Heterotopic Ossification (HO)

Author(s):	Thomas Kiser	Peer Reviewed:		Finalized:	
Drafted:	3/2/2024	Date:		Published:	

I. Definition, Assessment, Diagnosis

A. Definition.

1. Heterotopic ossification (HO) is a process by which ectopic bone is formed in the soft tissue surrounding peripheral joints[5]. Osteoprogenitor stem cells lying dormant in the surrounding soft tissues with a stimulus (such as hip surgery, spinal cord injury (SCI), traumatic brain injury or stroke) differentiate into osteoblasts and cell lines involved in bone formation. These cells then calcify and form well-organized bone over a several month period.
    a. Studies[13] suggest that ectopic bone formation require three conditions: osteogenic precursors, an inducing agent, and an environment permissive to osteogenesis. There is likely a connection between stimulation of mesenchymal cells followed by osteoprogenitor maturation and osteoblast activation.
    b. Histopathologic studies show normal endochondral osteogenesis at heterotopic sites. They noted six distinct histological stages: (1) perivascular lymphocytic infiltration, (2) lymphocytic migration into soft tissue, (3) reactive fibroproliferation, (4) neovascularity, (5) cartilage formation, and (6) endochondral bone formation. [22]
    c. It is thought genetic predisposition, such as HLA B27, combined with presence of osteoblast stimulating factors and prostaglandins contribute to ectopic formation.[13] Studies show there are increased stimulating factors and osteoblastic activity in animals with SCI.[14]
    d. Though the relationship between central nervous system and bone is not completely understood, neurotransmitters likely have an effect on bone metabolism.
    e. Phagocytic macrophages, rather than osteoclasts, recruited in inflammatory muscle are also thought to be responsible for triggering neurogenic HO development.[9] Targeting phagocytic macrophage recruitment is a promising therapeutic approach to prevent neurogenic heterotopic ossification (NHO).
    f. These results supported the finding that naïve muscle progenitor cells are capable of mineralizing secondary to inappropriate CNS signaling that reprograms progenitor cells to osteogenesis instead of muscle repair.
        i. Risk factors: HO can be either acquired or neurogenic.
        ii. Acquired HO (AHO), which is more common, can occur after any type of musculoskeletal trauma or injury, such as total hip arthroplasty, fractures, burns or hip dislocations.
        iii. NHO is most common in patients with SCI, traumatic brain injury (TBI), and is less common in stroke.

iv. HO is reported to occur in 16-53% of patients after SCI. Most common locations are hip, knee, shoulder, and elbow.
v. Incidence after TBI ranges from 11-28%[5] commonly affected by immobility, spasticity, and fractures. Dysautonomia may also be a risk factor.
vi. One novel study, which explored the role of MicroRNAs (miRNA) in a clinically relevant mouse model, found an osteo-suppressive miRNAs response in injured muscle that was hindered when a spinal cord injury was present. In isolated fibro-adipogenic progenitors from damaged muscle (cells at the origin of ossification), spinal cord injury induced a downregulation of osteo-suppressive miRNAs while osteogenic markers were overexpressed.[i]
vii. Numerous sources have investigated potential factors contributing to development of NHO. A case-control study on patients with traumatic spinal cord injury who developed HO were identified through a database and assessed for signs/symptoms of HO at different time points in time following discharge. Findings showed that patients with complete spinal cord lesions had greatest risk for HO development. The presence of spasticity, thoracic trauma, pneumonia, and nicotine use increased risk for development. There was no correlation between age, sex, race, or length of hospital stay.[6,7]

B. Assessment
   I. Signs and Symptoms
      a. Warmth, swelling, and erythema over a joint.
      b. Fever. This may be the only sign, and can mimic infection.[6,11]
      c. Gradual decrease in joint mobility.
   II. Rule out other causes of symptoms
      a. Vascular System
         i. Deep Vein Thrombosis
      b. Infectious
         i. Cellulitis
         ii. Osteomyelitis
      c. Oncologic
         i. Osteosarcoma
         ii. Osteochondroma

C. Diagnosis
   I. Imaging
      a. Triple phase bone scan is the gold standard for diagnosis of HO as it shows findings earlier than radiographs, but can be negative in the first couple of days in the acute phase of diagnosis.

b. The early stage of HO maturation consists of immature bone not yet detectable by radiographs.[17] It often takes up to 6 weeks for bone to be seen on x-rays.[ii]
c. MRI can be used for the diagnosis of exclusively mature HO, since the signal associated with early HO lesions is heterogeneous. [23]
d. 3D CT scanning[1] offers a more accurate approach for guiding surgical excision of HO. Patients found to have significant HO of the hip following SCI or TBI were scanned and classified based on location; anterior, medial, lateral, posterior, and mixed. Use of 3D imaging was more accurate than classifying NHO based on radiologic findings. Other benefits include proper assessment of neurovascular structures, easier excision in cases of incomplete HO, and decreased risk of iatrogenic injury.
e. Ultrasound may be more specific in differentiating HO from other traumatic, inflammatory, or degenerative diseases of skeleton than bone scan. It has been shown to detect earlier than traditional radiographic studies and like 3D CT, can be used to visualize HO prior to surgical excision.[12] It can also reasonably be used to follow maturation of HO as documented in prior studies.[19] It is used more extensively in Europe, and has good sensitivity but specificity data is lacking. [25]

II. Laboratory Data
a. Alkaline phosphatase (ALP) levels can rise around first 2 weeks of injury in patients who develop HO and may return to baseline values at approximately 10-12 weeks.[2]
b. Although ALP is a nonspecific for osteogenic activity, this inexpensive test may be useful adjunct in diagnosis of early HO.
c. Elevated prostaglandin 24-hour urinary excretion in patients with suspicious symptoms may be helpful when determining need for bone scan.[15]
d. Although nonspecific, Creatinine Kinase (CK) is typically higher in HO SCI patients and often suggests more involvement of surrounding muscle.[16]
e. C-Reactive Protein correlates better with inflammatory activity of HO after SCI than does ESR. ESR was found to remain elevated even when clinical signs and symptoms weren't present.[8]

II. Management and Treatment Recommendations

A. Management and Treatment Recommendations.
I. Recognition of signs, symptoms, and risk factors.
II. Physical examination of joint and interpretation of available imaging and lab values.
III. Obtain appropriate imaging study. Triple phase bone scan should be first line.
IV. Treatment Strategies:

a. If initial bone scan is negative but clinical findings are highly suggestive of HO, NSAIDs such as Indomethacin can be used to down regulate prostaglandins thought responsible for cell differentiation into new bone formation. [4, 24]
b. Prophylactic use of three weeks of indomethacin vs three weeks of placebo in SCI patients showed a significantly lower incidence of HO in treatment group vs placebo, and those in treatment group developed HO significantly later than placebo. [4] NSAID prophylaxis appears to help prevent HO development during the acute phase after SCI. [24]
c. Use of the Bisphosphonate, Etidronate in groups with positive bone scan and negative radiographic findings vs. positive for both imaging modalities. Showed that clinically significant HO can be prevented if treatment started before HO visible on radiographs. Ultimately, no significant difference was found between the two groups in development of HO. [2,3] Etidronate is no longer commercially available in the US market.
d. Alendronate (ALN) use and HO incidence was assessed in a retrospective study in an acute rehab setting. There was no evidence of HO prevention but Significant correlation was found between abnormal serum alkaline phosphatase (ALP) levels and HO appearance ($P < 0.001$) as well as normal serum ALP and ALN intake ($P < 0.05$). This evidence could suggest that ALN may play a role in preventing HO, especially in patients with acute SCI with increasing levels of serum ALP. [20]
e. Radiotherapy can be used as primary or secondary prevention, either in conjunction with surgical excision or prophylactically in patients with severe injuries in whom HO development is high.[12,17] It has been shown to be safe and effective for treatment of HO, but long term follow-up is lacking for late radiation side effects. [26]
f. Botulinum toxin A injected to cause transient muscle paralysis in a mice model of HO mitigated the formation of HO in this model. This may suggest another treatment strategy to manage HO in the acute phase of development. [21]
g. Surgical excision of the HO is done to improve mobility and function. It is typically only performed: if HO interferes with self-care or sitting in wheelchair; or it contributes to development of pressure ulcers, or causes compression of nerves and blood vessels.[17] Previous studies suggested waiting for maturation of heterotopic bone prior to excision. However, recent studies suggested there is no relationship between surgical intervention relative to onset and risk of recurrence. Therefore, HO excision should occur when it begins to be troublesome, as soon as comorbid factors are under control, and the HO is mature with minimal inflammation and is ready for surgical excision.[10]
h. One the major post op risks of surgical HO resection is bleeding and there are several case reports of using embolization of the feeding artery to the HO mass can decrease the risk of bleeding. Preoperative contrast-enhanced three-dimensional CT can show the HO and any supplying

arteries extending to the HO so interventional radiology can perform embolization the day before surgery.[iii]

III. Prevention and Education

A. Potential complications
   I. If HO not addressed and managed in a timely manner multiple problems can develop: loss of joint mobility, decreased range of motion for ADLs and a loss of mobility can result.
      a. Peripheral nerve entrapment
      b. Decreased ROM progressing to ankylosis
      c. If HO overlies bony prominence, this directly predisposes to pressure ulcer/skin breakdown.[12,17]
      d. Exercise and aggressive ROM may exacerbate HO formation, In one study using a genetically modified mouse model susceptible to HO of multiple ligaments those involved in treadmill training had increased formation of HO.[iv]

B. Prevention
   I. Prophylaxis.
      a. Evidence shows that early treatment with NSAIDs in acute SCI reduces the incidence of HO. [24]
      b. Warfarin has been associated with decreased HO and may be beneficial if administered after SCI. More studies are likely needed to validate this conclusion.
      c. Initiation of bisphosphonates such as Etidronate is most effective if initiated early. However, long term use in patients with concomitant bone injures may impair fracture healing. Etidronate is no longer available in the US market and alendronate may be the next best option.
      d. Radiotherapy is thought to halt progression of HO by irradiating mesenchymal pleuripotential cells. Studies show when used as secondary prevention, it may improve joint range of motion and help prevent recurrence.[18]
      e. There may be a functional association between gram-negative bacterial infections and HO development and infection management needs to be managed well to decrease the risk HO development.[v]

C. Education
   I. After diagnosis is confirmed, completion of prescribed medication with a NSAID, and gentle Stretching program to maintain joint range of motion in the joint with HO present. Consider adding alendronate due to low risk and the potential for benefit is recommended to minimize the secondary complications of HO.
   II. Close follow-up with physician is key in management of this condition and prevention of recurrence.
   III. If the HO is limiting function and impairing the quality of life, surgical excision of the heterotopic bone, combined with NSAID's is recommended, the addition of post op radiation of 700-800 cGy can be added if the concern for HO recurrence is very high. This is not used very often due to the long-term risks of radiations side effects, especially in the younger population with a longer life expectancy.

This guideline was developed to improve health care access in Arkansas and to aid health care providers in making decisions about appropriate patient care. The needs of the individual patient, resources available, and limitations unique to the institution or type of practice may warrant variations.

Guideline Developers

Guideline developed by Amanda Price, MD, in collaboration with the TRIUMPH team led by Thomas S. Kiser, MD, and Rani H Lindberg, MD.

Selected References

1. Arduini, M., Mancini, F., Farsetti, P., Piperno, A., & Ippolito, E. (2015). A new classification of peri-articular heterotopic ossification of the hip associated with neurological injury: 3D CT scan assessment and intra-operative findings. *The Bone & Joint Journal, 97-B*(7), 899-904. doi:10.1302/0301-620X.97B7.35031 [doi]
2. Banovac, K., & Gonzalez, F. (1997). Evaluation and management of heterotopic ossification in patients with spinal cord injury. *Spinal Cord, 35*(3), 158-162.
3. Banovac, K., Sherman, A. L., Estores, I. M., & Banovac, F. (2004). Prevention and treatment of heterotopic ossification after spinal cord injury. *The Journal of Spinal Cord Medicine, 27*(4), 376-382.
4. Banovac, K., Williams, J. M., Patrick, L. D., & Haniff, Y. M. (2001). Prevention of heterotopic ossification after spinal cord injury with indomethacin. *Spinal Cord, 39*(7), 370-374. doi:10.1038/sj.sc.3101166 [doi]
5. Braddom, R. (2011). *Physical Medicine and Rehabilitation.* Philadelphia, PA: Elsevier.
6. Citak, M., Grasmucke, D., Salber, J., Cruciger, O., Meindl, R., Schildhauer, T. A., et al. (2015). Heterotopic ossification mimicking infection in patients with traumatic spinal cord injury. Technology and Health Care : Official Journal of the European Society for Engineering and Medicine, doi:THC--1-THC1070 [pii]
7. Citak, M., Suero, E. M., Backhaus, M., Aach, M., Godry, H., Meindl, R., et al. (2012). Risk factors for heterotopic ossification in patients with spinal cord injury: A case-control study of 264 patients. *Spine, 37*(23), 1953-1957. doi:10.1097/BRS.0b013e31825ee81b [doi]
8. Estrores, I. M., Harrington, A., & Banovac, K. (2004). C-reactive protein and erythrocyte sedimentation rate in patients with heterotopic ossification after spinal cord injury. *The Journal of Spinal Cord Medicine, 27*(5), 434-437.
9. Genet, F., Kulina, I., Vaquette, C., Torossian, F., Millard, S., Pettit, A. R., et al. (2015). Neurological heterotopic ossification following spinal cord injury is triggered by

macrophage-mediated inflammation in muscle. *The Journal of Pathology, 236*(2), 229-240. doi:10.1002/path.4519 [doi]

10. Genet, F., Ruet, A., Almangour, W., Gatin, L., Denormandie, P., & Schnitzler, A. (2015). Beliefs relating to recurrence of heterotopic ossification following excision in patients with spinal cord injury: A review. *Spinal Cord, 53*(5), 340-344. doi:10.1038/sc.2015.20 [doi]

11. Lee, J. W., Jo, Y. S., Park, J. S., Kim, J. M., & Kim, S. K. (2015). Heterotopic ossification in a tetraplegic patient with prolonged fever. Journal of Rehabilitation Medicine, 47(7), 669-671. doi:10.2340/16501977-1984 [doi]

12. Ranganathan, K., Loder, S., Agarwal, S., Wong, V. C., Forsberg, J., Davis, T. A., et al. (2015). Heterotopic ossification: Basic-science principles and clinical correlates. *The Journal of Bone and Joint Surgery.American Volume, 97*(13), 1101-1111. doi:10.2106/JBJS.N.01056 [doi]

13. Sakellariou, V. I., Grigoriou, E., Mavrogenis, A. F., Soucacos, P. N., & Papagelopoulos, P. J. (2012). Heterotopic ossification following traumatic brain injury and spinal cord injury: Insight into the etiology and pathophysiology. *Journal of Musculoskeletal & Neuronal Interactions, 12*(4), 230-240.

14. Schurch, B., Capaul, M., Vallotton, M. B., & Rossier, A. B. (1997). Prostaglandin E2 measurements: Their value in the early diagnosis of heterotopic ossification in spinal cord injury patients. *Archives of Physical Medicine and Rehabilitation, 78*(7), 687-691. doi:S0003-9993(97)90074-5 [pii]

15. Shehab, D., Elgazzar, A. H., & Collier, B. D. (2002). Heterotopic ossification*. *Journal of Nuclear Medicine, 43*(3), 346-353.

16. Singh, R. S., Craig, M. C., Katholi, C. R., Jackson, A. B., & Mountz, J. M. (2003). The predictive value of creatine phosphokinase and alkaline phosphatase in identification of heterotopic ossification in patients after spinal cord injury. Archives of physical medicine and rehabilitation, 84(11), 1584-1588.
Chicago

17. Sullivan, M. P., Torres, S. J., Mehta, S., & Ahn, J. (2013). Heterotopic ossification after central nervous system trauma: A current review. *Bone & Joint Research, 2*(3), 51-57. doi:10.1302/2046-3758.23.2000152 [doi]

18. Teasell, R. W., Mehta, S., Aubut, J. L., Ashe, M. C., Sequeira, K., Macaluso, S., et al. (2010). A systematic review of the therapeutic interventions for heterotopic ossification after spinal cord injury. *Spinal Cord, 48*(7), 512-521. doi:10.1038/sc.2009.175 [doi]

19. Yeh, Tian-Shin et al. (2011). Serial Ultrasonography for Early Detection and Follow-up of Heterotopic Ossification in Stroke. *Journal of Medical Ultrasound,* 20 (2), 119-124.

20. Ploumis A , Donovan J , Olurinde MO,, et al. Association between alendronate, serum alkaline phosphatase level, and heterotopic ossification in individuals with spinal cord injury. J Spinal Cord Med 38 (2), 193-8. Mar 2015. PMID 24820653.

21. Ausk BJ, Gross TS, Bain SD. Botulinum Toxin-induced Muscle Paralysis Inhibits Heterotopic Bone Formation. Clin Orthop Relat Res (2015) 473:2825–2830.

22. Foley KL, Hebelab N, Keenan MA, Pignolod RJ. Histopathology of Periarticular Non-Hereditary Heterotopic Ossification. Bone 109, 65-70. Apr 2018. PMID 29225159.

23. Dey D, Wheatley BM, Cholok D, et al. The traumatic bone: trauma-induced heterotopic ossification. Transl Res. 2017 August ; 186: 95–111.

24. Zakrasek EC, Yurkiewicz SM, Dirlikov B, et al. Use of Nonsteroidal Anti-Inflammatory Drugs to Prevent Heterotopic Ossification After Spinal Cord Injury: A Retrospective Chart Review. Spinal Cord 57 (3), 214-220. Mar 2019. PMID 30254206.

25. Rosteius T, Suero EM, Grasmücke D, et al. The sensitivity of ultrasound screening examination in detecting heterotopic ossification following spinal cord injury. Spinal Cord (2017) 55, 71–73.

26. Müseler AC, Grasmücke D, Jansen O, et al. In-hospital outcomes following single-dose radiation therapy in the treatment of heterotopic ossification of the hip following spinal cord injury—an analysis of 444 cases. Spinal Cord (2017) 55, 244–246.

---

[i] Gueguen J, Girard D, Rival B, Fernandez J, Goriot ME and Banzet S. Spinal cord injury dysregulates fibro-adipogenic progenitors miRNAs signaling to promote neurogenic heterotopic ossifications. COMMUNICATIONS BIOLOGY | (2023) 6:932 | https://doi.org/10.1038/s42003-023-05316-w.

[ii] Sun E, Hanyu-Deutmeyer AA. Heterotopic Ossification. 2023 Jul 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 30085571.

[iii] Takahiro Igei, Satoshi Nakasone, Masato Ishihara, Masamichi Onaga, Kotaro Nishida. Embolization followed by resection of the heterotopic hip joint ossification with spinal cord injury. Journal of Orthopaedic Science 29 (2024) 454e457. doi.org/10.1016/j.jos.2022.10.006.

[iv] Zhu Z, He Z, Tang T, Wang F, Chen H, Zhou J, Lin C, Chen G, Wang J, Li J, Liu X, Zhou Z and Liu S (2023), Effect of mechanical stimulation on tissue heterotopic ossification: an in vivo experimental study. Front. Physiol. 14:1225898. doi: 10.3389/fphys.2023.1225898

[v] Salga , M, Samuel , SG[4], Tseng , HW, Gatin L, et al. Bacterial Lipopolysaccharides Exacerbate Neurogenic Heterotopic Ossification Development. J Bone Miner Res. 2023 Nov;38(11):1700-1717. doi: 10.1002/jbmr.4905. Epub 2023 Sep 23.