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Heterotopic Bone Formation after TMJ surgery — A Literature Review

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Heterotopic Bone Formation after TMJ Surgery

A Literature Review

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ABSTRACT

Background. **Heterotopic ossification (HO) is defined as the formation of lamellar bone in soft tissues where normally bone does not exist. It is a rehabilitative disease that can be associated with any joint in the body; however, its pathogenesis and management in the temporomandibular joint (TMJ) is infrequently mentioned in the literature.**

Types of studies reviewed. **The authors searched various articles, including systematic reviews, meta-analyses, randomized clinical trials, Cohort studies, case reports and literature review on heterotopic bone formation and treatment in PubMed, Google Scholar and Scopus.**

Results. **Identification of patients who are classified as high risk for the development of HO is vital for its prevention and management. Postoperative range of motion exercises, prophylactic medication with indomethacin and etidronate could reduce the incidence of HO. Similarly, the role of external beam radiation in the prevention of HO is well-documented. Additionally, several studies mentioned the inhibitory role of novel medication, such as rapamycin (RAPA), palovarotene and imatinib mesylate. Furthermore, clinical trials are underway to test the efficacy of saracainib, Garetosmab and IPN60130.**

Practical implications. **HO is most frequently diagnosed in patients who undergo total hip and knee replacement surgeries; its mention in the temporomandibular joint is rarely found in literature. The risk factors for HO in TMJ include trauma, infections, ankylosis, recurrent ankylosis, intra-articular corticosteroid injections, recurrent inflammatory conditions and total TMJ replacement with alloplastic or autogenous grafts. Its formation is unpredictable and, hence, patients with identifiable risk factors should be told about the risks and benefits of surgery and encouraged to strictly follow the prescribed postoperative regimen. Surgery is the final treatment of choice; however, placement of a fat graft in the surgical site has shown promising results to prevent HO at the surgical site.**

HO is defined as the formation of lamellar bone inside soft-tissue structures where bone normally does not exist.[1] It has also been defined as the presence of bone in nonosseous tissues or, more accurately, formation of ectopic lamellar bone in muscles or joint apparatus.[2] The first

description of the condition (HO) dates to 1692, by Patin, in children with myositis ossificans progressive. Eileen M. Shore and Frederick S. Kaplan have categorized this disorder as pathological.[3]

Synonyms of this condition are heterotopic bone, ankylosis and myositis ossificans, as well as fibrodysplasia ossificans progressive, which is a hereditary autosomal dominant variant.[4] Similarly, myositis ossificans is a variant of HO and refers to a condition in which ectopic bone is formed within muscles and other soft tissues.

While HO and ectopic bone formation may seem to be similar entities, histologically, ectopic bone formation is merely a calcium deposition in soft tissues, while HO is new lamellar bone. However, there is as yet no agreement on the definition of this condition.

Incidence and Demographics

This condition is seen in rehabilitative patients, and any joint in the body can be affected; however, it is most frequently seen in people who have undergone total hip and knee replacement surgeries. The incidence ranges between 16% and 53% after total hip arthroplasty.[1] L. G. Mercuri and B. M. Saltzman state that the incidence of acquired HO after total knee and hip replacement is as high as 23% to 30% after primary surgery, and 56% after revision surgery.[4]

The incidence of HO is twice as frequent in males than in females; however, females older than 65 years have an increased risk of developing HO.[5] A recent systematic review conducted by Schoenmaker et al. stated that HO is slightly more common in females as compared to males and trauma-induced HO occurred at a younger age than spontaneous HO.

Although rare, FOP of the temporomandibular joint (TMJ) has been described in the literature by Heba Saleem, Herford and Chicahreon et al.[6,7] Many causative factors are listed for HO in the TMJ; nevertheless, infection and alloplastic TMJ replacement (TMJR) account for 2.7% and 1.2%, respectively.

Etiology and Risk Factors

The etiology of HO can broadly be classified as hereditary or acquired. Fibrodysplasia ossificans progressive (FOP) is the genetic variant of the hereditary variant of HO. The hallmark sign of this is the malformation of big toes at birth. This is caused by a mutation of the bone morphogenic protein (BMP) receptor called activin receptor type –1 (ACVR1) receptor, also known as activin receptor-like kinase –2 (ALK-2), which results in arginine to histidine substitution at position 206. This substitution renders the receptor hyperactive to BMP ligands.[8]

Acquired causes include traumatic (fracture, arthroplasty, muscular trauma, joint dislocation, burns) and neurogenic (stroke, spinal cord injury, traumatic brain injury and brain tumors).[5] Additionally, HO has also been reported in patients with a gamut of crystal deposition diseases secondary to systemic illnesses, such as hyperparathyroidism and tumors.[9]

Risk factors for developing HO include the following: spasticity, older age, pressure ulcer and the presence of deep vein thrombosis (DVT); long bone fractures, prior injury to the same area; and edema. Nonambulatory patients, such as those in a long-term coma and severe injury (trauma, traumatic brain injury, spinal cord injury, stroke), can also be contributing factors.

Similarly, risk factors for the development of HO in TMJ are: trauma, infections, ankylosis, recurrent ankylosis and previous surgery to the same area; recurrent inflammatory conditions and total temporomandibular joint replacement with alloplastic or autogenous grafts; and patients uncooperative with post-implantation physical therapy.[10] It is postulated that the blood clot that forms after extensive joint debridement or total joint replacement promotes the migration of pluripotent cells and differentiation into osteoblasts. So, the more fibrotic the joint, the greater the loss of vascularity and, subsequently, a hypoxic environment is created.

Another study stated that intra-articular corticosteroid injections for inflammatory conditions of the TMJ lead to a 20% incidence of HO of the TMJ.[9,11,12] Also, individuals diagnosed with juvenile idiopathic arthritis (JIA) are more prone to develop HO. It is stated that a 38% increase in risk is associated with each passing year after the diagnosis is established.[9,10]

Classification

The various grades of heterotopic ossification of the temporomandibular joint were described by Turlington and Durr in 1993. Depending on the radiographic presentation, four grades were described. They are:

- Grade 0: no bone islands visible
- Grade 1: islands of bone visible within the soft tissue around the joint
- Grade 2: periarticular bone formation
- Grade 3: apparent bony ankylosis

Grades 1,2 and 3 are further classified as symptomatic (s) and asymptomatic (a). The symptomatic ossification includes severe pain, decreased interincisal opening, closed locking of the jaw, or decreased lateral or protrusive movement.[13]

Pathophysiology

The exact mechanism in the formation of HO is still being ascertained; however, research into the molecular struc-

ture of this condition is showing promising results. The pathogenesis for hereditary and acquired variants of HO is almost similar, albeit it differs at a few stages. However, regardless of the variant of HO, most authors agree that the initial inciting factor is the development of an inflammatory state leading to hypoxic environment[14] (Figure 1).

Hypoxia can be localized or generalized; nevertheless, it triggers the formation of hypoxia-inducible factor-1α (HIF-1α). HIF-1α further activates the release of cytokines, vascular endothelial growth factor (VEGF), bone morphogenic protein (BMP) and promotes mesenchymal cell differentiation. Furthermore, HIF-1α promotes chondrocyte differentiation, proliferation and survival.

BMPs are a part of the transforming growth factor-β (TGF- β) family of cytokines. BMP ligands transduce signal through the ACVR-1/ALK transmembrane receptors. Inside the cell, the signal is transported to the cell nucleus via the SMAD pathway. Additionally, BMP ligands can also transport signal to the nucleus via the Smad-independent pathways, such as TGF-β-associated kinase 1 (TAK1), mitogen-activated protein kinase (p38MAPK) and c-Jun N-terminal kinase (cJNK). Once the signal reaches the nucleus, transcription leads to transformation of pluripotent cells and deposition of osteoid, which eventually results in HO.

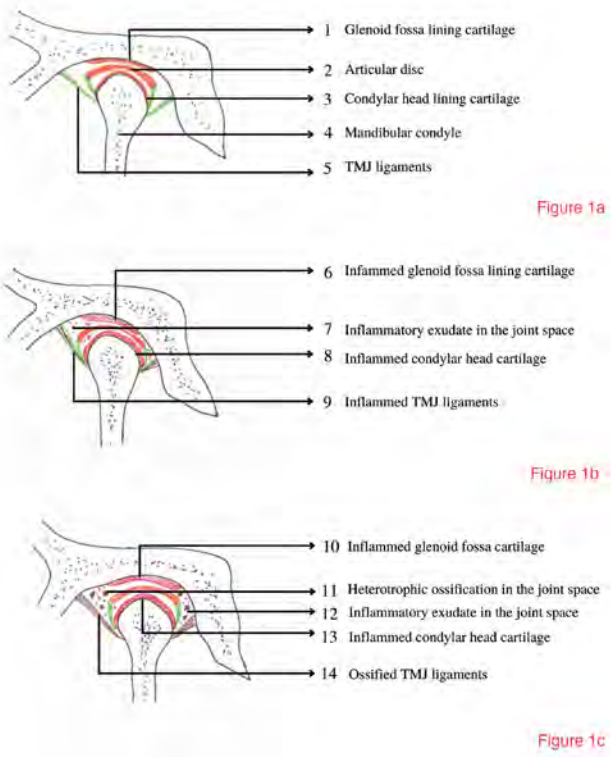

Figure 1. Formation of HO in TMJ. **(a)**: Normal anatomy of TMJ. **(b)**: Inflammatory condition of TMJ. **(c)**: Formation of HO subsequent to chronic inflammation.

However, in patients with FOP due to a genetic mutation in the ACVR-1/ALK transmembrane receptor, the response to the BMP/activin A ligands is exaggerated through the Smad pathways.[15,16]

Another signaling pathway which has gained popularity in the recent past is the mammalian/mechanistic target of rapamycin (mTOR). This kinase is present in two forms, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 is involved in various physiological processes in the body, such as responding to growth factors, stress, hypoxia, and it regulates several anabolic processes. It has also been stated that mTOR signaling pathway plays a vital role in the osteoblast differentiation and bone formation.[17]

Laboratory Investigations

Alkaline phosphatase is the most frequently requested lab parameter; unfortunately, it may not be elevated in the early phases of HO development. Nevertheless, serum alkaline phosphatase greater than 250 has been shown to correspond with HO. It should be borne in mind that alkaline phosphatase is also elevated in long-bone injuries; hence, it is not a specific marker for HO. Another lab parameter which could signal HO formation is erythrocyte sedimentation rate (ESR). Similarly, C-reactive protein is another such parameter that foretells the development of HO5. However, these are nonspecific markers that could foreshadow the formation of HO.

Management

The primary step in the management of this condition is to identify high-risk patients for developing HO. History is vital because intramuscular injection of lignocaine should be avoided in those previously diagnosed with FOP18. Current literature states that gentle range-of-motion (ROM) exercises should be implemented immediately or within five days from the day of replacement surgery. Aggressive physiotherapy after a period of immobilization has been shown to favor the formation of HO; therefore, gentle ROM should be instituted.[1] Other measures to prevent HO include prophylactic medication with indomethacin and etidronate and external beam radiation (Figure 2).

Indomethacin is the most commonly used NSAID for prophylaxis, although meloxicam, celecoxib, rofecoxib and ibuprofen have also been used.[5] Its action is twofold: first, it inhibits the differentiation of mesenchymal cells into osteogenic cells; and second, it prevents post-traumatic bone remodeling by suppression of the prostaglandin-mediated response.[1] Moreover, these drugs reduce pain and, consequently, patients can carry out gentle ROM exercises.

The recommended dose of indomethacin is 75 mg to 100 mg per day for 7 to 14 days postoperatively.[5] Complications of this regimen include risk of bleeding and gastrointestinal ulcers. To overcome such untoward occurrences, supplementation therapy with misoprostol 200mg/day can be instituted, or a selective cox-2 inhibitor can be substituted for indomethacin.[1] A recent study that compared the efficacy of celecoxib and indomethacin in the prevention of HO stated that there was no significant difference between the outcomes of the two drugs; however, patients who were on celecoxib had fewer side effects.[19]

Sodium etidronate, a bisphosphonate, is routinely used for prevention of heterotopic ossification in spinal cord injuries and complications of total hip arthroplasty. Its action is threefold: inhibition of calcium phosphate precipitation; slowing of hydroxyapatite crystal aggregation; and, finally, inhibition of the transformation of calcium phosphate to hydroxyapatite.[1] Thus, it is clear from the above description that this drug prevents bone formation by its effect on the crystallization process only and bears no effect on the bone matrix formation. Hence, after cessation of treatment a phenomenon called "rebound effect" can precipitate where the matrix undergoes mineralization. Consequently, it is essential to start treatment as soon as possible and continue it for a sufficiently long period of time, i.e., at least six months.[1]

Another modality gaining popularity in prevention of HO is irradiation therapy. Its prophylactic effect after hip surgery is well-known. Radiation therapy is most effective when given early in the postoperative period, that is, within five days.[20] Ionizing radiation interferes with the processing of nuclear DNA formation during cell division and may, thus, interfere with the differentiation of osteoprogenitor cells.[21]

This therapy was first described in hip joint surgery and later was utilized in other locations. The recommended radiation dose to prevent HO in TMJ is 10 Gy in five fractions, scheduled over a median range of five days. It is advised that the radiation be delivered to the surgical field within 72 hours postoperatively.[20]

Jensen et al., conducted a study to test the long-term results of radiation prophylaxis to prevent HO in TMJ and stated that postoperative RT prevented reformation of TMJ HO in 50% of treated patients, and late toxicities from RT were mild and infrequent.[22] The question of radiation-induced cancer is of great concern; however, the likelihood of cancer induction is very low with doses less than 30 Gy in three weeks. No patient had developed a radiation-induced malignancy in doses less than 30 Gy in three weeks over a 50-year study period at Memorial-Sloan Kettering.[23] Although some patients are prone to radiation-induced parotitis and xerostomia, this condition is transient. While much literature is available on the effectiveness of RT and NSAIDS in the prevention of HO, it states there is no statistical difference between the effectiveness of the two modalities.[24]

A recent study demonstrated the effectiveness of rapamycin (RAPA) as a prophylactic measure to prevent HO. RAPA is an effective immunosuppressant and an anti-fungal agent. It prevents the formation of HO through the inhibition of mTOR signaling pathway. Consequently, it prevents angiogenesis and vascular permeability in experimental mice; reduces the total leuco-

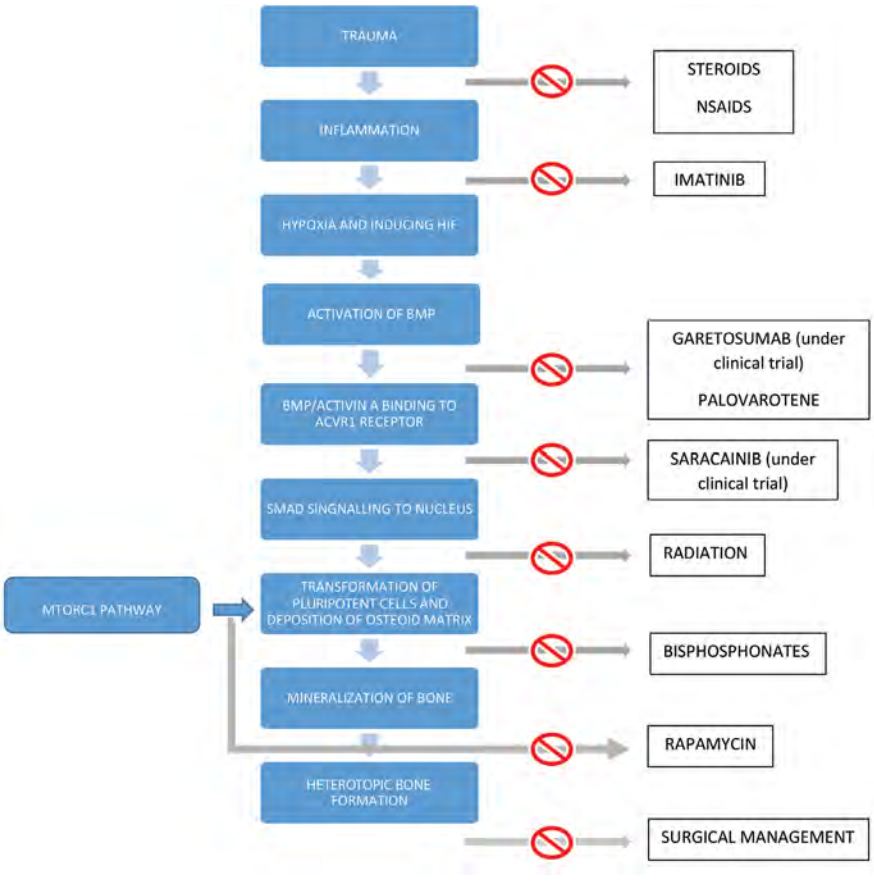

Figure 2. Flow chart showing HO formation and action of various medications at different steps.

cyte count (TLC); and prevents hypoxic and oxidative stress in the injured tissue, which influences the development of HO.[16,17]

Similarly, palovarotene is a selective retinoic acid receptor (RAR)γ which is under phase trials for the prevention of HO, particularly in patients suffering from FOP. By virtue of its agonist (RAR)γ action, it inhibits BMP and SMAD 1/5/8 signaling. Interfering with these pathways prevents chondrogenesis and, ultimately, HO.[8,16]

Another novel drug used for the prevention of HO in FOP patients is imatinib mesylate, a tyrosine kinase inhibitor, which is used for chronic myeloid leukemia (CML). It works by means of preventing the hypoxic environment that is created in the inflamed tissues. This medication has anti-proliferative and immunomodulatory actions in WBCs. Remarkably, imatinib is also used in the management of systemic mast cell diseases and inhibits pro-inflammatory cytokines, which are also involved in the pathogenesis of HO.[25]

In addition to the above-mentioned, saracainib, Garetosmab and IPN60130 are under clinical trials for prevention of HO in FOP patients. Saracainib functions by blocking the mutated ALK receptor, to prevent the exaggerated response to BMP, and Garetosmab is an antibody to Activin A which triggers Smad pathway when it binds to ACVR1 receptor.

Surgical Management

The classic treatment for HO of the TMJ is surgical management.[21] Various treatment options are available, including resection of the heterotopic tissue, temporary spacer and removal of the prosthesis with replacement at a secondary procedure. This technique is more tiresome and would require two admissions and a second surgery at a later date. However, a novel technique is replacement of the prosthesis, followed by packing fat around the articular surfaces simultaneously.[26] This technique precludes the need for two admissions and, consequently, overall treatment costs are reduced.

Also, packing fat around the articular surface promotes neoadipogensis, which inhibits growth of new bone and cartilage.[27]Similarly, Larry M. Wolford used abdominal fat graft and stated that it is a useful adjunct to prosthetic TMJ reconstruction. The occurrence of excessive joint fibrosis and heterotopic calcification are minimized and, therefore, the range of motion is improved.[28,29] Dimitroulis interposed dermis fat graft harvested from the groin in the TMJ and reported favorable outcomes.[27] However, harvesting fat from other sites causes a second surgical site morbidity. Hence, Rattan V. described a simple technique where buccal pad of fat was interposed between the articular surfaces of TMJ. This precluded the need for a second surgical site and patient comfort was enhanced.[30]

Since patients with heterotopic bone formation who undergo TMJ replacement may continue to have the tendency to reform heterotopic bone, further surgery may be required, which adds to morbidity, scarring and the risk of dysesthesia. Therefore, any solution to reduce the number of procedures should be considered.

Conclusion

HO is a rehabilitation complication after joint arthroplasty. The implication of this review article is to reinforce the preventive aspect of heterotopic ossification of TMJ. Its formation is unpredictable and, hence, patients with identifiable risk factors should receive special consideration.

Prevention with ROM, control of spasticity, NSAIDs (indomethacin, COX-2 inhibitors), bisphosphonates (etidronate) and external beam radiation after joint replacement should be considered. Absolute management involves surgery; however, as an adjunct to surgery, fat graft should be packed in the surgical site to prevent recurrence of heterotopic ossification.

The authors have declared no conflict of interest. Queries about this article can be addressed to Dr. Gandhi at sg7245@nyu.edu.

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