

Heterotopic Ossification: Cellular Basis, Symptoms, and Treatment

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A Senior Thesis submitted in partial fulfillment
of the requirements for graduation
in the Honors Program
Liberty University
Spring 2012

Acceptance of Senior Honors Thesis

This Senior Honors Thesis is accepted in partial fulfillment of the requirements for graduation from the Honors Program of Liberty University.

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Abstract

Heterotopic ossification (HO) is the process by which calcified bone develops in soft tissues. Because of the abnormal calcification, complications such as bone deformation, loss of range of motion, and joint immobility adversely affect patients. There are many genetic types of heterotopic ossification, namely fibrodysplasia ossificans progressiva, progressive osseous heteroplasia, and Albright hereditary osteodystrophy. However, this condition can also arise from surgery, burns, or traumatic injuries, so it is seen as an important area for research in the future. There are various treatments available such as non-steroidal anti-inflammatory drugs and radiation therapy, as well as combinations of the two. The molecular basis of HO is currently being explored in hopes of developing drugs that prevent the development of heterotopic bone. Additionally, new methods of treatment that offer fewer side effects may be promising for patients in the future.

Heterotopic Ossification: Cellular Basis, Symptoms, and Treatment

Background

Heterotopic ossification (HO) is the process by which bone calcifies in soft tissues where it does not belong. In contrast to orthotopic ossification, which is the formation of tissue in the correct anatomical positions, HO causes bone to grow between muscle planes, eventually leading to some form of physical debilitation for patients (Mania et al., 2009). Because heterotopic bone can form on muscles, ligaments, and tendons, there are many different complications that can arise from its presence, depending on the location of the body. This process of bone formation can arise in different ways, including genetics, traumatic injury, and surgery.

Heterotopic ossification was first reported in literature in 1692 by Patin as *myositis ossificans progressiva* syndrome, but there were similar reports given later on from different cases. There were records of HO occurring from neurological injuries and traumas, and in paraplegic patients. Although various types of heterotopic ossification have been recognized and treatments have been utilized for years, there is still not a complete understanding of this condition. A fully successful prevention of heterotopic bone is still of interest to researchers, as this problem affects the lifestyle of those who have it (Baird & Kang, 2009).

As a result of the unclear differentiation between the naturally occurring ossification process and the heterotopic calcification, researchers and physicians find it hard to investigate what actually causes the buildup of bone to occur. Since there are multiple factors that are contributing to this process, especially on a molecular basis, the

challenge of preventing this condition will continue to exist for years to come. However, society now has access to the latest advances in technology that were not available when HO was first reported. Advancement has come through imaging techniques and medical technology, such as being able to prepare tissue samples for analysis. Because heterotopic bone may interact with proximal tissues, it is important to identify differences in composition. The configuration of the periosteum, a membrane that lines the outermost surface of bone, is not affected by the development of new bone, although the existing skeletal structure can be covered with more calcified bone (Baird & Kang, 2009).

Types of HO

Since heterotopic ossification is the process by which bone tissue develops outside of the skeleton, it is common for HO to occur in the vicinity of joints. Overall, it decreases range of motion and can cause complete joint ankylosis in which surgical intervention is required. Usually, the development of HO occurs through one of three routes: genetic predisposition, post-traumatic injury, or post-surgery. Most cases of HO come from the two latter categories, so studies focused on preventing HO is especially important for the medical field.

HO may be classified in a rare hereditary form or a most common acquired form, due to injuries or joint replacements. To this day, there are three distinct genetic hereditary forms known to humans: fibrodysplasia ossificans progressiva, progressive osseous heteroplasia, and Albright hereditary osteodystrophy. When it is acquired, HO occurs frequently after neurologic injuries including spinal trauma or a head injury. In addition, it can occur in areas of the body where a joint is replaced, such as the hip, shoulder, or elbow.

Heterotopic ossification is often classified by its anatomic position or by the effects seen with the patient's range of motion (ROM). In the case of traumatic injuries, Hastings and Graham have developed a classification of HO based on range of motion. The first group, Class I, includes patients that are known to have HO, but do not present any difficulties with ROM, making the heterotopic bone less clinically relevant. Class II HO patients tend to have limitations with ROM, such as lack of full extension and/or flexion of the elbow. Also, there may be problems associated with pronation and supination along with the flexion and extension. Depending on which plane of motion is involved, Class II HO can be divided into three further subcategories. The last type, Class III HO, includes patients that have ankylosis (joint stiffness) in addition to the problems with flexion/extension and pronation/supination (Casavant & Hastings, 2006).

Genetic case: fibrodysplasia ossificans progressiva (FOP). In this genetic disorder, heterotopic ossification begins at an early age and progressively develops at multiple periarticular sites. Because of the extensive progression, it eventually causes the patient to be completely immobilized. This condition is very rare, as it is estimated to affect only about 400 patients in the United States. It is thought to occur by random mutations and there has been no linkage to gender, race, or ethnic group. However, there have been reported cases of autosomal dominant familial transmission, suggesting that it may not occur primarily through random mutations. Its primary classification may not be identified with familial transmission because those with FOP have a weakened ability to reproduce.

FOP develops in patients at a young age, initially identified through lesions on the back, as soft masses are present on the upper back and shoulder girdle (Cohen et al.,

1993). Due to the nature of the disorder, more lesions develop as the patient ages, moving from the axial skeleton to the appendicular skeleton. The axial skeleton consists of the bones that lie along the central axis of the human body, including the skull, ribcage, sternum, and vertebral column. On the other hand, the appendicular skeleton contains bones that are involved in movement, including the upper and lower limbs (Chen, Yang, Chuang, Huang, & Yang, 2009).



Figure 1: In FOP, ossification begins with the axial skeleton and moves to the appendicular skeleton. This x-ray picture shows ossification of the posterior muscles of the cervical spine (McCarthy, 611).

Therefore, patients are more prone to developing a severe scoliosis, or curving of the spinal cord. As predicted, this causes a severe problem with movement, leading most

patients to be crippled by age thirty. Various skeletal abnormalities develop such as shortened thumbs and toes, and short and wide femoral necks. It is these common characteristics that help identify the disorder for physicians (Smith, Russell, & Woods, 1976). Most patients do not live to middle adulthood, eventually dying from pneumonia.

Genetic case: progressive osseous heteroplasia (POH). Progressive osseous heteroplasia, POH, was identified in 1994 after a group of patients were thought to have had fibrodysplasia ossificans progressiva (FOP). The new patients had a different bone formation pattern than those of FOP, leading to the identification of a new disorder with a different mutation. Rather than the extensive ossification identified in FOP, typical POH presents with ossification of subcutaneous tissue and the skin. The early signs of POH can be seen in infancy, where a maculopapular rash develops on the skin. This part of the skin will eventually develop into future sites of intradermal ossification. Unlike FOP, there is no malformation of the toes, and the ossification occurs within a membrane (intramembranous) rather than the endochondral ossification identified with FOP (Kaplan et al., 1994).

The genetic basis for POH is the inactivating mutation of the *GNAS1* gene, which codes for the alpha subunit of the activating G protein complex at chromosome 20 (Eddy et al., 2000). A signaling protein, the G protein helps to transmit information from the nucleus to the cell membrane and vice versa. The mutation of the G protein in POH also causes Albright's hereditary osteodystrophy (AHO), which is another genetic disorder that presents problems with ossification. Patients with AHO (formerly known as pseudohypoparathyroidism) have a resistance to parathyroid hormone (PTH), resulting in high levels of PTH, which then circulates throughout the body.

Major physical symptoms include soft tissue calcification, short stature, and mental retardation. The mutation of the *GNAS1* gene can cause both AHO and POH, but researchers have been able to link the distinction to genetic imprinting. When the mutated gene results from a male, it causes POH, while AHO results from a maternal gene mutation (Weinstein, Chen, & Liu, 2002). While there has only been overexpression of bone morphogenetic receptor (BMP) proteins in certain types of heterotopic ossification from the mutation of the G protein, it may provide pathways to understanding how and why calcification occurs in soft tissue.

Neurogenic heterotopic ossification. It is common for neurological lesions, or neurological tissue damage to cause the development of heterotopic bone near joints (Botte et al., 1997). For example, almost a quarter of spinal cord injury patients have heterotopic bone forming near the spine, many times causing severe joint limitations. Those with neurogenic HO have damage continuing to occur in larger joints, such as the hip, knees, and elbows. Because those joints are vital to movement and everyday activity, heterotopic bone can prevent patients from being able to walk or have any type of active lifestyle. Heterotopic ossification can begin in the joint(s) two months after the neurologic injury. Complete development of the osseous bone takes place within two years of the injury, many times causing ankylosis of the affected joint. Ankylosis is known to cause stiffening and immobility of a joint due to a disease, trauma, injury, or abnormal bone fusion.

Ossification following surgery. One of the most common procedures done by modern orthopaedic surgeons is a total hip arthroplasty, commonly known as a hip replacement. Although this surgery assists patients with regaining an active lifestyle, it

commonly causes about 60 to 90 % of patients to have heterotopic ossification. While the majority of HO cases do not present symptoms and are clinically insignificant, there exists a 1-2% of patients that are affected by the presence of heterotopic bone. However, there are risk factors that can help predict and identify those that would be expected to have HO. For example, the elbow is seen as an unforgivable joint, meaning that traumatic injuries to the elbow usually result in some complication, even after treatment. However, surgeons can take measures in order to reduce the potential for heterotopic bone growth so that the amount of bone that does develop after surgery is of little clinical significance (Kantor, Cummins, & Tanzer, 2005).

HO following burns. While most heterotopic ossification is rare, it is not uncommon to be present after burns, occurring in about 1 to 3% of burn patients (Kolar & Vrabec, 1959). For patients that have sustained thermal burns, the joint most affected by HO is the elbow. The elbow tends to have limited movement after thermal burns, leading to loss in ROM and/or ankylosis. It is speculated that the elbow is greatly affected due to the compression of the ulnar nerve (Evans, 1991).

HO and traumatic injuries. Some causes of heterotopic ossification are related to traumatic injuries. Due to the nature of certain injuries, areas of the body deal differently with heterotopic development, as it is known to cause numerous complications and varying levels of severity. The onset of heterotopic ossification can occur naturally, or from a posttraumatic injury. It is commonly known that its occurrence is higher in patients that undergo open reduction and internal fixation of a fracture. In particular, with an elbow fracture, dislocation, or fracture-dislocation, the incidence of traumatic HO approaches 90%. When HO develops in the elbow joint, it causes loss of range of motion

(ROM), disabling the patient from having terminal extension and severely limiting flexion. The observed loss in ROM is due to the inability of the muscles to contract while the heterotopic bone exists and/or develops in the muscle plane.

For traumatic injuries, the most common place for HO to develop is at the joints or within the spinal cord. Sports-related injuries that require surgery involving open reduction and internal fixation can lead to HO. For example, injuries that occur at the elbow, humerus, or hip are commonly linked to HO due to its location. The site of the bone fracture helps determine the extent of the HO that develops (amount in size) and the ability for the joint to continue working properly. If the injury site is proximal to a joint, the precursors to osteoblasts are able to aggregate and form bone away from the necessary location. A large majority of patients that have hip fractures develop HO, and that percentage increases if hip replacement and/or open reduction and internal fixation are performed. This parallels with similar occurrences in the upper and lower extremities.

Cellular/Genetic Basis

Prior research conducted by various institutions of health has shown how HO can occur and the genetic basis, including gene expression. The exact biological mechanisms of acquired HO formation are yet to be determined. However, studies have mainly focused on two different approaches including the research of a humoral factor as an inductive agent in neurogenic HO and the measure of the osteoblast activity in HO-isolated cells. Advances in genetics have led to the identification of many genes involved in the different steps of osteoblast differentiation. In recent years, there have been a variety of powerful and sensitive methods to quantify mRNA expression.

Structure and Bone Mineral Content

In the past, it was thought that heterotopic ossification occurred as a result of cancellous bone, woven bone, or cortical bone. Additionally, the results from radiographic assessments and light microscopy have given doubts about the bone structure and mineral content, due to the lack of fine resolution. However, a recent study was able to find a more accurate HO characterization. Using scanning electron microscopy (SEM) and backscatter electron (BSE) imaging, researchers found that heterotopic bone is composed a mixture of cortical and cancellous bone, along with fibrocartilage. A case study demonstrated that mineralization levels were dependent on the individual patients, with a great amount hypermineralization occurring among older patients. Using BSE and histologic stains, researchers found that the composition of HO was still changing, even though initial bone developed up to three years ago. It was osteoclastic resorption and osteoid deposition that demonstrated this phenomenon. Overall, BSE was able to provide an accurate understanding of HO bone mineralization and structure. This insight may be able to improve surgical planning and change treatment strategies for patients in the future (Isaacson, Brown, Brunker, Higgins, & Bloebaum, 2011).

Genetic Basis for FOP

The classic phenotype of ossification suggested that the primary molecular pathology involves the bone morphogenetic protein (BMP) signaling pathway. A number of discoveries provided evidence of profound dysregulation of the BMP signaling pathway in cells from patients who had FOP.

In FOP, scientists have identified a linkage to 2q23–24.9, the gene that encodes activin receptor IA (ACVR1). ACVR1 is a BMP type I receptor, so its DNA sequence revealed that the same heterozygous missense mutation in the glycine–serine (GS) activation domain (c.617G>A;R206H) occurs in all classically affected individuals examined. Hypothetical protein structure models are being developed to understand both inter- and intramolecular interactions of the mutant receptor. It is still unclear how the R206H mutation in ACVR1/ALK2 is able to interfere with BMP signaling in FOP, but it could involve dysregulation of BMP receptor oligomerization, internalization, and/or degradation.

Other genetic studies suggest that FOP is due to overexpression of BMP4. Although there has been no proven mutation in the gene for BMP4, researchers have identified two possible genetic mutations associated with this disorder: mutations on chromosome 4 (4Q 27–31), a region known to contain at least one locus involving the BMP pathway, and mutation of the *noggin* gene. *Noggin* is one of several BMP4 antagonists. The gene for *noggin* is normally upregulated when BMP4 is secreted. However, in FOP the upregulation of *noggin* is reduced, and this may result in unopposed BMP stimulation (Kaplan et al., 2009).

Pathogenesis of HO

In order for heterotopic bone to form, there are four things that must happen. First, there must be an inciting event, such as a trauma. Secondly, a signal from the site of injury, most likely a protein secreted from the cells of the injured tissue or from inflammatory cells arriving in response to the tissue injury, must be present. Third, a supply of mesenchymal cells whose genetic machinery is not fully committed must be

available for osteogenesis. When given the appropriate signal, genes that synthesize osteoid and chondroid (matrix) are activated and cause mesenchymal cells to differentiate into osteoblasts or chondroblasts. Lastly, there must be an environment where heterotopic bone can continue to develop and thrive (McCarthy & Sundaram, 2005).

Symptoms

Symptoms of heterotopic ossification, including loss of range of motion (ROM), the presence of heterotopic bone, and the impact that it has on areas of the body non-proximal to the site of injury will be examined.

A major topic on the discussion of heterotopic ossification is the impact that it has on people and their normal physical activity. One of the major impacts that heterotopic ossification has on patients is a significant change in the range of motion for patients. ROM is the distance and direction that a joint can move between the flexed position and the extended position. In the case of HO, it severely limits the ROM in patients, so that it inhibits regular day-to-day activity. The reduced range of motion may be a mechanical problem with the specific joint or injury, from diseases such as osteoarthritis, rheumatoid arthritis, or bone fracture that requires open reduction and internal fixation. The ROM lost in a joint can be determined using a goniometer, which measures (in degrees) how well the joint can undergo flexion and extension. Often, it is used during physical therapy to determine progress, as the ROM is measured before and after treatment. Sometimes, the practice of physical and/or occupational therapy will not help increase ROM, especially if therapy is not completed soon after the injury. It is often the case that patients cannot have a full range of motion because of the nature of the injury.

For example, fractures to the elbow and humerus cause a decrease in ROM, even after open reduction and internal fixation. This loss in ROM is caused by the presence of heterotopic bone, which blocks the joint from full movement. The bone develops in the muscle proximal to the site of injury. Excision of the heterotopic bone can significantly help patients with ROM, but physical therapy must be completed soon after the surgery and for a number of months. Although surgery will help, HO is likely to develop again, but with a smaller amount of bone present.

Normally, an x-ray will confirm the presence of heterotopic bone. In most traumatic injuries, it will take at least two weeks for it to be visible on an x-ray, but as time goes on, the heterotopic bone will continue to grow. Orthopedic surgeons, along with the help of radiologists, are able to monitor its activity and determine when action should be done to correct it. Furthermore, it is common for a CT (computed tomography) scan to be done in order to get a three dimensional view of the developing bone. This is especially important when HO develops in multiple locations where there are pieces of bone rather than the formation of one large fragment.



Figure 2: The presence of heterotopic bone effectively blocks extension of the triceps.

Because the heterotopic bone lies in the muscle plane, the triceps are not able to extend fully, leading to a loss in ROM. The heterotopic bone can be seen developing behind the elbow, proximal to the site of injury.

Because heterotopic bone can cause a loss in ROM in the elbow, patients can have severe limitations for normal activities such as being able to straighten the arm fully (extension) and flex the arm to bring it closer to the face. In severe cases, the joint may not be able to extend or flex at all, meaning that the patient will require surgery to remove the heterotopic bone to make use of the joint again.

While HO affects joints and movement, it also has an impact on the rest of the human body. If a patient is severely limited from using one of their knees or elbows, the other joint will have to compensate for the loss in movement. For example, elderly patients that undergo surgery to the elbow still tend to use the injured joint less often, even after physical therapy. When patients need to get up from a sitting position, they often use their arms to assist them. Because the elbow is injured and there may be a significant loss in ROM, the non-injured elbow must bear the patient's weight that normally would have been split between the two arms. Perhaps this imbalance in movement could cause damage to the glenohumeral joint (shoulder joint) over time. This damage would likely accelerate the need for a shoulder replacement.

The example of the elbow injury is not necessarily unique, as the development of bone near the spinal cord would affect walking movement. Any type of heterotopic bone that develops near a joint, or that could affect movement, will limit the ability of patients to have a functional use of their bodies. In the severe genetic diseases, it is only a matter of time before immobilization occurs.

Treatment

Different types of treatment are available to patients, including the taking of drugs (Indomethacin), prophylactic radiation, excision of heterotopic bone, and external beam radiation. Statistical data showing the effects of these various types of treatment will be examined, as many case studies have been performed in the past. Numerous ideas are available for future treatment by physicians and researchers, which may prove to be invaluable for the elimination of heterotopic bone.

There are many types of treatment available to physicians to treat heterotopic ossification, and experimental studies are underway to come up with more ways to treat it. Perhaps the most common form of treatment is the administration of various drugs, such as Didronel, which is a bisphosphonate that prevents calcium from being deposited in the bony matrix that HO has already formed. Didronel is an inhibitor of the conversion of amorphous calcium phosphate to hydroxyapatite crystals (Evans, 1991). This treatment seeks to prevent mineralization of the bone matrix. It is only a preventative drug and it will not have an effect on existing ossification. Therefore, it is routinely administered before surgery that may induce HO. However, in the case of traumatic injuries, it may not be able to prevent the ossification that begins once the injury occurs. Another drug, Indomethacin, is a prostaglandin synthase inhibitor, serving as an anti-inflammatory drug that suppresses mesenchymal cells, preventing further bone growth.

Radiation therapy has been used on HO since the end of the twentieth century, and is typically performed within a few days after the excision of the heterotopic bone. Following surgery, patients may have an active range of motion, but must go through intense physical therapy multiple times per week in order to prevent the joint from stiffening. In addition to physical therapy, home exercises must be completed to keep the joint as active as possible. This helps to decrease the chance of loss of ROM due to the development of scar tissue and the onset of ankylosis, which is commonly linked to joint stiffness.

Treatment Options

Non-steroidal anti-inflammatory drugs (NSAIDs). Today, the most popular treatment for heterotopic ossification is the use of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are known to have anti-inflammatory effects and are generally taken before and/or after excision of heterotopic bone. Most doctors agree that the drug Indomethacin is the best choice among NSAIDs to not only prevent HO, but also to slow down the process of development. The drug works by preventing inflammation, inhibiting bone remodeling by prostaglandins, and by inhibiting osteoprogenitor cells (precursor to osteoblasts) from differentiating (Vanden Bossche & Vanderstraeten, 2005).

In a study conducted by Banovac, thirty-three patients classified as either paraplegic or tetraplegic following a spinal cord injury participated in a double-blind, randomized, placebo-controlled clinical trial. Patients were divided into two groups, receiving either the drug Indomethacin (dose of 75 mg/day) or a placebo for a total of three weeks (Banovac, Williams, Patrick, & Haniff, 2001). Only males participated in the study, as men are more prone to developing HO, and also the size of the heterotopic bone is much larger than those in women. Bone scintigraphy was used to allow early bone detection, demonstrating a significant difference between the two groups. The group receiving the NSAIDs showed both a decrease in early bone development and a retardation of inflammation, including swelling, fever, and redness. In contrast, late bone development was present in only 12.5% of those taking Indomethacin compared to 41% of the other group that were given the placebo (Vanden Bossche & Vanderstraeten, 2005). Thus, the use of anti-inflammatory drugs can help prevent the development of heterotopic bone and slow the growth process occurring from traumatic injuries.

Different NSAIDs such as methylprednisolone, verapamil, warfarin, and calcitonin have been tested against the effectiveness of Indomethacin, but there has been no observed benefit to using alternative NSAIDs (Van Kuijk, 2002).

Radiation treatment. For heterotopic ossification, radiation treatment is often seen as a supplement to the use of NSAID's, but not as a complete substitute. Radiation treatment is used because it helps to prevent the differentiation of mesenchymal cells into osteoblasts. Therefore, it is useful to use radiation both pre- and postoperatively for bone fractures and operative treatment, such as a total hip replacement.

Although studies have shown radiation therapy to slow the development of HO, there is concern that it may cause carcinogenesis. However, there is also reasonable doubt among physicians concerning carcinogenesis because of the low dose of radiation used. Most of the patients that undergo radiation therapy are elderly, and the onset of malignancy does not begin until fifteen years after radiation. It is difficult to predict malignancy since most patients do not live long enough for the effects to be observed (Baird & Kang, 2009). If radiation therapy were to be used to prevent HO from a bone fracture in a young person, it would be worth researching in the future to ensure that any treatments are not harmful to the patient.

Combination therapy. An increasingly popular treatment for heterotopic ossification is the use of combination therapy, which combines the effectiveness of both radiation treatment and the use of NSAIDs. In a study by Pakos, it was demonstrated that only 1 out of 54 patients had clinically significant HO when using combination therapy. There was an overall incidence rate of 20.4%, but most patients were not affected by the development of HO (Pakos et al., 2006). Although this rate is higher than those seen in

other similar studies, it shows that combination therapy may be able to play a significant role in the future. Because there were fewer patients affected by the HO, it could be useful for keeping the ossification irrelevant rather than preventing it altogether. Researchers agree that more trials involving a larger number of patients should be implemented to test the utility or lack thereof of combination therapy treatments.

Surgical excision. In order to prevent the reoccurrence of HO, surgical excision of the heterotopic bone is completed after the bone is able to reach radiological maturation and there is no significant activity involving bone development. The average wait time for surgery is about 18 to 24 months, allowing the bone to become stable and discourage regrowth (Garland, 1991). Because patients must wait a long time for surgery, there is a significant loss in physical independence, an increase in soft-tissue contractures, and a decrease in muscle functionality (Tsionos, Leclercq, & Rochet, 2004). The lack of muscle mobility during the waiting period may not bode well for patients, even after surgical excision is complete.

There is much debate as to the appropriate time to remove heterotopic bone, but doctors strive to complete it in a way that not only helps patients regain their mobility, but also to prevent HO from developing in the future. Although the chance of reoccurrence is high, the amount of bone present following surgical excision will be significantly smaller than the HO present after the initial injury.

Future Treatment

As the popularity for the use of NSAIDs and radiation therapy has gone up, so have the prospects for new treatment options. Indomethacin, although effective for treating HO, has resulted in the development of gastric ulcers and gastrointestinal

hemorrhages in some patients (Karunakar et al., 2006). In addition, radiation therapy has its drawbacks, including carcinogenesis, gonadal dysfunction, and bony nonunion (Balboni, Gobezie, & Mamon, 2006). Many of these side effects have a larger impact on patients rather than the HO itself, so there is also no consensus as to what the best options are today. Thus, new studies are underway to discover treatments that have an increased efficacy and fewer side effects (Baird & Kang, 2009). The following section will address treatment options that researchers hope will be more effective for patients with heterotopic ossification.

Noggin. As discussed previously, HO is thought to develop due to overexpression of BMPs (bone morphogenetic proteins). Along with the upregulation of BMPs, the downregulation of BMP antagonists could provide an environment suitable for the development of heterotopic bone. Noggin, a BMP antagonist, is an extracellular protein that binds to BMPs and causes inactivation (Baird & Kang, 2009). A study by Hannallah showed that when Noggin was delivered to tissue following trauma, there was an 83% decrease in area of HO (Hannallah et al., 2004). Other studies have shown that the direct delivery of Noggin using an adenovirus vector blocks BMP-4-induced heterotopic ossification (Glaser et al., 2003).

Today, research is focused on systemic delivery of Noggin in order to prevent heterotopic ossification in animal models. Although it has been tested on animals, it may not be safe for human use. The overall goal of Noggin treatment is to be able to use the antagonistic nature of the protein to suppress BMPs, and help patients with fractures. It is unknown whether this type of treatment can be used before surgeries such as a hip arthroplasty as a preventative measure, or if it can only affect the activity of BMPs

following an injury or surgery.

Pulsed electromagnetic fields (PEMF). Research is now being directed to the area of pulsed electromagnetic fields (PEMF) to prevent heterotopic ossification following traumatic injuries and surgeries. PEMF is of interest due to its ability to increase circulation and oxygenation rates in soft tissue. HO is suspected to occur, in part, because of a local hypoxia, or lack of oxygen to areas that have been affected by injuries. Studies with PEMF have shown that early treatment can help prevent the development of HO following total hip arthroplasty, especially in severe cases (Kocic et al., 2006). There have not been enough studies to make an appropriate prophylaxis, but PEMF is being tested on humans rather than animals, which may give more conclusive results. The positive outcomes of recent studies show that it may help patients, but the side effects of using electromagnetic fields on the body could be dangerous.

Free radical scavengers. In the human body, there is oxidative stress when the reactive oxygen species (free radicals) are produced at a faster rate than their rate of elimination (Vanden Bossche & Vanderstraete, 2005). Treatment making use of free radical scavengers includes exercise that assists with reperfusion of soft tissue, or the bringing of blood flow to the tissue of interest. When blood is able to flow to an area that has been deprived of oxygen, it allows the cells to replenish their supply of nutrients necessary for functionality. Free radical generation occurs as a result of the exercise treatments, allowing the rate of elimination to come close to the rate of production. With heterotopic ossification, muscle atrophy occurs as a result of the decrease in protein synthesis, which weakens the repair mechanisms of cells. To disturb the environment suitable for HO, free radicals may be used in the future as a preventative measure.

Allopurinol and N-acetylcysteine were used as free radical scavengers in an animal experiment that tested the development of HO. The study concluded that the reactive oxygen species were as effective as NSAID's in preventing heterotopic bone formation (Vanden Bossche & Vanderstraete, 2005). Again, additional studies will be needed to allow treatment on humans and the potential side effects remain unknown.

Overall, it is the hope of researchers that these new treatments will be investigated further and made available for regular use. With these new techniques, there may be reduced complications with HO following surgery or trauma, along with fewer side effects. For now, the use of NSAIDs, radiation treatment, and combinations of the two seem to reduce the incidence of HO effectively. However, there may be better options for patients in the future, so it is only a matter of time before the best alternative arises from continued research.

Conclusion

Heterotopic ossification is known as the process by which bone develops in soft tissue where it does not normally reside. Because of its presence, it has many effects on patients including loss of range of motion, swelling, pain, joint immobility, and bone deformation. Over time, many of these symptoms seem to adversely affect the lifestyle of patients, ranging from slight discomfort to complete immobility. There are many ways that heterotopic ossification is able to develop, whether it is from genetics, surgery, injury, or burns. For every genetic case, there are symptoms to help identify the disorder, but there are not many options available for treatment. The degree of immobility is higher among those who inherit the disease genetically, which usually comes with a shortened

life expectancy. For those that develop HO as a result of a surgery or injury, there are many treatment options available.

The most popular forms of treatment are radiation therapy and non-steroidal anti-inflammatory drugs. While they may be effective at suppressing the development of heterotopic bone, there is no physiological solution to completely eliminating HO. For every treatment available, there are reasons to be wary of its use. Therefore, new treatment options for patients are being researched in hopes of reducing the number of side effects and being more effective at eliminating HO. Future treatment may include Noggin, PEMF, and free radical scavengers.

The complete genetic basis for heterotopic ossification remains unknown to researchers, although certain types such as FOP have been linked to BMP's. Mutations in the human genome will lead to a genetically-based form of HO, while stress to the body resulting from injury or surgery will lead to an obtained form. It is believed that all types of HO can be linked to the activity of mesenchymal cells, the precursor to osteoblasts, which build bone. Research is being done to inhibit the activity of the BMP signaling pathway and prevent unnecessary bone growth.

While heterotopic ossification remains a medical mystery, there is much to be researched in order to treat patients effectively. The disorder is relatively unknown, but it complicates the lives of those who have it. In the future, scientists hope to have a better understanding of HO and what causes it to occur. For now, patients have limited resources and may never be able to have a full physical healing. The prospects for enhanced treatment look promising, and it is only a matter of time before scientists, along with the help of technology, discover the cure to heterotopic ossification.

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