ORAL DISEASES
Leading in Oral, Maxillofacial, Head & Neck Medicine

Oral Diseases (2017) 23, 141–151 doi:10.1111/odi.12489

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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.

Oral Diseases (2017) **23**, 141–151

Keywords: therapies; wound healing; hyperbaric oxygen; osteonecrosis

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 (HBO_2) 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; Beumer *et al*, 1984; Emami *et al*, 1991; Thorn *et al*, 2000; Lee *et al*, 2009). A reasonable estimate of ORN prevalence in the irradiated population is 5–15% (Cheng and Wang, 1974; Bedwinek *et al*, 1976; Murray *et al*, 1980; 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; Schaaf *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

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Received 23 March 2016; accepted 24 March 2016

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 impedes healing.

Clinical data

HBO_2 therapy for ORN. HBO_2 therapy 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, HBO_2 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). HBO_2 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 HBO_2 *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 HBO_2. A 2002 review of 14 papers (13 case series and 1 small RCT) confirmed a role of HBO_2 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 HBO_2 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) HBO_2 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 HBO_2 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 HBO_2 for ORN. Not all retrospective reviews agree on the utility of HBO_2 therapy for ORN. In a 2011 review of 19 articles, the authors determined that while prophylactic HBO_2 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 HBO_2 therapy reduced ORN incidence after tooth extractions, although only half of studies cited actually tested HBO_2, making any conclusion on HBO_2's efficacy inherently weak.

A highly criticized randomized controlled trial (RCT) by Annane *et al* (2004) did not support the use of HBO_2. However, the methodology and endpoints were flawed. Sixty-eight subjects were enrolled from 12 different hospitals, making adherence to one standard of care unachievable. HBO_2 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 HBO_2. Most concerning, however, was the decision to define treatment failure as the need for surgery. HBO_2 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: 'HBO_2 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 HBO_2. In a recent

Australian case study, treatment for radiation cystitis with HBO_2 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 HBO_2, 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 HBO_2 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). HBO_2 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 HBO_2 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

HBO_2 for extraoral facial osteoradionecrosis. Vudiniabola *et al*, (2000) treated 14 patients with osteoradionecrosis of the facial bones with HBO_2, 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 HBO_2 for external auditory canal osteoradionecrosis with successful results. Other recent series failed to show a benefit (Sharon *et al*, 2014).

HBO_2 for femoral head osteonecrosis. Idiopathic femoral head osteonecrosis may be a candidate for HBO_2 therapy. Camporesi *et al* (2010) conducted a double-blind, prospective RCT of 20 patients suffering idiopathic, unilateral femoral head necrosis. The HBO_2 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 HBO_2 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 HBO_2 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 $\pm$ 5.1 year follow-up. HBO_2 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 HBO_2 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*,

2006; Leite *et al*, 2006) and reviewed in the literature (Freiberger *et al*, 2012) (Spanou *et al*, 2015; Williams and O'Ryan, 2015). The biologics denosumab, bevacizumab, and sunitib also cause anti-resorptive osteonecrosis of the jaw (Neuprez *et al*, 2014) (Troeltzsch *et al*, 2012; Ramirez *et al*, 2015), and a recent case report shows that they can affect grafted bone (Gryseleyn *et al*, 2016). Bisphosphonate-related osteonecrosis of the jaw (BRONJ) prevalence varies based on the type of bisphosphonate administered, dosing, administration route, and the patient population (Khan *et al*, 2015). In osteoporosis patients, BRONJ prevalence is between 0.001% and 0.01%, but it climbs to 1–15% in oncology patients (Durie *et al*, 2005; Hoff *et al*, 2008; Stumpe *et al*, 2009; Lo *et al*, 2010; Solomon *et al*, 2013; Khan *et al*, 2015; Kim *et al*, 2015). Intravenous administration of bisphosphonates is associated with higher risk (0–0.348%) compared to the oral route (0–0.04%) (Filleul *et al*, 2010) (Lo *et al*, 2010; Walter *et al*, 2010) (Khan *et al*, 2015; Kim *et al*, 2015). The mean time to the onset of BRONJ after starting bisphosphonate was found by Durie *et al* (2005) to be 18 months for those receiving zoledronic acid and 6 years for patients on pamidronate, whereas it was 14.3 months for pamidronate and 9 months for zoledronate in a case series of 119 mostly myeloma and breast cancer patients (Marx *et al*, 2005), illustrating that the time to onset is population dependent. Observed incidences may differ based on indication, attention to prescreening, and avoidance of invasive dental procedures (Coleman, 2008).

Alveolar trauma after dental surgery, intubation, and denture impressions are reported as precipitators of BRONJ (Marx *et al*, 2005) (Ruggiero *et al*, 2014; Yazdi and Schiodt, 2015). Diabetes is an identifiable risk factor (Molcho *et al*, 2013; Peer and Khamaisi, 2015), and other comorbidities include age, anemia, history of steroid use, and other dental diseases (Khan *et al*, 2015; Kim *et al*, 2015). A delay in the time from exposure to bisphosphonate to clinical manifestation of disease is often noted (Migliorati, 2003; Ruggiero *et al*, 2004; Marx *et al*, 2005). Physical findings include gingival ulceration with exposed bone, intraoral or extraoral fistula (Ruggiero *et al*, 2014) (Ruggiero *et al*, 2009, 2014; Fedele *et al*, 2010; Yarom *et al*, 2010). Painful tongue ulcers responsive to bone debridement or intralesional steroid are also reported (Treister *et al*, 2008).

Mechanistic data

Bisphosphonates inhibit RANKL-dependent signal transduction cascades normally leading to osteoclast formation *in vitro* (Green and Clezardin, 2010; Tsubaki *et al*, 2014). Human bone biopsy confirmed the presence of dysfunctional giant, multinucleated, apoptotic osteoclasts resistant to phagocytosis after bisphosphonate treatment (Jain and Weinstein, 2009; Bi *et al*, 2010). The net clinical effect is to inhibit osteoclastic resorption and remodeling in bone turnover (Ruggiero *et al*, 2014). Bisphosphonates also inhibit angiogenesis (Wood *et al*, 2002; Bezzi *et al*, 2003) and other processes critical to oral wound healing (Freiberger, 2009; Green and Clezardin, 2010; Tsubaki *et al*, 2014) (Landesberg *et al*, 2008; Williams *et al*, 2014). A biochemical basis for bisphosphonates as farnesyl pyrophosphate synthase inhibitors and disruptors of the mevalonate pathway with the resultant accumulation of isopentyl pyrophosphate is 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; Boff *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; Kikuiri *et al*, 2010; Ashihara *et al*, 2015; Park *et al*, 2015).

Animal evidence suggests that a subclinical variant of BRONJ exists. Anti-resorbant 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

HBO_2 for BRONJ. Case reports and case series suggesting that HBO_2 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 HBO_2 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. HBO_2 was associated with the improved pain and quality of life scores. HBO_2 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 HBO_2 (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-Cardesa *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 HBO_2 therapy relative to surgical resection and debridement in BRONJ have yet to be analyzed, but bear reporting (Rollason *et al*, 2016).

HBO_2 mechanistic data

As outlined in the UHMS Hyperbaric Oxygen Therapy Indications manual (Undersea and Hyperbaric Medical Society. Hyperbaric Oxygen Committee and Weaver), HBO_2 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 dental extractions 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, HBO_2 tends to be a well-tolerated therapy (Thom, 2011; Camporesi, 2014).

Under hyperbaric conditions, the alveolar partial pressure of oxygen (P_AO_2) 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 (P_aO_2) 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 HBO_2 in humans (Thom *et al*, 2006; Heyboer *et al*, 2014). Within 24 h of exposure to HBO_2, 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 metallothioneins, but no such experimental data exist for the cells of bone origin.

HBO_2 affects immune function. It inhibits the bacterial growth and augments an antibiotic activity (Cimsit *et al*, 2009; Zanon *et al*, 2012). Phagocytic activity assays on neutrophils from diabetic foot ulcer patients remained elevated after 2 weeks of HBO_2 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 HBO_2 exposure, without affecting the circulating numbers of leukocytes (Thom *et al*, 1997). Taken together, such observations support the ongoing and multifactorial effects of HBO_2 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 HBO_2 likely benefits irradiated tissues (Feldmeier, 2012). HBO_2 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 HBO_2 treatment reduced the development of tissue fibrosis (Feldmeier *et al*, 1995, 1998). Rabbit model work showed that HBO_2 at 2.4ATA × 90 min, but not normobaric 100% oxygen, increased angiogenesis in irradiated tissue (Marx *et al*, 1990). Svalestad *et al* (2014) found that HBO_2 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-HBO_2 therapy (Svalestad *et al*, 2015).

HBO_2 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). HBO_2 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, Dc-STAMP, and HIF-1alpha expression (Al Hadi *et al*, 2013). Increased osteoblast proliferation and bone nodule formation in cell culture models are also described after the treatment with HBO_2 (Wu *et al*, 2007; Al Hadi *et al*, 2015). HBO_2 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 HBO_2 improved the parameters associated with bone health, including decreased osteoclast numbers, increased bone viability, and increased bone volume (Spiegelberg *et al*, 2015). HBO_2 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 HBO_2 therapy upon bony tissue and its

precursor cells. The mechanisms explain some HBO_2 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 HBO_2 therapy would enhance patient care. For example, positron emission tomography shows a promise in predicting which BRONJ patients benefit from HBO_2 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 HBO_2 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 HBO_2 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 HBO_2 treatment protocol familiar, the HBO_2 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 HBO_2 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. Keilman 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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