INVITED MEDICAL REVIEW

Hyperbaric oxygen therapy and osteonecrosis

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Osteonecrosis of the jaw may be caused by radiation, medication, or infection. Optimal therapy requires a multimodal approach that combines surgery with adjuvant treatments. This review focuses on the use of adjunctive hyperbaric oxygen therapy for this condition. In addition to evidence regarding the basic and clinical science behind hyperbaric oxygen therapy, controversies in the field and economic implications are discussed.

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Introduction

This review will discuss clinical, mechanistic, and economic data regarding radiation- and medication-induced osteonecrosis of the jaw and highlight some current controversies in the field. It will also discuss the mechanisms of hyperbaric oxygen (HBO2) therapy as they relate to these conditions.

Osteoradionecrosis of the Jaw (ORN)

Background

Osteoradionecrosis of the Jaw is a delayed complication of radiation therapy presenting months to years after the treatment for head and neck cancers (Epstein et al, 1987; Balogh and Sutherland, 1989; Lee et al, 2009; O’Dell and Sinha, 2011). Prevalence varies with the total dose of head and neck irradiation. ORN below the doses of 60 Gray (Gy) radiotherapy is uncommon, but increases in a dose-dependent fashion over 60 Gy (Cheng and Wang, 1974; Bedwinek et al, 1976; Morrish et al, 1981; Marx, 1983b; Epstein et al, 1987; Wong et al, 1997) (Balogh and Sutherland, 1989; O’Dell and Sinha, 2011). Prevalence also varies with the radiation delivery method and adherence to dental hygiene protocols. Intensity-modulated radiotherapy combined with a careful hygiene and extraction practice may lower the rates of ORN (Sulaiman et al, 2003) (Ben-David et al, 2007; Ahmed et al, 2009). Mean time from the cessation of radiotherapy to the onset of ORN varies, but is reported at between 22 and 47 months (O’Dell and Sinha, 2011). The development of symptomatic ORN is frequently preceded by dental trauma or extraction (Marx, 1983b), although 10–48% may be spontaneous cases (O’Dell and Sinha, 2011). When ORN occurs, it resolves in approximately 85% of patients with postirradiated, exposed mandibular bone through a conservative management alone (Million and Cassisi, 1994).

The fibro-atrophic and destructive vascular effects of head and neck radiation therapy manifest along a wide spectrum. Inside the oral cavity, any combination of dysgeusia, pain, paresthesia, exposed bone, gingival ulceration, poor dentition, fractured teeth, pathologic mandibular fracture, xerostomia, and orocutaneous fistula with associated discharge may be found. Palpation of soft and bony tissue may elicit pain (O’Dell and Sinha, 2011; Turner et al, 2013; Omolehinwa and Akintoye, 2016). Soft tissue woody fibrosis may be apparent, with severe cases experiencing a reduced range of motion at the temporomandibular joint or cervical spine. Serial photographs to document lesion progress throughout care are prudent (Ettorre et al, 2006; Schaad et al, 2006).

Mechanistic data

Osteoradionecrosis of the Jaw results from radiation-induced vascular fibrosis and thrombosis (Bras et al, 1990), marrow damage, death of lacunar osteocytes, and a subsequent impairment of bone and soft tissue healing (Wong et al, 1997; Jacobson et al, 2010). Initial theories focused on the anti-angiogenic effects of radiation (Teng and Futran, 2005). However, recent work suggests that stem cell depletion and radiation-induced fibrosis cause a combination of fibrosis and atrophy, the ‘fibro-atrophic effect’ (Lyons and...
Ghazali, 2008; Lyons et al, 2014) (Feldmeier, 2012; Rice et al, 2015). A concurrent cascade of cytokine release, particularly transforming growth factor beta (Fleckenstein et al, 2007), causes additional inflammation, tissue damage, and a decreased capacity for healing (Delanian and Lefaix, 2007; Omolehinwa and Akintoye, 2016). The use of tobacco products (Freiberger et al, 2009) or alcohol (Oh et al, 2009) also impede healing.

Clinical data
HBO2 therapy for ORN. HBO2 is endorsed to treat the late effects of radiation therapy in a variety of affected tissues including the jaw (Bennett et al, 2012; Feldmeier, 2012; Undersea and Hyperbaric Medical Society. Hyperbaric Oxygen Committee and Weaver). However, HBO2 is adjuvant therapy for ORN and is not recommended without concomitant surgery (Marx and Ames, 1982; Marx, 1983a; Peleg and Lopez, 2006; Freiberger et al, 2009). HBO2 as a treatment for ORN was first reported by Mainous in the 1970s (Mainous et al, 1973; Mainous and Hart, 1975). A randomized prospective trial then demonstrated an ORN incidence of 5.4% in a group pretreated with HBO2 vs 29.9% in those pretreated with penicillin prior to dental extractions (Marx and Ames, 1982: 478; Marx et al, 1985). Infection was not the cause of ORN, but rather extraction-related trauma to a fibro-atrophic and hypovascular irradiated mandible (Marx, 1983b). Retrospective data support the use of HBO2. A 2002 review of 14 papers (13 case series and 1 small RCT) confirmed a role of HBO2 therapy in ORN in all but one paper reviewed (Feldmeier and Hampson, 2002). An additional analysis from 2009 (Freiberger et al, 2009) reported that 57 of 65 (87%) of similar ORN patients treated with HBO2 maintained a long-lasting improvement out to a mean of 86 months if they remained cancer and tobacco free. A recent, 411 patient dataset prospectively collected over 8 years found that 92% of 166 patients undergoing a 20/10 (pretreatment/post-treatment) HBO2 protocol for dental extractions in an irradiated jaw and 73% of 43 patients undergoing a 30/10 protocol around ORN surgery showed complete healing (Hampson et al, 2012). A 2012 Cochrane review of 11 trials encompassing 669 subjects found that HBO2 therapy was likely to result in mucosal coverage for ORN patients (risk ratio (RR) 1.3; 95% confidence interval (CI) 1.1–1.6, P = 0.003, the number needed to treat for an additional beneficial outcome 5) (Bennett et al, 2012).

Controversy regarding the utility of HBO2 for ORN. Not all retrospective reviews agree on the utility of HBO2 therapy for ORN. In a 2011 review of 19 articles, the authors determined that while prophylactic HBO2 therapy appeared to reduce the risk of developing ORN after tooth extractions, the conclusions were ‘based on weak evidence’ (Nabil and Samman, 2011). A systematic review by Fritz et al (2010) also stated that there was insufficient evidence from 14 articles to prove that HBO2 therapy reduced ORN incidence after tooth extractions, although only half of studies cited actually tested HBO2, making any conclusion on HBO2’s efficacy inherently weak.

A highly criticized randomized controlled trial (RCT) by Annane et al (2004) did not support the use of HBO2. However, the methodology and endpoints were flawed. Sixty-eight subjects were enrolled from 12 different hospitals, making adherence to one standard of care unachievable. HBO2 treatment schedules were not provided, and one quarter of the treated subjects received less than 22 sessions, a subtherapeutic dose without a statistical power to find a difference between therapies (Moon et al, 2005). These flaws enabled the report of a lower ORN resolution rate in the hyperbaric group (19%) than in the control group (32%) (Feldmeier et al, 2005) (Freiberger and Feldmeier, 2010). This observation is not seen in clinical practice, suggesting a selection bias in group assignment with more severely affect subjects being assigned to receive HBO2. Most concerning, however, was the decision to define treatment failure as the need for surgery. HBO2 is recommended as an adjunct to surgery, not as a sole therapeutic modality (Undersea and Hyperbaric Medical Society. Hyperbaric Oxygen Committee and Weaver). The 2004 trial confirmed what the field already knew: ‘HBO2 therapy does not obviate the need for complete surgical debridement’ (Feldmeier et al, 2005) and that ‘necrotic bone cannot be resuscitated by any therapy, let alone hyperbaric oxygen’ (Moon et al, 2005). Additional data are forthcoming. An ongoing randomized trial called Hyperbaric Oxygen for the Prevention of Osteoradionecrosis (HOPON) will compare patients receiving oral antibiotics and mouthwashes, with or without a 20/10 hyperbaric oxygen therapy protocol, pre- and postprocedure (available at: www.lctu.org.uk).

Other therapies for ORN. Other medical therapies for ORN are in development. Pentoxifylline is a medication that increases erythrocyte flexibility to optimize the microcirculatory flow and is tolerated clinically up to 60 weeks (Fan et al, 2014). It also has antitumor necrosis factor alpha effects, causes vasodilation, inhibits human dermal fibroblast proliferation and extracellular matrix production, and increases collagenase activity (Fan et al, 2014). Tocopherol is a fat-soluble antioxidant with vitamin E activity that protects cell membranes from lipid peroxidation, and can inhibit transforming growth factor beta1 and pro-collagen gene expression (Fan et al, 2014). Clodronate is a newer-generation, non-nitrogenous bisphosphonate that reduces osteoclast numbers and activity to minimize bone resorption, increases bone formation, and reduces the fibroblast proliferation (McCaul, 2014). Glicksman et al (2015) observed a clinical benefit after administering a combination of pentoxifylline, tocopherol, and clodronate therapy for osteoradionecrosis of the temporal bone. Other reviews report the benefit in similar medical treatment for osteoradionecrosis refractory to surgery (Delanian et al, 2005, 2011). The addition of a bisphosphonate to pentoxifylline and tocopherol regime may provide an increased efficacy (McLeod et al, 2012).

Economic data
The economic impact of radiation injuries may be ameliorated by the therapeutic use of HBO2. In a recent
Australian case study, treatment for radiation cystitis with HBO2 was found to lower the costs of hospital admissions, consultations, investigations, and procedures, for an estimated cost savings of approximately $A187 483 over 2.5 years (Smart and Wallington, 2012). Although the costs of clinical progression of osteonecrosis are high, very few economic analyses specifically address HBO2 therapy in this broad clinical setting (Guo et al, 2003). Surgical manipulation of irradiated bone is associated with the high rates of complications requiring multiple subsequent surgical procedures with a significant associated cost and morbidity. Marx’s work found savings of over fifty percent when HBO2 was used as an adjunct to surgical treatment of mandibular osteonecrosis: $140 000 vs $42 000 in 1992 USD (Marx et al, 1985). Kelishadi et al (2009) studied a population of patients with intractable ORN, most of whom failed conventional therapy and reported a decreased in-hospital cost from $30 030 to $25 010 when HBO2, minor surgical debridement, and hospital stay were offered as an alternative to resection and microvascular flap reconstruction. Although this study did not consider the role of HBO2 in the optimization of tissue health for microvascular flap reconstruction, avoiding the more invasive but ‘definitive’ procedure effectively doubled the cost (Kelishadi et al, 2009). HBO2 is best utilized to maximize the likelihood of graft success rather than as a salvage therapy for graft failure, and the UHMS recommends that a utilization review takes place after the provision of 60 HBO2 treatments for radiation injuries (Undersea and Hyperbaric Medical Society. Hyperbaric Oxygen Committee and Weaver).

Non-mandibular Osteonecrosis

Background
Osteonecrosis may occur throughout the skeletal system, including temporal bone (Vudiniabola et al, 2000), ribs (Nicholls et al, 2015), femoral head (Camporesi et al, 2010), humeral head (Gruson and Kwon, 2009), lunate (Lutsky and Beredjiklian, 2012), and bones of the foot (Gross et al, 2014; Callachand et al, 2016). The epidemiology of many types of osteonecrosis is less well characterized than for ORN, although non-traumatic femoral head osteonecrosis cases are estimated to occur at an annual incidence of 1.91/100 000 in Japan with a male-to-female ratio of 2.1:1 (Ikeuchi et al, 2015). Similar to jaw, temporal bone osteoradionecrosis shows a delayed presentation with a mean latency of 7.5–7.9 years, but as late as 20–22 years postradiation therapy (Ramsden et al, 1975; Thornley et al, 1979; Sharon et al, 2014). It presents with pain, discharge, exposed bone (Vudiniabola et al, 2000; Sharon et al, 2014), or persistent otitis externa (Thornley et al, 1979).

Mechanistic data
Corticosteroids (Weinstein, 2012b), coagulation abnormalities (Orth and Anagnostakos, 2013), trauma (Lutsky and Beredjiklian, 2012), alcohol abuse (Jones and Hungerford, 2004; Callachand et al, 2016) (Fajardo-Hermosillo et al, 2013; Mont et al, 2015), and increased atmospheric pressure experienced by divers and tunnel workers (Kindwall, 1997; Sharareh and Schwarzkopf, 2015) are causes of osteonecrosis other than radiation or anti-resorptive medications. Precise mechanisms are not well established across all of these causes. However, it is appreciated that corticosteroids cause osteoblast and osteoclast apoptosis, decreased vascular endothelial growth factor levels, decreased blood supply at the femoral head, and may shunt osteoprogenitor cells toward an adipocyte vs osteoblast phenotype (Assouline-Dayan et al, 2002; Zalavras et al, 2003; Li et al, 2005) (Sheng et al, 2009; Wang et al, 2010; Weinstein, 2012a).

Clinical data
HBO2 for extraoral facial osteoradionecrosis. Vudiniabola et al (2000) treated 14 patients with osteoradionecrosis of the facial bones with HBO2, including three with affected temporal bone. Follow-up at 3 and 13 years revealed no recurrence of osteoradionecrosis or cancer. Metselaar et al (2009) also published a series of four patients who received HBO2 for external auditory canal osteoradionecrosis with successful results. Other recent series failed to show a benefit (Sharon et al, 2014).

HBO2 for femoral head osteonecrosis. Idiopathic femoral head osteonecrosis may be a candidate for HBO2 therapy. Camporesi et al (2010) conducted a double-blind, prospective RCT of 20 patients suffering idiopathic, unilateral femoral head necrosis. The HBO2 treatment group showed a statistically significant improvement in both pain and range of motion compared to a sham hyperbaric air group. After 30 treatments, the sham group was offered a compassionate crossover, and both groups received a total of 90 HBO2 treatments over 1 year. At the 7-year follow-up, beneficial effects persisted in all patients with minimal pain and no contralateral disease or arthroplasty. Furthermore, Koren et al (2015) found that HBO2 therapy led to radiographic improvement of stage I and II femoral head osteonecrosis, and survival of 93% of the joints at a mean of 11.1 ± 5.1 year follow-up. HBO2 has also been administered as adjuvant therapy in treating osteonecrosis of other bones, such as ribs (Nicholls et al, 2015), but these less common cases still await rigorous study.

Economic data
Veenstra et al (1999) reported an estimated $61 700 ten-year cost for avascular necrosis of the hip as a result of corticosteroid use in renal transplant patients. Reports to analyze the impact of HBO2 therapy on such costs are not available.

Anti-resorptive medication-associated osteonecrosis of the jaw

Background
Beginning in 2003, reports by Marx (2003), Migliorati (2003), and Ruggiero et al, (2004) established an association between intravenous bisphosphonate therapy and osteonecrosis of the jaw. This recalcitrant disease has since been reported by others (Ashcroft, 2006; Badros et al, 2006; Bagan et al, 2006; Dimitrakopoulos et al,
farnesyl pyrophosphate synthase inhibitors and disruptors of the mevalonate pathway with the resultant accumulation of isopentyl pyrophosphate being elucidated (van Beek et al., 1999; Russell, 2011). Excess isopentyl pyrophosphate modulates osteoclast signaling (Russell, 2011) and gamma-delta T-cell activity (Sanders et al., 2005; Ashihara et al., 2015). Bisphosphonates bound to bone also affect the adjacent tissue in vitro through the induction of soluble mediators (Cornish et al., 2011). Whether the mechanism of action of denosumab as a RANKL inhibitor (Kostenuik et al., 2009) represents a common pathway between this drug and bisphosphonates to osteonecrosis is unknown.

The oral microbiome plays a role in BRONJ. Biofilm formation may promote the symptomatic disease through binding exposed bone and propagating osteomyelitis (Hansen et al., 2006; Sedghizadeh et al., 2009; Kumar et al., 2010; Lumerman, 2013a,b; Boiff et al., 2014; Crincoli et al., 2015; Jabbour et al., 2016). Mandibular bone exposed to bisphosphonate shows an increased susceptibility to necrosis after the exposure to bacterial lipopolysaccharide (Sakaguchi et al., 2015). Immune cell function is also altered. Differences in surface markers are apparent on macrophages from mandibles of human BRONJ vs ORN patients (Hoefert et al., 2015). Macrophages in vitro exhibit a decreased survival and adherence after bisphosphonate treatment (Hoefert et al., 2016) and an increased sensitivity to lipopolysaccharide-induced apoptosis (Muratsu et al., 2013). These drugs exert actions on both the innate and adaptive immune systems, as T-cell function is also altered by bisphosphonates (Sanders et al., 2005; Kikui et al., 2010; Ashihara et al., 2015; Park et al., 2015).

Animal evidence suggests that a subclinical variant of BRONJ exists. Anti-resorptive inhibition of bone turnover may promote senescence-related islands of necrosis in the jaw of experimental animals. A dog model of BRONJ showed a silent matrix necrosis in jaw and rib after the chronic exposure to bisphosphonates (Allen and Burr, 2008). This and other BRONJ animal models provide a platform for further investigation (Bi et al., 2010; Pautke et al., 2012; Williams et al., 2014).

**Clinical data**

**HBO₂ for BRONJ.** Case reports and case series suggesting that HBO₂ could help or augment the treatment for BRONJ are summarized elsewhere (Freiberger, 2009). RCT data are available from 46 patients enrolled in a study to test the utility of HBO₂ as an adjunct to surgery and antibiotics (Freiberger et al., 2012). Although the study was underpowered, lacked blinding, and experienced a high attrition rate (Rollason et al., 2016), 17 of 25 patients treated with hyperbaric oxygen improved compared to 8 of 21 controls. HBO₂ was associated with the improved pain and quality of life scores. HBO₂ was recommended as an adjunct to surgery in cases where the involvement is extensive and infection is a problem (Freiberger et al., 2012; Spanou et al., 2015). A recent review had an overall positive review of HBO₂ (Fliefel et al., 2015) for BRONJ patients, based on two case series (Freiberger et al., 2007; Chiu et al., 2010) and the above-cited RCT.
Alternate therapies for BRONJ. The roles for vitamin D, calcium, and parathyroid hormone have been postulated in mandibular recovery from BRONJ (Spanou et al., 2015; Leizaola-Carcesa et al., 2016). Laser biostimulation (Martins et al., 2012) and platelet-rich plasma (Lee et al., 2007) treatments are also described, but all these options await full characterization (Spanou et al., 2015; Rollason et al., 2016).

Economic data

The treatment for BRONJ demands the integrated efforts of multiple medical, and sometimes surgical, services. Najm et al. (2014) demonstrated the direct relationship between increasing patient costs and the progression of BRONJ. This retrospective analysis of resource utilization selected 92 cancer patients with BRONJ, and of the five categories the authors outlined (clinical visits, diagnostic studies, procedures, medications, and laboratory investigations), surgical procedures and diagnostic studies were the primary expenses in patients with the highest cost of care (Najm et al., 2014). The costs of clinical protocols for HBO2 therapy relative to surgical resection and debridement in BRONJ have yet to be analyzed, but bear reporting (Rollason et al., 2016).

HBO2 mechanistic data

As outlined in the UHMS Hyperbaric Oxygen Therapy Indications manual (Undersea and Hyperbaric Medical Society. Hyperbaric Oxygen Committee and Weaver), HBO2 therapy may be used as an adjuvant to surgical debridement, to promote the healing of both gingiva and underlying bone in ORN. The ‘Marx’ protocols have been used for decades to prepare irradiated oral tissues for den- 
tal extractions and as multimodal therapy in the cases of additional treatments, and as multimodal therapy in the cases of ORN with exposed bone. The total number of treatments, rather than the temporal frequency, should determine the course of therapy (Hampson and Corman, 2007). In addition, HBO2 tends to be a well-tolerated therapy (Thom, 2011; Camporesi, 2014).

Under hyperbaric conditions, the alveolar partial pres- sure of oxygen (PaO2) is acutely elevated proportionally to the atmospheric pressure (Otis et al., 1948). At 2 atmospheres pressure (Moor et al., 1965; Salzano et al., 1984), blood arterial oxygen partial pressures (Pao2) greater than 1500 mmHg and tissue levels over 200 mmHg can be achieved in patients with healthy lungs and normal arterial flow (Weaver and Howe, 1992; Weaver, 2011) (Thom, 2011). Such levels reverse tissue hypoxia during treatment and generate reactive oxygen species (ROS) and reactive nitrogen species (RNS) with signaling properties (Thom, 2009, 2011; Camporesi and Bosco, 2014). RNS generation leads to endothelial nitric oxide synthase activity, nitric oxide production, and mobilization of circulating CD34+ stem/progenitor cells, appreciated between 1 and 20 treatments with HBO2 in humans (Thom et al., 2006; Heyboer et al., 2014). Within 24 h of exposure to HBO2, microarray analysis of cultured endothelial cells showed a significant up- or down-regulation of over 7000 genes (Godman et al., 2010a,b). Among the top responding genes were metallothionein, but no such experimental data exist for the cells of bone origin.

HBO2 affects immune function. It inhibits the bacterial growth and augments an antibiotic activity (Cimsit et al., 2009; Zanon et al., 2012). Phagocytosis activity assays on neutrophils from diabetic foot ulcer patients remained elevated after 2 weeks of HBO2 therapy (Top et al., 2007). In vitro experiments using human neutrophils demonstrated that a decreased adherence to endothelia, as mediated by beta2 integrin, is sustained up to 21 h after a single HBO2 exposure, without affecting the circulating numbers of leukocytes (Thom et al., 1997). Taken together, such observations support the ongoing and multifactorial effects of HBO2 therapy dependent on pressure, well after PaO2 has returned to normal.

In vitro, in vivo, and human data support the decreased fibrotic injury and the increased vascularity as plausible mechanisms by which HBO2 likely benefits irradiated tissues (Feldmeier, 2012). HBO2 induces increased levels of growth factors that may alter the fibro-atrophic and depleted vascular nature of irradiated tissue. Those include vascular endothelial growth factor (Sheikh et al., 2000), angiopoietin-2 (Lin et al., 2002), and other effects relevant to healing tissue and improved vascular function (Thom, 2011; Drenjancevic and Kibel, 2014). Work on a murine model of irradiated small bowel showed that HBO2 treatment reduced the development of tissue fibrosis (Feldmeier et al., 1995, 1998). Rabbit model work showed that HBO2 at 2.4ATA x 90 min, but not normobaric 100% oxygen, increased angiogenesis in irradiated tissue (Marx et al., 1990). Svalestad et al. (2014) found that HBO2 treatments in a clinical population of 51- to 90-years-olds with a history of 50- to 70-Gy orofacial irradiation increased tissue oxygenation and vascularity of facial skin and gingival mucosa, as investigated by transcutaneous oximetry and laser Doppler flowmetry. Later, both blood vessel and lymphatic density within buccal mucosa were shown to increase in an irradiated human patient population post-HBO2 therapy (Svalestad et al., 2015).

HBO2 may increase the molecular signaling that promotes bone remodeling. It induced the osteogenic differentiation of mesenchymal stem cells via a Wnt-dependent pathway (Lin et al., 2014a,b). HBO2 also decreased RANKL-mediated osteoclast formation and bone resorption in cell culture (Al Hadi et al., 2013). This observation was seen on the backdrop of modulating signaling cascades important to bone cell differentiation, including reduced RANK, NFATc1, De-STAMP, and HIF-1alpha expression (Al Hadi et al., 2013). Increased osteoblast prolif- eration and bone nodule formation in cell culture models are also described after the treatment with HBO2 (Wu et al., 2007; Al Hadi et al., 2015). HBO2 decreased the inflammation and accelerated the bone formation after acute injury to the femur in a rat model (Rocha et al., 2015). In a higher-fidelity model of human ORN, a murine model of mandibular radiation damage found that HBO2 improved the parameters associated with bone health, including decreased osteoclast numbers, increased bone viability, and increased bone volume (Spiegelberg et al., 2015). HBO2 may also lead to increased testosterone levels (Passavanti et al., 2010) that could affect the bone health. These mechanistic data support the beneficial effects of HBO2 therapy upon bony tissue and its...
precuror cells. The mechanisms explain some HBO2 therapy effects and reinforce that more work is required to deepen our understanding in this field of research.

Conclusions and future directions
There is a need for further rigorously designed randomized controlled trials in the field of hyperbaric medicine, and specifically as an adjunctive modality in ORN and BRONJ treatment. Improved methods to select patients likely to benefit from HBO2 therapy would enhance patient care. For example, positron emission tomography shows a promise in predicting which BRONJ patients benefit from HBO2 therapy (Fatema et al, 2015). Future trial design should administer sham treatments to randomized subjects in a crossover design, when ethically and logistically feasible (Freiberger and Feldmeier, 2010), assess optimal HBO2 dosing, and study long-term follow-up of patients. Multimodal therapy targeting vascular and fibro-atrophic effects of radiation will suggest whether a more broad approach to treatment is beneficial. Beyond clinical work, basic science knowledge of HBO2 mechanisms needs to be expanded. Preventative cost models are complex and difficult to study, but given the high cost of treatment failure, in terms of both patient morbidity and medical expenditures, the economics of osteonecrosis treatment protocols need more clear definition. Lastly, while many patients who have undergone courses of chemotherapy or radiotherapy may find the burden of time and logistics associated with an extended HBO2 treatment protocol familiar, the HBO2 therapy provider must consider the emotional cost of time away from family and the disruption of a patient’s daily routine. While research is ongoing, patients diagnosed with osteonecrosis should continue to benefit from existing supported HBO2 therapy protocols.

Conflict of interests
None to declare.

Author Contributions
P. Ceponis drafted sections on radiation and bisphosphonate-induced osteonecrosis of jaw, coordinated authors, and revised serial drafts. C. Kellman drafted sections on osteonecrosis of non-facial bones and edited serial drafts. C. Guerry drafted sections on economics and edited serial drafts. J. Freiberger edited and revised serial drafts, provided mentorship in scientific writing, and coordinated the entire process.

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