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Heterotopic Ossification of the Elbow: A Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author SQ helped design the study performed the literature search and wrote the first draft of the manuscript. Author JR performed an independent literature search and edited the first draft of the manuscript. Authors HA and JT designed the study protocol, oversaw the literature searches and reviewed the final draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Aberrant ectopic bone formation of the elbow is a common clinical presentation after neurologic, burn, and traumatic injuries to the joint. This represents a significant source of patient burden, delayed recovery times and increased medical costs. Although there is an abundance of literature on heterotopic ossification (HO) of the hip, there is little literature on HO of the elbow in comparison.

Aims: This literature review seeks to summarize consensus regarding the appropriate system of classification, pathophysiology, clinical presentation, risk factors, and prophylactic treatment options associated with HO formation of the elbow. Clinicians may utilize this information to identify high risk patient populations for potential prophylactic therapy to prevent the occurrence/complications of HO at the elbow.

Methods: A PubMed literature review was conducted using combinations of the key words "heterotopic ossification," "elbow," and "fracture/dislocation." All study types were considered and relevant articles were utilized for this review.

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Results: Higher levels of injury, severe neurologic and burn injuries, delay to surgery, delay in fixation/stabilization of the elbow, multiple surgical treatments, and genetics were correlated with ectopic bone formation. Single dose pre/postoperative radiotherapy with 700cGy or preoperative NSAID regiments were found to be the main prophylactic treatments.

Conclusion: Clinicians must consider the HO risk profile of their patients as well as the risk factors of treatment before deciding on prophylactic options. Surgical resection is reserved for the most severe cases.

Keywords: Heterotopic; ossification; elbow; fracture; dislocation; injury.

1. INTRODUCTION

Heterotopic ossification (HO) is the abnormal formation of mature and metabolically active lamellar bone in soft tissue [1]. HO most commonly presents after traumatic injury and/or surgery, significant burns and neurological injuries. HO is a significant cause of discomfort, leading to impaired ability to complete daily tasks, complications, and dissatisfaction for patients postoperatively. Additional surgical treatment is often required when joint spaces and/or impinged neuro-vasculature is involved. In one study of 142 patients with elbow fractures and fracture-dislocations, as many as 37% developed HO, with 20% of patients presenting with clinically relevant symptoms and up to 10% requiring additional surgical intervention [2]. The prominence of HO in traumatic and other forms of injury requires a better understanding of factors contributing to ectopic bone formation. Understanding the common clinical presentation and risk factors of HO formation is important in identifying at risk populations for prevention and treatment strategies, as well as minimizing patient burden.

There is a paucity of literature on the development and prophylactic treatment of HO of the elbow. The high incidence of elbow HO formation, combined with patient burden and high costs associated with additional medical intervention, warrants an in-depth understanding of HO pathophysiology and understanding of current preventative treatment modalities other than surgery. This literature review evaluates current research to establish a consensus on the pathophysiology, presentation, risk factors, and prophylactic treatments associated with elbow HO.

2. CLASSIFICATION

In order to systematically categorize HO severity and progression, many different classification methods have been created. The Brooker classification is popularly referenced in the literature, but like many other classification systems it was originally used for HO about the hip. We recommend clinicians instead utilize the Hastings and Graham classification [3] system which is specific for HO of the elbow and forearm. This offers a standardized approach to describing HO severity and functional limitation in the clinical setting. Class I is formation of HO without functional limitation. Class II is HO formation with functional limitation. Class III is HO formation with associated joint ankyloses. Classes II and III can be further subdivided into A, B, & C, subcategories that are utilized to describe the plane in which range of motion is compromised. These classifications may serve useful to identify the progression of elbow HO in patients, and quickly identify deficits in function. The classification is summarized in Table 1.

Table 1. Hastings and graham classification

Class I	HO without functional limitation		
Class II	HO with functional limitation (limited ROM)	Class IIA	flexion/extension limitation
		Class IIB	pronation/supination limitation
		Class IIC	Both A and B
Class III	HO with ankylosis	Class IIIA	flexion/extension limitation
		Class IIIB	pronation/supination limitation
		Class IIIC	Both A and B

3. PATHOPHYSIOLOGY

Several mechanisms have been suggested for the multifactorial process of HO bone formation. Ectopic bone is thought to be the result of mesenchymal stem cells that migrate to areas of insult and are prompted to differentiate into osteocytes [4,5]. This newly formed bone resembles normal bone, but is metabolically hyperactive and lacks a true periosteal layer [1,4]. Studies suggest that many other body processes including the immune system, inflammatory response, and the CNS are involved in bone formation [6]. The impairment of these processes during severe neurologic injury in trauma cases may play a role in the development of ectopic bone formation. However, the exact mechanism of HO formation due to nervous system dysfunction remains unknown.

Several authors suggest the role of tissue expression of increased levels of Bone Morphogenic Protein (BMP), an impaired BMP pathway, and elevated alkaline phosphatase levels (ALP) in the pathogenesis of HO [4,7,8]. BMP is thought to contribute by stimulating the differentiation of pluripotential cells into osteoblast [9]. One of the many roles of ALP is to remove factors that prevent mineralization of bone. One study found a significantly elevated difference in ALP levels in patients that developed HO versus patients who did not, suggesting a possible correlation [10]. Inflammation is also thought to play a pivotal role in the formation of HO. An exact pathway has yet to be identified, but many factors are potentially implicated. Leukotrienes and PGE2 released during the inflammatory process are responsible for increased periosteal lamellar bone formation, and PGE2 specifically is thought to stimulate mesenchymal cells to osteoblasts [11]. Despite the close connection with the inflammatory process, there is a gap in evidence in the current literature on whether elevated inflammatory markers such as c-reactive protein (CRP), creatine kinase (CK), and erythrocyte sedimentation rate (ESR) may be useful in identifying high risk patients and monitoring HO progression. These markers are non-specific for HO. Nevertheless, the majority of cases of HO seem to most commonly be triggered by acute traumatic injury and resultant hyperactive growth and inflammatory conditions. Due to the close relationship of HO and inflammation, prophylactic therapy often focuses on NSAID (Indomethacin) treatment [12,13].

There are also rare cases where patients have a genetic predisposition towards the formation of ectopic bone in soft tissue. This could include genetic mutations anywhere along the implicated BMP pathway [7]. Patients with known genetic mutations in the BMP pathway, or family history of conditions such as fibrodysplasia ossificans progressiva [FOP] should be considered prime candidates for prophylactic therapy.

4. CLINICAL PRESENTATION

Not all cases of HO are clinically significant. Symptoms may range from mild to severe depending on a case to case basis. After surgery or other traumatic event, it can take up to 3-4 weeks for HO formation to occur. Upon the onset of bone formation, patients may typically present with warmth, redness, swelling, and varying degrees of pain (from none to severe) [7]. More often, patients present to the clinic when faced with severe symptoms such as elbow stiffness or contractures, compromised range of motion (ROM), neurovascular compression, pain/ discomfort, and in rare cases, bony elbow ankylosis [7,14]. Elbow ankylosis is a more severe clinical finding but can reduce elbow ROM by up to 90%, debilitating the patient [15]. Such symptoms can severely compromise patients' ability to complete even the simplest of daily tasks, interfering with quality of life and impinging on patient independence. Furthermore, these symptoms may be severe enough to warrant surgery (recurrent in some cases), which contributes to increased costs of management. Clinicians should be mindful that patients with certain heritable bone and connective tissue diseases are also at increased risk for HO bone formation. Examples include sclerotic bone disorders such as Paget's disease, osteogenesis imperfecta, and Forestier disease. Clinicians should be able to recognize common clinical phenotypes and lesions. Patients should be screened thoroughly for their specific clinical, radiological, and histological phenotype and be managed accordingly.

Diagnosis of HO is primarily via clinical findings and confirmed via radiography of the affected area. Ultrasound is a rapid, cost efficient modality that may be utilized to detect early HO, but its efficacy is user dependent and requires a trained operator and experienced radiologist [16]. Triple phase bone scans remain the most sensitive method of detecting early HO and assessing maturity of HO bone formation [17]. MRI and CT scans can be utilized when neurovasculature is at risk of being compromised by HO, and can aid in planning for surgical resection approaches. MRI is useful for identifying well-developed HO, but recent research indicates that CT joint imaging may help in distinguishing early vs late HO in soft tissue [18,19]. The addition of CT scanning allows the operator to recognize early HO foci and differentiate them from other soft tissue lesions. Using both clinical and radiological evidence, physicians can Earlier recognition could identify patients ideal for prophylactic treatment.

5. RISK FACTORS

5.1 Trauma

Since HO is a multifactorial disease process, it is difficult to ascertain direct risk factors. The results are often mixed depending on the type of study, the patient population, and the statistical analysis utilized. However, a great majority of the literature agrees that HO formation is generally greater in patients who have previously had HO [20], as well as those who have been exposed to acute traumatic injury, thermal burns, or neurogenic insult [4,7,18,21]. The incidence and severity of HO correlates with the extent of injury and degree of surgical trauma [4]. In acute injury, the presence of fracture and dislocation of the elbow, as well as joint instability is linked to increased risks of HO formation [2,4,12,13]. Severe elbow injuries such as open fractures and a delay in fracture fixation were found to be risk factors for HO [2,12,13,22,23]. One study found the surgical approach used, total operating time, formation of a hematoma, extensive dissection and disseminated bone dust to be potentially implicated [4]. The research on this is not conclusive. Multiple studies emphasized delay to surgical treatment of elbow trauma to be a risk factor for HO [2,12,13,23]. This may be the result of longer periods of joint immobilization, which can increase the risk of developing HO [12,20]. Additionally, Wiggers, et al. found that the number of surgeries (within the first 4 weeks) was also an independent predictor based on their 417 adult elbow fracture patient sample [23]. They suggested this is due to high muscle manipulation and retraction during operative procedures. Waiting over a week before surgery for fracture fixation was found to result in 10 times the odds of radiographic HO formation, and 7 times the odds of clinically relevant HO formation [12]. Studies further suggest that fixation of unstable fractures within 48 hours of injury may reduce the chances of ectopic bone formation [14,24]. For these reasons, it is important for surgeons to weigh the risks of delayed ORIF and consider early definitive fixation when treating elbow fracture/dislocation injuries.

5.2 Neurogenic Injury

The high incidence of HO formation related to neurogenic injuries represents significant risk factors as well. In patients with combined neurological and elbow injuries, one study found the incidence of HO to be up to 70% [4]. Perhaps this is due in part to the high incidence of elbow fracture injuries, accounting for up to 30% of upper limb injuries [12]. A systematic review of clinical reports on 626 patients undergoing HO excision of the elbow found that 55% of cases were in patients with trauma, 28% in burn patients, and 17% in patients with traumatic brain injury [7,25]. In many cases, these injuries may not even directly involve the elbow, yet HO of the elbow is still commonly found [7]. The mechanism behind CNS dysfunction and HO formation remains unclear, but several authors suggest theoretical mechanisms. In patients with head and spinal cord injury, the healing response can often be found to be accelerated [4]. Dysfunction of this pathway is thought to lead to new bone formation in abnormal locations such as joint spaces and soft tissue. Interestingly enough, Bidner et al. found that the serum of patients with head injuries contained increased growth factor activity of cells of the osteoblast phenotype [26]. This suggests a central humoral and/or neurological mechanism involved in enhanced osteogenesis following head/CNS injury [26]. In one study, paroxysmal sympathetic hyperactivity and dysregulation of the CNS as a result of brain injury was found to be associated strongly with HO formation [27]. The authors identified sympathetic hyperactivity as paroxysmal increase in heart rate, respiratory rate, diaphoresis, motor hyperactivity with or with- out increased blood pressure and/or hyperthermia. Although a strong association was found, a causal role remains to be identified.

5.3 Burn Injury

Burn injury is another complex risk factor for HO that also consists of multiple pathways. In a study of nearly 3000 patients, there were 11.5 times higher odds of developing HO if the patient had suffered more than 30% total body surface area burns [28]. A literature review of 51 studies on HO and bony ankyloses formation in post burn injuries found incidences ranging anywhere from 0.1 to 35.3% [29]. Similar to neurologic injury, burn injuries activate multiple pathways that induce hyperactive inflammatory and resultant growth responses. Inflammation sets in motion pathways that prepare healthy cells to proliferate and replace dead cells and injured/necrotic tissue and matrix [18]. It may be relevant to note that even in patients without HO formation, severe burns can lead to post burn contractures that limit the effected joint mobility quite significantly, thereby producing similarly debilitating symptoms. This highlights how the elbow is especially susceptible to becoming stiff after injuries. Early mobilization is important in prophylaxis, and active range of motion (AROM) or passive range of motion (PROM) can help prevent stiffness of the elbow joint after injury or surgery [1].

5.4 Genetic Risk Factors & Heritable Disease

Genetic risk factors and heritable bone and connective tissue diseases represent additional risk factors to HO formation that patients may present with in clinic. There are a wide range of heritable diseases with aberrant bone and connective tissue metabolism that can present with a spectrum of phenotypes, some of which may encompass HO formation at the elbow. We will discuss a few heritable diseases that are known to commonly present with HO formation at the elbow. Although some patients may already have a known history of disease, many patients with mild forms of disease may present for the first time with symptoms and require a diagnosis. Identifying the clinical, radiologic and histological phenotype may help narrow the differential.

Known genetic risk factors include a statistically significant association amongst three SNP variants (beta2-adrenergic receptor, toll-like receptor 4, complement factor H) to the development of HO or lack of protection against it [6]. Other genetic risk factors may include mutations along the BMP pathway such as those seen in Fibrodysplasia Ossificans Progressiva (FOP) and other heritable diseases where patients have disseminated HO formation of ligaments and soft tissues [4,8]. Non-hereditary forms (non-hereditary myositis ossificans) exist as well, thought to be due to post traumatic inflammatory changes. Progressive osseous heteroplasia (POH) is another condition caused by a mutation in the GNAS gene which can cause cutaneous and subcutaneous HO formation at soft tissue sites depending on the severity of disease [30]. FOP and POH represent some of the most severe type of progressive HO that can cause lifelong debilitation.

Sclerotic bone disorders such as Paget's disease and disseminated idiopathic skeletal hyperostosis (DISH) may also present an increased risk of HO formation, particularly after trauma [31,32]. There is aberrant osteoclast metabolism and regulation in the Paget's disease patient, as well as irregular formation of new woven bone. This creates an environment for heterotopic bone formation. There are a number of studies investigating the increased incidence of HO of the hip following total hip arthroplasty [33,34], but little literature on the elbow in particular. Interestingly, the histological composition of osteoclasts in these patients suggest a viral etiology, suggesting a different etiology for this aberrant bone [34]. Forestier disease or DISH is also characterized by thickening, calcification and ossification of soft tissues. This is more commonly seen in the elderly, as prevalence increases with age [35]. A characteristic feature of this disease is the formation of large osteophytes due to abnormal bone growth. The classical site implicated in DISH is the axial skeleton, however peripheral lesions are often seen. Peripheral entheseal lesions can be seen that are often ossified, with the elbow being commonly involved [35]. Typically, findings are bilateral and symmetric with a distinct cortex. Other common sites involved include the tibial spine, heel, patella, and ligaments of the hip [35].

Osteogenesis imperfecta (OI) are a group of inherited connective tissue disorders that occur due to a defect in collagen synthesis. They can cause a wide range of clinical phenotypes, with some of the most severe features including increased bone fragility that may present as numerous and recurring fractures. OI has significant genetic and clinical heterogeneity, with the predominantly associated mutations often being found on the COL1A1 or COL1A2 genes [36]. However, a subset of OI, OI type V has been found has been found to be predominantly due to a mutation in IFITM5 gene [36]. Clinical symptoms may once again vary widely but in a study of 13 patients with a molecularly confirmed mutation in the IFITM5 gene, 12 presented with interosseus radioulnar membrane ossification of the proximal forearm [36]. Other studies in the literature confirm this is a common clinical finding [37-39]. Other common clinical findings that might point to OI as a diagnosis include teeth brittleness, bluish sclera, hearing loss, long bone deformities, and joint laxity [37].

5.5 Additional Risk Factors

Other risk factors found to be significant by some studies include male gender [12,20,22], and excessive stretching of affected joints [4]. Demographic data such as age and sex also remain a source of debate in the literature, as some studies report no age [12] or other patient related demographic factors to be significantly related to formation of symptomatic HO [20,23].

6. PROPHYLAXIS/TREATMENT

Physicians can take three overarching approaches to HO management and treatment. One is prophylaxis in high risk patients who have not developed HO but may be likely too. Second, to opt for no treatment in patients whose HO formation is minimal, not interfering with daily activity, or causing pain and/or discomfort. The third and most invasive approach would be surgical treatment and resection of HO in patients with advanced bone formation. This approach should be reserved to patients with significantly limited range of motion, neurovascular impediment, and/or pain and discomfort.

6.1 Radiotherapy

Prophylactic treatment can be either radiotherapy or pharmacologic treatment. The accepted approach for radiotherapy currently seems to be 700cGy single-dose radiologic treatment 24 hours preoperatively or within 24-48 hours post operatively [7,14,40-42]. Single dose peri-operative radiation therapy (700cGy) has been reported to reduce HO formation after surgical treatment for elbow fractures [12,40,41,43]. Despite the effective results, these patients are exposed to higher risks of nonunion. Post-operative single radiation therapy was found to potentially play a role in increasing the rate of nonunion at fracture sites [5,44]. Hamid, et al. had to terminate their study prematurely due to the significantly higher rate of nonunion in the radiotherapy group [44]. Other potential risks of radiation at the elbow are adverse skin effects such as ulceration and infection [5]. Physicians that choose to utilize radiotherapy for their high risk HO patients must follow up closely due to these potential adverse effects.

6.2 NSAIDs

NSAIDs offer a cheaper alternative to prophylactic care. This is also a better option for patients who do not want to be exposed to radiation therapy. By reducing inflammation and interfering with BMP pathways, NSAID administration has the potential to interfere with the environment conducive to ectopic bone formation [7]. There are a number of recommendations as to the type and dosing of NSAID therapy. Indomethacin is the most commonly used NSAID that can be prophylactic for complex elbow fracture cases [13]. It is typically administered as an oral dose of 75mg two times per day or 25 mg 3 times per day for 3-6 weeks preoperatively. Indomethacin however can be toxic with cardiac risk, GI bleeding, and reduced fracture healing [7,12,45]. Factors to consider before use are patient's hemodynamic stability and cardiac risk status. These patients may be better candidates for radiotherapy. Other options include COX-2 inhibitors, which have less GI risks. In a retrospective review of 152 patients treated prophylactically with COX-2 inhibitor celecoxib, Sun, et al. found more common and severe cases of HO in the untreated group [46]. Their regimen included celecoxib (200mg) administration daily for 28 days and produced a significant difference.

Surgical treatment of HO should be reserved for the most severe cases since it is in itself a form of soft tissue trauma. Of the various surgical approaches and fixation options, the least invasive and traumatic resection approach should be selected to optimize recovery and decrease recurrence of ectopic bone formation.

7. CONCLUSION

Heterogenic ossification is a relatively common clinical finding and can lead to significant patient burden. The highest incidence of HO seems to be related to degree of severity of acute trauma to the elbow and severity of burn or neurological injuries. The pathological mechanism thought to be implicated is an overactive inflammatory response due to injury, leading to hyperactive growth and resultant ectopic bone formation. The overarching trend seems to follow the higher the level of injury and aggravation to soft tissue, the higher the chance of ectopic bone formation. These patients should be screened for prophylactic therapy to prevent HO. Other than traumatic injury, the literature supports delay to surgery, delay in fixation or stabilization of the elbow, multiple surgical interventions and genetics as significant risk factors for HO bone formation. Physicians are recommended to minimize delay to surgical treatment/stability over 48 hours after elbow trauma to avoid increased risks of HO formation. Furthermore, the least invasive surgical approach that will minimize soft tissue manipulation is also recommended. Imaging modalities such as triple phase bone scans, ultrasound and CT can help detect early HO in high risk patients that are candidates for prophylactic treatment, and measure HO severity before considering prophylaxis and/or surgical treatment.

There seemed to be mixed or very little to no support for other patient demographics such as age and gender. Despite HO being closely related to the inflammatory response, there is little research showing the utility of monitoring serum inflammatory molecules such as ALP, CRP, CK and ERP to predict risks of HO formation.

In regard to prophylaxis, 700cGy seems to be the one of the mainstay prophylactic treatment but has been cited in the literature to be associated with many potential adverse outcomes. NSAIDs are a cheaper alternative. Both therapies however are related to potential increases in fracture healing and present with their own side effect profiles that must be considered on a case by case basis. In high bleed risk patients, radiotherapy may be a better alternative. In hemodynamically stable patients with low cardiac risks and whom may be averse to radiotherapy, NSAIDs offer an effective option.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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