Review Article

HETEROTOPIC OSSIFICATION IN CRITICAL ILL PATIENTS : A Review

Anna Christakou [1*], Maria Alimatiri [2], Alexsandros Kouvarakos [3], Emmanuel Papadopoulos [4], Irini Patsaki [5], Anastasia Kotanidou [6] & Serafeim Nanas [7].

[1*]Physiotherapist, M.Sc., Ph.D., General Hospital "Evagelismos", First Critical Care Department, University of Athens, Greece.

[2, 3]Physiotherapist, General Hospital "Evagelismos", First Critical Care Department, University of Athens, Greece.

[4]Physiotherapist, M.Sc., Ph.D., General Hospital "Evagelismos", First Critical Care Department, University of Athens, Greece

[5]Physiotherapist, M.Sc., General Hospital "Evagelismos", First Critical Care Department, University of Athens, Greece.

[6]Professor, M.D. "Evagelismos" Athens General Hospital, First Critical Care Department, Athens, Greece.

[7]Professor, M.D. "Evagelismos" Athens General Hospital, First Critical Care Department, Athens, Greece.

ABSTRACT

Background of the study: Heterotopic ossification is a bone formation in soft tissues around large joints. It is a serious complication affecting critical ill patients following central nervous system disorders, multiple injuries (e.g., neurological and orthopedic injuries), severe respiratory diseases (e.g., ARDS), and burns. It can have long-lasting effects on patient's recovery, functional status and quality of life. The present review examines the incidence, clinical symptoms, pathophysiology, risk factors, diagnostic methods, classification of HO in intensive critical care unit setting. Also, physiotherapy as prophylaxis and treatment modality in HO management will be reviewed, providing future recommendations.

KEY WORDS: HETEROTOPIC OSSIFICATION, INTENSIVE CARE UNIT.

Address for correspondence: Christakou Anna, PT., M.Sc., Ph.D., Bachelor in Physical Education and Sports Science, General Hospital "Evagelismos", First Critical Care Department, Medical School, National and Kapodistrian University of Athens. **Email:** achristakou@phed.uoa.gr

Access this Article online

Quick Response code

International Journal of Physiotherapy and Research
ISSN 2321- 1822
www.ijmhr.org/ijpr.html

Received: 24 July 2013 Accepted: 10 September 2013
Peer Review: 24 July 2013 Published: 11 October 2013

INTRODUCTION

Heterotopic ossification (HO) is a true osteoblastic activity and abnormal formation of mature lamellar bone within extra-skeletal soft tissues where bone does not normally exist.[1] It is characterized by proliferation of fibrous tissue and by formation of new bone with cartilage. The lesions may occur on the external surface of a bone or in soft tissues at a distance from the periosteal surface.[2] HO has been classified as post-traumatic, non traumatic or neurogenic, and myositis or fibrodysplasia ossificans progressive.[1]

In intensive care unit (ICU), HO appeared in traumatic brain injury[3,4], in spinal cord injury[5], in ARDS[6], in pancreatitis[7], in Guillain-Barré Syndrome[8] and in burn injuries.[9] The most common clinical findings are a decreased joint range of motion, a peri-articular swelling due to edema of the soft tissues and pain in the affected area.[10]

The progression of HO may lead to severe anchylosis of the joint which has a negative impact on patient's rehabil-itation process. In particular, severe reduction of lower extremities joints movement may lead to loss of an adequate walking and sitting position and also compromise transfers and activities of daily living. Thus, HO expects to provoke long-lasting morbidity in critical ill patients during ICU stay and after ICU discharge, impairing basic daily activities, such as walking, standing and sitting.[11] Due to the great importance of the functional status and quality of life during and after the ICU stay, HO's pathophysiology, early detection and high risk factors are necessary to be thoroughly investigated. Also, therapists' concern is the primary care of patient during HO's therapy management.

Accordingly, the purpose of the present review is to examine the incidence, clinical symptoms, pathophysiology, risk factors, diagnostic modalities, classification, and physiotherapeutic approach of HO in ICU setting. We performed a computerized search of English-language publications listed in the electronic databases of PubMed up to March 2013. We also hand searched bibliographies of retrieved articles to identify additional potentially relevant articles.

INCIDENCE AND CLINICAL SYMPTOMS

HO is a frequent complication after central nervous system damage as well as in patients with long staying in ICU. The incidence of HO in patients that are mechanically ventilated with traumatic brain injury is referred about 13% [3,4] and 20% after spinal cord injury.[5] There is a report of 5% incidence of HO in survivors of ARDS 6. HO after burns have low incidence of .15%, from which the 75% of the patients had been admitted to ICU and 50% had received mechanical ventilator support[9]. The incidence of HO in peripheral nervous system disorders as Guillain-Barré Syndrome comes up to 6%.[8]

This pathological situation is expected to occupy more than one joints referred as multi-site HO with a percentage presented with a bilateral symmetry.[12,13] HO due to neurological insult seems to influence more frequently the hip joint with large repercussions on functional ability, such as the ability to sit, walk and stand.[5,12,13] Elbow joint has higher incidence in HO after burn injury.[9]

The development of HO leads to a functional deficit, resulting in longer rehabilitation length of stay, and lower functional scores in kinetic activities and quality of life.[6,8] The early clinical symptoms of HO in the inflammatory stage are swelling, erythema, and warmth of the affected joint.[10] In particular, the first two clinical signs which become apparent are the limitation of joint's range of motion and pain, if there is sensory and consciousness background. These signs will be apparent within the first 2 months of injury or surgery, but may be revealed one year after the insult.[14] There is also referred a sign of locking at the end of the join's motion which remind the bony end-feel by Cyriax.[9] Our findings are consistent with the current literature, i.e., the passive range of motion of hip and elbow in two of 20 patients with HO had been reduced statistically significant, while the pain of hip and elbow was significantly increased.[15]

PATHOPHYSIOLOGY

According to Chalmers et al[16] it is necessary the mediation of three conditions in bone formation: the (a) osteogenic precursor cells, such as apparently exists in muscle or fascia, (b) inducing agents, stimulus, such as decalcified bone and the (c) permissive environment which is favorable to osteogenesis.

The pathophysiology of HO is still not completely understood. However, humoral, neural and local factors may all contribute to the pathophysiology of HO. [17] Firstly; humoral factors may play a role in the osteo-inductive process. An osteo-inductive protein released could be identified from the demineralized bone tissue concerning the in vitro induction of ectopic bone. Bone morphogenic protein (BMP) is named this factor.[18] It is, therefore, possible that bone resorption and collagen degradation in neurological patients may well release osteo-inductive factors. Secondly, the neural influence on neurogenic HO (NHO) development cannot be disregarded taking into account its high incidence in neurologic disorders. For example, in spinal cord injuries, damage to the intermedio-lateral sympathetic columns of the traumatized

spinal cord might predispose to NHO through autonomic dysregulation. Also, metabolic and vascular changes may occur. The initial stage of NHO is characterized by local micro vascular alterations, such as an increased vascularity, venous hemostasis and arterio-venous shunting in the involved tissues. These modifications in the blood perfusion and oxygen levels of the soft tissues might be important factors in the appearance of NHO.[19] Thirdly, the local factors, which have a vital role in HO's development, are venous thrombosis or hemostasis, (local) infection, decubitus ulcers and (micro) trauma. These factors may lead to tissue damage and inflammatory reactions provoking edema and tissue hypoxia and may predispose to ectopic bone formation either by providing a permissive environment or by releasing humoral factors through the inflammatory process.

HO can occur through either intramembranous without a cartilage precursor or endochondral through a cartilage precursor mechanism.[20] Stem cells become abnormally activated to form bone. With muscle satellite cells, bone marrow-derived stromal cells, fibroblasts and adipose-derived stromal cells have been the most commonly investigated tissue source for identification of the cellular origin implicating to HO's process. Adipocytes seem to have been contributing in the formation of HO through inducing tissue hypoxia.[20] Mesenchymal stem cells are traditionally considered to be the primary cell type involved in HO, although distinct populations of skeletal muscle-derived stem cells and migrated osteoblastic cells may further play an important role.[21] More investigation into the identification of putative osteogenic factors that enter the systemic circulation, using human tissues and new techniques, is proposed.[22]

RISK FACTORS

Neuromuscular blockage interfering has an important role in the occurrence of HO in patient with ARDS, referring it as pharmacologically paralysis, which could be in parallel with damage in the central nervous system.[23,24] Goodman et al[23] reported that neuromuscular blocking agents are important risk factor for the development of HO in 6 cases of ARDS patients. Also, Dellestable et al[25] found that the duration of sedation is a potential risk factor for the development of HO to 5 ICU patients with ARDS who did not be treated with neuromuscular blocking agents. Similarly, Sagita et al[26] reported a case of development of HO on bilateral hips and knees in terms of prolong sedation. All of the aforementioned studies are case reports without performing valid statistical analysis. There is no current large prospective multivariable study to support that either neuromuscular blocking agents or sedation are risk factors for the development of HO in critical ill patients.

Immobilization has been referred in several articles as a potential risk factor for the development of HO.[9,27] Immobilization in ICU patients has been linked with disuse atrophy, pro-inflammatory state and muscle loss which could lead to prolong ICU stay and mechanical ventilation.[28] This pro-inflammatory stage of immobilization is a permissive environment for HO. Inflammation subsequent to trauma or burn leading to edema and tissue hypoxia is referred to play a significant role in ectopic bone formation.[17,20] Future research should investigate which is the inflammatory profile of patients that finally develop HO, as inflammatory have been shown to be necessary in HO formation and can also lead to bone damage and desorption.[20] However, van Kampen et al[4] did not found significant predictive value of immobilization period and HO formation in ICU patients with severe traumatic brain injury, maybe, due to the small sample size of their study. Furthermore, after a period of immobilization, micro-traumatism due to aggressive mobilization is a possible mechanism where passive movements shear and tear soft tissues provoking the development of HO.[19]

Another factor widely discussed to contribute in HO triggering is mechanical ventilation.[3,4,8,29,30] Newman et al[31] suggested that respiratory artificial hyperventilation in severe head injured patients, in terms of reducing intracranial pressure or the independent hyperventilation, could lead to a respiratory alkalosis, consequently to a pH alteration; thus, change of the precipitation kinetics of calcium and phosphate salts, leading to accelerate fracture union.

Hendricks et al[3] found that those patients with brain injury who developed HO had been in mechanical ventilation longer than those who have not developed (22.33±13.47 days versus 7.25±7.78 days, z =3.68, p<0.001). Also, van Kampen et al[4] reported statistically significant longer period in mechanical ventilation in patients who develop HO than those who did not develop (M= 16.5 days versus 6.87 days, z=-3.05, p=0.002). Future studies with larger sample size may confirm the relationship of mechanical ventilation and HO and to investigate the exact mechanism of their interrelationship in developing HO.

The coma duration and the severity of injury have also been reported as risk factors for the development of HO.[3,4] Hendricks et al[3] found that patients with HO sustained more severe brain injuries as this determined by coma duration, days of mechanical ventilation, diffuse axonal injury and spasticity. Also, Simonsen et al[32] reported significant positive correlation between HO and Injury Severity Score. More research needs to confirm the importance of these risk factors in HO's occurrence.

Autonomic dysregulation is referred as a possible mechanism in the occurrence of HO in spinal cord injury patients.[17] Hendricks et al[3] and van Kampen et al[4] reported strong relationship between autonomic dysregulation and HO in traumatic brain injury. Chauveau et al[33] suggested an association between hypothalamic leptin signaling and brain injury related HO. Although the causal mechanism between autonomic dysregulation and development of heterotopic bone formation has not yet been confirmed, autonomic nervous system may have an important regulating role in bone formation in traumatic brain injury patients.

Other risk factors which have been investigated in HO's development are the complete spinal lesion[5,34,35], the pressure ulcers [34,35] and the spasticity.[5,34] Also, urinary tract and respiratory infections have been observed before and after HO's development due to metabolic changes and the release of inflammatory mediators.[5,35] In particular, according to Citak et al[5] the inflammatory processes seem to be of great importance. The aforementioned authors found association of HO and pneumonia, thoracic trauma, necessity of tracheostomy and nicotine abuse; factors that linked with lung inflammatory reaction. Furthermore, there is higher incidence of HO in those patients with greater total body burn surface area at approximately 40%.[9] At last, HO have been referred to dominate in male gender and young age [7,13] due to higher repercussion of trauma in males.[7]

DIAGNOSIS AND CLASSIFICATION

Radiography is a fast, cheap modality and it contributes to confirm clinically a suspected HO. Radiographs allow detection of HO approximately 4–5 weeks after the initial neurological trauma.[13] Magnetic Resonance Imaging (MRI) has been used in early diagnosis of HO in critically ill patients. Positive MRI findings appeared simultaneously with clinical signs (1.4±1.2 days following clinical diagnosis), whereas X-ray diagnosis was evident at 23±4.3 days. However, there were risks of transporting critical ill patients and the cost of this method poses limitations for more extensive use.[29] Also, there is low specificity of MRI in the initial stages of HO.[10,36] The bedside ultrasonography (US) is a safe, cheap and useful tool in diagnosis of NHO. It detects HO sooner than does conventional radiography.[37,38] It is the best investigative modality not only for the early identification, but also for the follow-up of HO. It has high sensitivity and specificity for the early diagnosis of HO 1 week after total hip arthroplasty.[39] Also, Thomas et al[40] were able to identify nearly 80% of the patients 1 week following surgery who would suffer from HO 2 weeks later. Thus, ultrasound might play an essential role in the early detection of HO, thus adapt or initiate prophylactic treatment. However, US have strongly been associated with the operator's expertise.[13,17]

The most widely used classification system is still the one developed by Brooker et al[41] which referred to the HO of hip joint in patient underwent total hip arthroplasty. This was based on anteroposterior roentgenogram findings 6 months postoperatively.

In Brooker's classification there are four classes, namely Class I represents islands of bone within the soft tissues about the hip to Class IV the apparent bone ankylosis of the joint which has functional impact. The major limitation of this classification is that it is referred to post-traumatic ossification and not to NHO. Recently, Mavrogenis et al[42] develop a method of classification according to the mechanism of neurological injury (spinal cord injury or brain injury) and the location of HO presented in axial computed tomography (anterior, posterior, anterior, medial circumferential). This classification tries to guide the surgical approach and estimates the prognosis regarding the blood loss, transfusion requirements and recurrence of neurogenic HO. Another general system of classification is the modified radiological and functional GCG-BD classification of HO formation referred in all joints.[43] The GCG-BD classification (Table 1) allows integration of any imaging method and taking into account functional deficits and clinical symptoms by adopting the four classes of Brooker's classification. Genet et al[44] reported a strong correlation between GCG-BD and Brooker's classification method.

Class I	1-3 islands of bone within the soft tissues %2cm; no functional deficit or symptoms of the involved joint or body segment
Class II	>3 islands of bone within the soft tissues or at least one >2cm; no or minor functional deficit or symptoms of involved joint or body segment
Class III	Class II definition related to number and size of bone islands, but major functional deficit or symptoms of involved joint or body segment
Class IV	Class II definition related to number and size of bone islands, But complete functional loss or severe symptoms of involved joint or body segment

Table 1. Modified radiological and functional GCG-BD classification of HO (Seegenschmiedt et al[43]).

PHYSIOTHERAPEUTIC PROPHYLAXIS AND TREATMENT

According to the literature there are three methods of prophylaxis and treatment for NHO:
(a) The pharmacological (i.e.,NSAID, Disphosphonates)
(b) The non-pharmacological (i.e., pulse low intensity electromagnetic field therapy, radiotherapy, passive range motion therapy, surgical excision), and
(c) The combination of the above two aforementioned methods.[45]

Regarding the non-pharmacological methods, Michelsson et al[46] used forceful daily manipulation to induce heterotopic bone formation in soft tissues of rabbits of an immobilized knee joint. Moreta-Suarez et al[47] in a case report of 2 patients with NHO recommended early starting of range of motion exercises while patient is still in the ICU as a preventive method. Also, early mobilization is recommended after a surgery of HO excision for preventing recurrence of HO.[9,48,49] In particular, continuous passive motion (CPM) machine have been used within the pain free range of motion early after a surgery of excision of HO to avoid recurrence of HO in the site of surgery.[9,49] Ippollito et al[49] resected ossification in 7 knee joints of 5 traumatic brain injury patients at an average of 23 month's post-comatose. Before surgery, patients had a fixed flexed position, walking disability and painful arc of motion. After surgery, there was a marked improvement of range of motion in all patients. Patients followed a program of 6 week CPM before full rehabilitation program to preserve this improvement and keep safe of a recurrent ossification. At average of 34 months follow up, all patients could walk, the joints were pain-free and no recurrence of HO occurred. Furthermore, Chen et al[9] reported that 12 patients with HO at the elbow joint due to a burn injury had been under surgical excision of HO. Patients started the first postoperative day with gentle passive physical therapy or CPM machine and active range of motion (ROM) exercises within the pain free range of motion. The mean ROM before and after surgery were 31±27° and 99±15°, respectively. At the follow up time, particularly 14±12 months after, only one joint from the 12 developed HO again. They concluded that early surgical excision that combined with gentle physical therapy had a satisfactory result. In another study, Meiners et al[50] examined 29 spinal cord injury patients who had been under resection of HO in 41 hip joints. All patients underwent irradiation the first post-operative day. Continuous passive motion exercises began the 15th post-operative day to achieve suitable flexion.

The range of motion increased from 21.95° preoperatively to 94.51° intra-operatively and to 82.68° at 4 years follow-up. Recently, Aubut et al[44] in their systematic review supported that combined treatment of surgical excision with post-operative passive ROM exercises in traumatic brain injury patients, and combined surgical excision, radiotherapy and passive ROM in spinal cord injury patients improve ROM of the joint.

CPM machine or physical therapy program have been used not only for prevention of HO and/or prevention of HO recurrence, but also to treat HO when is already present in the joint. Van Susante et al[51] attempted to test the hypothesis that CPM adversely stimulates the development and progression of HO by performing an experiment in rabbits. The rabbits after 3 weeks of immobilization and daily 5-minute forceful manipulation develop HO, according to Michelson et al.'s[45] experimental animal model study for inducing HO due to muscle injury. Then, the animals was separated in two groups, the CPM group (mobilization every 45min /24h daily for 2 weeks) and the control group (free to move in cages). The results showed that there was no progression of HO of initial grade in both groups at the end of 2 week period. They concluded that CPM did not stimulate the development or progression of HO. Linan et al[52], in a case report, applied a CPM machine in both knees with HO in a patient with traumatic brain injury combined with conventional physical therapy and painkiller drug treatment for 4 weeks. The ROM of the knees improved from 10-25° to approximately 80° in both knees. Additionally, Casavat et al[53] described a therapeutic program of a traumatic elbow injury and supported that even in HO presence, active and passive ROM exercises should be continued to maximize the join's range of motion and prevent functional deficits. In a case report, Knight et al[54] examined three different physiotherapeutic approaches in patients with NHO according to individual rehabilitation program. They referred to the usage of techniques like casting, proprioceptive neuromuscular facilitation, therapeutic positioning to reduce abnormalities of the neuromuscular system, like altered tone and to maximize the functional outcome of HO's surgery. They found an increase in patient's functional potentials. Ferreira et al[55] evaluated the impact of neuromuscular electric stimulation as an additional therapeutic option, aiming the reversion (regression or development halt) of HO of six tetraplegic patients in the hip joint. The results revealed no progression of HO on X-ray images noted in 4 of the patients with steady clinical picture and improvements on X-ray images in 2 patients after 16.6 months of treatment. In the aforementioned study, they were not reported whereas the X-ray image improvement was also accompanied with clinical improvement. The effectiveness of physiotherapy to heterotopic bone formation has not been confirmed widely, therefore there is a need to further examining the appropriate time starting exercising before a HO surgery or when HO is already present.

Synopsis

Heterotopic ossification is a pathologic condition with a high incidence in critical ill patients. It is also expected to lead in severe functional limitation of those patients in ICU. Although the precise pathophysiology of HO is still unknown; humoral, neural and local factors probably all play a role in the formation of ectopic bone. The diagnosis of HO is primarily based on clinical signs and likelihood. The first clinical signs of HO's development are a reduction in joints' range of motion, edema and pain. Different classification systems of heterotopic ossifications were developed, up to date; Brooker's system is the most commonly used around the hip joint. Studies have used physiotherapy as a prophylaxis and a treatment method of HO. Further research should confirm the prevention of HO's development using physiotherapeutic prophylactic modalities as range of motion exercises, radiotherapy, and electrical stimulation in orthopedic and neurological patients in an ICU setting. Future experiments should assess the above physiotherapy methods as treatment modalities in critical ill patients due to its advantage to be a non-invasive approach.

Conflits of Interest: None

REFERENCES

1. Garland DE. A clinical perspective on common forms of acquired heterotopic ossification. Clin Orthop Relat Res 1991;263:13–29.
2. Schajowicz F. Histological typing of bone tumours. Springer; 1993.
3. Hendricks HT, Geurts A, Van Ginneken B, Heeren A, Vos PE. Brain injury severity and autonomic dysregulation accurately predict heterotopic ossification in patients with traumatic brain injury. Clinical Rehabil 2007;21:545-553.
4. van Kampen PJ, Martina JD, Vos PE, Hoedemaekers CWE, Hendricks HT. Potential risk factors for developing heterotopic ossification in patients with severe traumatic brain injury. J Head Trauma Rehabil 2011;26(5):384–391.
5. Citak M, Suero ME, Backhaus M, Aach M, Gordy H, Meindl R, Schildhauer AT. Risk factors for heterotopic ossification in patients with spinal cord injury. A case control study of 264 patients. Spine 2012;37(23):1953-1957.
6. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F. et al. One-Year Outcomes in Survivors of Acute Respiratory Distress Syndrome. N Engl J Med 2003;348(8):683-693.
7. Mitsionis GI, Lykissas MG, Kalos N, Paschos N, Beris AE, Georgoulis AD et al. Functional outcome after excision of heterotopic ossification about the knee in ICU patients. International Orthop 2009;33:1619-1625.
8. Zeilig G, Weingarden HP, Levy R, Peer I, Ohry A, Blumen N. Heterotopic ossification in Guillain-Barré Syndrome: incidence and effects on functional outcome with long-term follow-up. Arch Phys Med Rehabil 2006;87:92-95
9. Chen HC, Yang JY, Chuang SS, Huang CY, Yang SY. Heterotopic ossification in burns: Our experience and literature reviews. Burns 2009;35:857-862
10. Choi YH, Kim KE, Lim SH, Lim JY. Early presentation of heterotopic ossification mimicking pyomyositis-Two case reports. Ann Rehabil Med 2012;36(5):713-718.
11. Griffiths JA, Gager M, Waldmann C. Follow–up after intensive care. Cont Educ Anaest 2004;4(6):202-205.
12. Genet F, Jourdan C, Lautridou C, Chehensse C, Minooee K, Denormandie P et al. The impact of preoperative hip heterotopic ossification extent on recurrence in patients with head and spinal cord injury: A case control study. PLoS One 2011;6(8):e23129.
13. Seipel R, Langner S, Platz T, Lippa M, Kuehn JP, Hosten N. Neurogenic heterotopic ossification: Epidemiology and morphology on conventional radiographs in an early neurological rehabilitation population. Skel Radiology 2012;41:61-66.
14. Hsu JE, Keenan MA. Current review of heterotopic ossification. University of Pennsylvania Orthopaedic Journal. 2010; 20: 126-130.
15. Christakou A, Alimatiri M, Patsaki E, Kouvarakos A, Papadopoulos M, Stefanidis K et al. Epidemiology and early diagnosis of heterotopic ossification in critical ill patients. Preliminary data. Poster session presented at: 25th Annual Congress of European Society Intensive Care Medicine LIVES 2012 October 13-17 Lisbon. Portugal.
16. Chalmers J, Gray OH, Rush J. Observation on the induction of bone formation in soft tissues. J Bone Joint Surg Br 1975;57;36-45.
17. van Kuijk AA, Geurts ACH, Van Kuppevelt HJM. Neurogenic heterotopic ossification in spinal cord injury. Spinal Cord 2002;40:313-326.
18. Sawyer JR, Myers MA, Rosier RN, Puzas JE. Heterotopic ossification. Clinical cellular aspects. Calcif Tissue Int 1991;49: 208 - 215.
19. Lotta S, Scelsi L, Scelsi R. Microvascular changes in the lower extremities of paraplegics with heterotopic ossification. Spinal Cord 2001;39:595-598.
20. Nelson ER, Wong VW, Krebsbach PH, Wang SC, Levi B. Heterotopic Ossification Following Burn Injury: The role of stem cells. J Burn Care & Research 2012;33(4):463-470.
21. Eghbali-Fatourechi GZ, Lamsam J, Fraser D, Nagel D, Riggs BL, Khosla S. Circulating osteoblast-lineage cells in humans. New England J Med. 2005;352: 1959–1966.
22. Toffoli AM, Gautschi OP, Frey SP, Filgueira L, Zellweger R. From brain to bone: Evidence for realese of osteogenichumoral factors after traumatic brain injury. Brain Injury 2008;22(7-8):511-518.
23. Goodman TA, Merkel PA, Perlmutter G, Doyle MK, Krane SM, Pollison RP. Heterotopic ossification in the setting of neuromuscular blockade. Arthritis & Rheum 1997;40(9);1619-1627.
24. Guo Y, Collaco CR, Bruera E. Heterotopic ossification in critical illness and cancer: A report of 2 cases. Arch Phys Med Rehabil 2002;83:855-9.
25. Dellestable F, Voltz C, Mariot J, Perrier JF, Gaucher A. Heterotopic ossification complicating long-term sedation. Br J Rheumatol 1996;35:700-1.
26. Sugita A, Hashimoto J, Maeda A, Kobayashi J, Hirao M, Masuhara K et al. Heterotopic ossification in bilateral knee and hip joints after long-term sedation. J Bone Miner Metab 2005;23:329-332
27. Lane JE, Dean RJ, Foulkes GD et al: Idiopathic heterotopic ossification in the intensive care setting. Postgrad Med J 2002; 78: 494-495.
28. Truong AD, Fan E, Brower RG, Needham DM. Bench-to-bed review: Mobilizing patients in the intensive care unit-from pathophysiology to clinical trials. Critical Care 2009;13(4):216.
29. Argyropoulou MI, Kostandi E, Kosta P, Zikou AK, Kastani D, Galiatsou E. et al. Heterotopic ossification of knee joint in intensive care unit patients: early diagnosis with magnetic resonance imaging. Critical Care 2006;10(5): R152.

30. Sakellariou VI, Grigoriou E, Mavrogenis AF, Soucacos PN, Papagelopoulos PJ. Heterotopic ossification following traumatic brain injury: insight into the etiology and pathophysiology. J Musculoskelet Neuron Interact 2012;12(4):230-240.
31. Newman R, Stone MH, Mukherjee SK. Accelerated fracture union in association with severe head injury. Injury 1987;18:241-246.
32. Simonsen LL, Sonne-Holm S, Krasheninikoff M, Engberg AW. Symptomatic heterotopic ossification after very severe traumatic brain injury in 114 patients: incidence and risk factors. Injury. 2007; 38(10):1146–1150.
33. Chauveau C, Devedjian JC, Delecourt C, Jeanfils J, Hardouin P, Broux O. Leptin receptors and â2-adrenergic receptor m RNA expression in brain injury-related heterotopic ossification. J Receptors Signal Transd 2008;28:347-359.
34. Bravo-Payno P, Esclarin A, Arzoz T, Arroyo O, Labarta C. Incidence and risk factors in the appearance of heterotopic ossification in spinal cord injury. Paraplegia 1992;30:740-745.
35. Wittenberg RH, Peschke U, Botel U. Heterotopic ossification after spinal cord injury. J Bone Join Surg1992;74-B:215-218.
36. van den Bossche L, Vanderstraeten G. Heterotopic ossification: A Review. J Rehabil Med 2005;37:129-136.
37. Falsetti P, Acciai C, Lenzi L. Sonographic diagnosis of neurogenic heterotopic ossification in patients with severe acquired brain injury in neurorehabilitation unit. J Clin Ultrasound 2011;39:12-17.
38. Snoecx M, De Muynck M, Van Laere M. Association between muscle trauma and heterotopic ossification in spinal cord injured patients: reflections on their causal relationship and the diagnostic value of ultrasonography. Spinal Cord 1996;34: 499–500.
39. Popken F, Konig DP, Tantow M, Rutt J, Kausch T, Peters KM. Possibility of sonographic early diagnosis of heterotopic ossification after total hip-replacement. Unfallchirurg 2003;106: 28–31.
40. Thomas EA, Cassar-Pullicino VN, McCall IW. The role of ultrasound in the early diagnosis and management of heterotopic bone formation. Clin Radiol 1991;43:190–196.
41. Brooker AF, Bowerman JW, Robinson RA, Riley LH. Ectopic ossification following total hip replacement: Incidence and a method of classification. J Bone Joint Surg Am 1973;55-A(8):1629-1632.
42. Mavrogenis FA, Guerra G, Staals L.E, Bianchi G, Ruggieri P. A classification method for neurogenic heterotopic ossification of the hip. J Orthop Traumatology 2012; 13(2):69-78.
43. Seegenschmiedt MM, Heyd R. Heterotopic ossifications: general survey for all sites. Medical Radiology, Radiother Non-Malignant Dis 2008; 3:333-335.
44. Genet F, Jourdan C, Schnitzler A, Lautridou C, Guillemot D, Judet T et al. Troublesome heterotopic ossification after central nervous system damage: A survey of 570 surgeries. PLoS ONE 2011,6(1):e16632.
45. Aubut JAL, Mehta S, Cullen N, Teasell RW. A comparison of heterotopic ossification treatment within the traumatic brain and spinal cord injured population: An evidence based systematic review. Neurorehabil 2011;28:151-160.
46. Michelsson JE, Rauschning W. Pathogenesis of experimental heterotopic bone formation following temporary forcible exercising of immobilized limbs. Clinic Orthop Related Research 1983;176:265-272.
47. Moreta-Suarez J, De Ugarte-Sobron OS, De Los Mozos M. Neurogenic heterotopic ossification of the hip. Presentation of two cases. Revespcirortop Ôraumato. 2011;55(4):292-297.
48. Ellerin BE, Helfet D, Parikh S, Hotchkiss RN, Levin N, Nisce L et al. Current therapy in the management of heterotopic ossification of the elbow: a review with case studies. Am J Phys Med Rehabil 1999;78(3):259-271.
49. Ippolito E, Formisano R, Farsetti P, Carterini R, Penta F. Excision for the treatment of periarticular ossification of the knee in patients who have a traumatic brain injury. J Bone Joint Surgery 1999;81-A(6).
50. Meiners T, Abel R, Bohm V, Gerner HJ. Resection of heterotopic ossification of the hip in the spinal cord injured patients. Spinal Cord 1997;35:443-445.
51. van Susante JLC, Buma P, Kim HKW, Salter RB. Traumatic heterotopic bone formation in quadriceps muscle. No progression by continuous passive motion in rabbits. Acta Orthop Scand 1996;67(5):450-454.
52. Linan E, O'Dell MW, Pierce JM. Continuous passive motion in the management of heterotopic ossification in a brain injured patient. Am J Phys Med Rehabil 2001;80(8):614-617.
53. Casavant AM, Hastings H. Heterotopic ossification about the elbow: A therapist's guide to evaluation and management. J Hand Therapy 2006;19(2):255-267.
54. Knight LA, Thornton HA, Turner-Stokes L. Management of neurogenic heterotopic ossification. Three case histories to illustrate the role of physiotherapy. Physiotherapy 2003;89(8):471-477.
55. Ferreira DBJ, Lippelt HC, Junior AC. Neuromuscular electric stimulation in heterotopic ossification regression. Acta Orthop Bras 2006;14(2):72-74.

How to cite this article: Anna Christakou, Maria Alimatiri, Alexsandros Kouvarakos, Emmanuel Papadopoulos, Irini Patsaki, Anastasia Kotanidou & Serafeim Nanas. Heterotopic Ossification in Critical ill Patients:A Review. Int J Physiother Res 2013;04:188-95.