adequate knee ROM.

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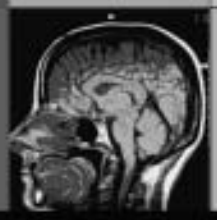

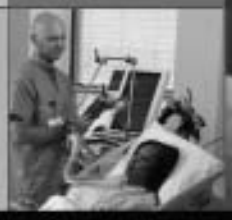

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