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The role of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers - A literature review☆

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ABSTRACT

Diabetic Foot Ulcers (DFUs) are chronic foot wounds, in a person with diabetes, which are associated with peripheral arterial insufficiency and/or peripheral neuropathy of the lower limb. Recent UK audit figures report that approximately 50–60 % of DFUs remain unhealed after 12 weeks. Previous research has suggested that ischaemia plays a key role in the pathophysiology of many chronic wounds, including DFUs. For this reason, hyperbaric oxygen therapy (HOT) has been investigated. The study aimed to investigate 1) Current understanding of the physiology of normal wound healing and the pathological mechanisms that occur in DFUs to interrupt these processes; 2) Effectiveness of current DFU treatment approaches; 3) Effectiveness from clinical trials and meta-analyses for any demonstrated therapeutic benefits of HOT in the treatment of DFUs, 4) Patient selection criteria for HOT, and patients who stand to benefit most from treatment.

The review found that wound healing is a complex process, involving many cells and signalling molecules, and it remains incompletely understood. However, current evidence suggests that hyperglycaemia, hypoxia, chronic inflammation (due to infection, immune-cell dysfunction or other causes), peripheral neuropathy, and macro- and micro-vascular dysfunction may all adversely affect DFU healing. The review found that current NICE guidelines do not approve HOT therapy in the UK for DFU's, despite encouraging clinical research findings. HOT shows theoretical promise and has been successfully used in the treatment of individual DFUs for several decades. Despite this, there remains a lack of strong clinical evidence of benefits to encourage HOT's wider use. The review found that there were four important patient selection criteria for HOT treatment, including glycaemic control, possible contraindications and complications associated with treatment, ulcer severity and resistance to first and second line treatments. The review concluded that further high-quality clinical research is needed to improve the evidence base.

1. Introduction

Diabetic Foot Ulcers (DFUs) are chronic foot wounds in a person with diabetes, associated with peripheral arterial insufficiency and peripheral neuropathy of the lower limb.[1] DFUs are a common complication of diabetes, estimated to affect 2–6 % of those with diabetes globally every year and 15–25 % in their lifetime.[2,3] In Scotland, approximately 270,000 people have diabetes, and the prevalence of type 2 diabetes has increased by approximately 40 % over the last decade, a trend expected to continue due to the country's ageing population.[4] DFUs already represent a significant cause of morbidity and account for one-third of diabetic treatment costs and an estimated 1 % of NHS costs. As DFUs mainly affect the elderly, it is likely their prevalence will also continue to increase in the United Kingdom.[5–7]

Recent UK audit figures report that approximately 50–60 % of DFUs remain unhealed after 12 weeks.[8,9] Approximately, 1–3 % of DFUs require amputation within 6 months and mortality rates within five years of developing a DFU are around 40 %, rising to 63 % if amputation is required.[8,10] Therefore, improving outcomes for those with DFUs is a vital area of clinical research.

Previous research has suggested that ischaemia plays a key role in the pathophysiology of many chronic wounds, including DFUs.[11] For

☆ What does this study/review add to the existing literature and how will it influence future clinical practiceThis study collates and analyses the research evaluating hyperbaric oxygen therapy as an adjunct to established treatment for diabetic foot ulcers.

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this reason, hyperbaric oxygen therapy (HOT), which involves providing 100 % oxygen for respiration to patients at pressures above standard atmospheric pressure (>1 ATA) within a specialised hyperbaric chamber, has been utilised as a therapy of potential benefit for wounds since at least the 1960s.[12,13]

2. Aims

The specific aims of this study were to perform a literature review to investigate:

1) Current understanding of the physiology of normal wound healing and the pathological mechanisms that occur in DFUs to interrupt these processes.
2) Effectiveness of current DFU treatment approaches.
3) Evidence from clinical trials and meta-analyses for any demonstrated therapeutic benefits of HOT in the treatment of DFUs.

3. Data sources & search strategy

Electronic searches were made in the Medline (Ovid) database (1946–2023) and Cochrane Library, to identify recent systematic reviews and meta-analyses. The search strategy made use of various search terms combined with Boolean operators and is summarised in Table 1. Additional relevant papers were identified through a manual review of the reference lists of these recent meta-analyses and systematic reviews (Table 1).

4. Physiology of wound healing

The physiological process of wound healing is the body's rapid, repairing response to injury, which helps to prevent infection. It can be broken down into four overlapping stages: haemostasis, inflammation, proliferation, and maturation.[14] These are summarised in Table 2. For successful healing to occur, progression through these stages must occur in the correct sequence and at a normal rate.[15] In health, wounds generally take 4–6 weeks to successfully heal, from initial injury to the time to complete the proliferation phase and enter the extended period of remodelling.[16]

4.1. Haemostasis

Haemostasis is triggered as soon as a wound occurs and is completed within minutes to several hours.[15] Platelets and the coagulation cascade are activated by contact with collagen and tissue factor released by damaged cells and this, combined with local vasoconstriction responses (driven by thromboxane release from endothelial cells and serotonin release from activated platelets), results in thrombus formation.[17,18] Activated platelets and damaged cells also release complex growth factors and cytokines, which trigger the subsequent phases of healing.[19]

Table 1
Summary of search strategy.

	Search details	Medline (ovid) papers found	Cochrane library papers found
Search 1	Diabetes Mellitus OR Diabetes Complications OR Diabetic Foot OR Foot Ulcer OR Leg Ulcer	175,635	111,816
Search 2	Hyperbaric oxygenation OR HBOT OR HBO OR HOT OR Hyperbaric oxygen therapies	12,600	1759
Search 3	Search 1 AND Search 2	424	215
Search 4	Limit to 'English Language' and 'Humans'	365	215
Search 5	Limit to 'Systematic Review' OR 'Meta Analysis'	22	14
Search 6	Limit to last 10 years	17	14
Manual review	Review of titles & abstracts to remove duplicates & irrelevant papers	16	2

Table 2
Summary of normal wound healing phases.

Healing stage	Events
Haemostasis	1. Vasoconstriction 2. Platelet Aggregation + Fibrin Clot Formation (thrombus)
Inflammation	1. Vasodilation 2. Increased Capillary Membrane Permeability 3. Immune Cell Recruitment (Neutrophils, Monocytes → differentiation to Macrophages, Lymphocytes)
Proliferation	1. Fibroblasts: Collagen & Extracellular Matrix Synthesis 2. Endothelial Cells: Angiogenesis 3. Re-epithelialisation
Remodelling	1. Collagen Remodelling 2. Vascular Maturation & Regression

4.2. Inflammation

Cytokines activate inflammation and immune-cell recruitment, causing mast cells to release histamine and other inflammatory mediators, leading to vasodilation and increased capillary permeability.[20] Neutrophils are rapidly recruited to the site to phagocytose bacteria, decontaminate the wound, and release further cytokines to boost the inflammatory response.[15] Subsequently, monocytes are recruited, where they differentiate into M1-phenotype macrophages, which release pro-inflammatory mediators, such as Interleukin-1 and Interleukin-6, and phagocytose microbes, cellular debris and apoptotic cells.[21] As the debris is cleared, the macrophages transition into an M2-phenotype and these cells help to resolve the inflammation by releasing anti-inflammatory mediators, such as Interleukin-10, and further growth factors.[15,22] Typically, the inflammation phase starts in the first 24 h and lasts 3–5 days and is associated with erythema and oedema.[15]

4.3. Proliferation

Proliferation normally begins within 3–4 days of injury and continues for several weeks.[15] This is the process of tissue repair and scar formation, stimulated by the growth factors released by the injured epidermis, activated platelets and M2-macrophages, including, platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF).[14,23] These growth factors activate fibroblasts to synthesise a collagen scaffolding, stimulate vasculogenesis and angiogenesis by recruiting endothelial progenitor cells to grow a new capillary network, and together, these processes fill the wound with new connective tissue, or 'granulation tissue'.[24] In addition, EGF stimulates the growth of new epithelial cells, which migrate to re-epithelise the external wound surface.[14]

4.4. Remodelling

Approximately 2–3 weeks after the initial injury, the phase of granulation tissue remodelling into mature scar tissue begins and can continue for months.[15] Myofibroblasts contract the wound edges and the collagen and capillaries of the granulation tissue are reconstructed, so the overall architecture returns to a similar organisation to normal connective tissue[25] (Table 2).

5. Pathophysiology of diabetic foot ulcer development & impaired healing

In chronic wounds, the physiological healing processes described

above are compromised, resulting in protracted or absent healing and an increased risk of infection or high-risk complications, including sepsis and amputation.[26] Many factors have been identified that negatively affect cutaneous wound healing in DFU's, including: poor glycaemic control, inattention to foot care, secondary infection, ischaemia from peripheral vascular disease, and many co-morbidities which may be present, including heart failure or respiratory diseases.[1,25,27] We will now review some of the evidence for the underlying causes of impaired healing in DFUs, with a focus on those that might potentially be alleviated by improved wound oxygenation.

6. The role of chronic inflammation in DFUs

Non-healing DFUs remain in a chronic state of ongoing inflammation, which delays or prevents the normal healing process.[15] Although the cellular mechanisms preventing the transition to the proliferation stage are not completely understood, the phenotype transition of macrophages from M1-M2 is believed to be crucial.[15] The ongoing presence of pro-inflammatory neutrophils in a wound, due either to pathological processes or bacterial infection, has been identified as one mechanism behind the chronic inflammation in DFUs. The phagocytosis and removal of apoptotic neutrophils by macrophages (a process known as 'efferocytosis') is believed to be the crucial factor that prompts their transition to the M2-phenotype, which stimulates the shift to proliferation in the wound.[28] Evidence of this impaired efferocytosis has been observed in non-healing DFUs, in both humans and mice.[29] There are several different factors believed to contribute to chronic inflammation in DFUs, discussed below.

6.1. Bacterial infection

The excessive inflammatory response of DFUs is often associated with a bacterial infection, as an estimated 60 % of all DFUs and 82 % of more serious DFUs requiring hospital admission, are infected.[30,31] The persistence of pro-inflammatory M1-macrophages and neutrophils is exacerbated by any bacterial infection, as this stimulates the release of reactive oxygen species (ROS) and proteases by these immune cells, both of which breakdown the extracellular matrix and growth factors, inhibiting the ability of the cells involved in proliferation to divide and migrate through the wound.[12,32]

6.2. Altered immune response

Diabetes has been characterised as a 'chronic state of inflammation', and recent studies have shown that people with diabetes (regardless of DFU presence or history) have elevated pro-inflammatory cytokines in their circulation and increased concentrations of inflammatory cells, including lymphocytes and dendrocytes, within their dermis.[23,33]

6.3. Dysregulation: MMPs & TIMPs

Matrix metalloproteinases (MMPs) are important molecules which support the later proliferation and remodelling phases of healing. However, the over-expression of MMPs earlier in the healing process inhibits its progression, as MMPs degrade both the collagen structure of the ECM, as well as cytokines and growth factors.[23] Research by Martins et al. has shown that, in DFUs, levels of MMPs and their endogenous inhibitors, TIMPs (Tissue Inhibitor of Metalloproteinases), are elevated and reduced, respectively, compared to wounds in people who do not have diabetes.[23,34–36]

7. The role of ischaemia & hypoxia in DFUs

Of relevance for this review is the potential fundamental role of ischaemia and consequent wound hypoxia in the impaired healing of DFUs. Several studies have measured the transcutaneous oxygen pressures (TcPO2) of DFUs and associated poorer wound healing and worse outcomes with reduced perfusion. Kalani et al. (1999) reported that 86 % of DFUs with TcPO2 <30 mmHg failed to heal, compared to 94 % of DFUs with TcPO2 >30 mmHg[1] which successfully healed. There are several mechanisms which may contribute to the ischaemia and hypoxic wound tissue seen in DFUs and, as Richner et al. have argued, it is likely many of these interact in the development of impaired healing in DFUs.[37]

7.1. Peripheral neuropathy

Peripheral neuropathy affects 30–50 % of people with diabetes and, according to Alexiadou and Doupis, is the common causative factor in around 90 % of DFUs.[1,38] The classic combination of causative events is that neuropathy of motor nerves leads to biomechanical changes in the foot and abnormal plantar pressure points, where repetitive trauma creates a wound that goes undetected, due to loss of sensory nerve function.[39] This loss of peripheral sensation can also contribute to poor healing of a DFU: if there is no pain detected and adequate care is not taken, then repetitive trauma of the wound is likely. Peripheral neuropathy also affects autonomic nerves, which reduces sweating and local vasodilation - factors linked to reduced skin integrity, increased vulnerability to microbial infection and impaired healing.[39]

Beyond this, neuropathy also plays a role in DFU ischaemia and hypoxia. This is due to its effects on impairing the normal neuropeptide signalling mechanisms involved in the 'Lewis triple-flare response' to skin injury, which is reduced or absent in areas of peripheral neuropathy.[40] This is due to the loss of c-nociceptive peripheral nerves, which would normally signal a vasodilation response to injury, leading to local hyperaemia, via the release of peptides (including calcitonin gene-related peptide (CGRP) and substance P), which stimulate mast cells to release histamine.[41] Investigations by Dinh and Veves identified that the impairment of this response leads to a functionally ischaemic microcirculation in peripheral neuropathy, even in the absence of PAD; and, on this basis, suggested this impairment may be an important mechanism contributing to the poor healing response seen in many DFUs.[41]

7.2. Peripheral arterial disease & microangiopathy

Peripheral Arterial Disease (PAD) is a contributing factor in an estimated 50 % of DFUs and 70 % in those aged >70 years. This macrovascular disease, linked to the metabolic dysfunctions of hyperglycaemia and dyslipidaemia seen in diabetes, leads to atherosclerosis and reduced peripheral perfusion.[42] Although the microvasculature remains less affected by occlusion in PAD, there is a dysfunction of the adaptive vasoreactivity to local ischaemia in diabetes, which aggravates peripheral capillary hypoperfusion.[43] Taken together, these compounding mechanisms may produce significant local ischaemia, and DFUs associated with PAD have been observed to have worse overall healing rates (69 % vs 84 %) and approximately triple the rate of major amputations (8 % vs 2 %).[42,44,45]

8. Standard therapy approach for diabetic foot ulcers

The standard care for DFUs includes routine debridement of necrotic tissue, to reduce infection risk and remove debris; application of moist sterile dressings, to facilitate the development of granulation tissue and healthy re-epithelialisation; secondary infection control with antibiotics (as required); and 'offloading' of the affected limb, through the use of orthotic walkers or total contact casting, to relieve pressure on the wound and local ischaemia.[5,9,46,47] Support for improved glycaemic control, smoking cessation and adequate nutrition are also important supportive measures.[46,47] In addition, some guidelines recommend that all those with DFUs should be assessed for PAD and whether they might benefit from vascular intervention, to improve the likelihood of healing.[47,49]

9. Amputation

If the standard care approach fails, amputations are often performed to ensure that the infection and necrotic tissue is removed and as much of the limb is preserved as possible. 85 % of diabetic amputations come about following a DFU.[50] Whilst they may be necessary in the short-term, the longer-term risks of amputation make it a controversial and somewhat unsatisfactory procedure for clinicians and patients. This is primarily because mortality rates associated with amputation are high: Dubský et al.[51] reported 5-year mortality rates following minor amputation (below the ankle) of 46.6 %, and 56.6 % following major amputation (above the ankle) in the Eurodiale study. In addition, the preventative benefits are unclear, as rates of DFU recurrence post-amputation appear to be similar to those with healed DFUs (without amputation) at around 40–50 % within 1–2 years.[52,53]

10. Effectiveness of HOT from meta-analyses

A meta-analysis by Margolis et al. found that this standard care approach resulted in average healing rates of 24 % after 12 weeks and 31 % after 20 weeks; and Europe-based outcome data suggests that 77 % of DFUs heal within 1 year, with this therapeutic approach.[31,48] Of particular note is the evidence for total contact casting, which is often considered the gold standard of care for DFUs that are neuropathic, and are *not* infected or ischaemic as it has been shown to increase average rates of healing for these types of DFUs from 60–77 % to over 90 %.[5,46,59]

11. Effectiveness of HOT from clinical trials

Although many RCTs have attempted to investigate HOT therapy for DFUs, the pattern of results has been conflicting. Some of this is likely to relate to the lack of specificity of studies controlling for varied presentations and precipitating causes of DFU.[54] The presence of a few well-conducted RCTs, such as that of Löndahl et al., which reported improved healing rates of 52 % with HOT compared to 29 % in the placebo group, offers some positive encouragement.[55]

The latest Cochrane review found that HOT had significant short-term benefits on DFU-healing in the first 6 weeks, but the evidence of overall longer-term benefits was less clear, although HOT significantly reduced the frequency of major amputations by around two-thirds compared to controls (RR 0.36).[56]

A more recent meta-analysis, conducted by Zhang et al. of 20 prospective RCTs, was less equivocal, concluding that HOT was associated with a 20 % reduction in overall DFU healing times (although only two RCTs reported on this outcome), a 1.9 times more successful healing rate (across 17 RCTs), a 48 % reduced risk of major amputation, but no benefit in terms of the risk of minor amputation (across 6 RCTs).[57]

Sharma et al.'s smaller systematic review of 14 RCTs and 2 CCTs concurred with the findings of Zhang et al., reporting similar benefits of approximately doubled complete healing rates and a halved incidence of major amputations with HOT; but no benefits in terms of reduced rates of minor amputation.[57,58]

However, all of these reviews also stressed that larger RCTs were needed to verify their findings, as there was significant heterogeneity of results across the studies. This was echoed in another recent review, by Vas et al., who identified heterogeneity between RCTs in terms of patient selection criteria, patient PAD severity (where recorded), selected end points of the studies, number of HOT sessions and specific regimens employed, and patient follow-up periods.[59]

The common limitations of the RCTs were that they contained relatively small populations, combined with differing wound characteristics between participants, which acted as confounding variables. This is perhaps to be expected, as DFUs present in complex ways, and the presence of individual differences related to peripheral circulation/ischaemia, hypersensitivity reactions, co-morbidities, secondary trauma or infections, previous scarring and so on, all affect the healing process and make it challenging for researchers to run definitive clinical trials. Recent individual studies have evidenced some of these complex pathological factors and co-morbidities which can be linked to DFU-healing outcomes, including venous insufficiency, smoking history, and specific infective organisms, but further research is needed to elucidate these more clearly.[60,61] Additionally, as Levett et al. underlined, there are often practical and ethical difficulties in organising RCTs in parts of the world where current protocols recommend the use of HOT, based on the evidence of reduced mortality provided by cohort studies, such as that of Wilkinson et al.[62,63]

Whilst this research provides promising results, there have been complications noted in association with HOT therapy.

12. HOT & current NICE/SIGN guidelines

The current NICE guidelines recommend that HOT should not be used in the treatment of DFUs, due to a lack of evidence.[46] Alternative adjuncts, with a stronger evidence base, including dermal substitutes and negative pressure therapy are, however, recommended for consideration.

The current SIGN guidelines state there is insufficient evidence to recommend for or against HOT. However, the SIGN guidelines do specifically recommend that negative pressure wound therapy should be considered, as the evidence suggests benefits over standard moist wound dressings.[47]

13. Patient selection criteria

There is evidence to suggest that HOT may provide better outcomes for some patients compared to others. Several characteristics must be taken into consideration when deciding which DFU patients stand to benefit most from HOT. There are two main domains from which patient selection should be evaluated: response to conventional treatment, and severity of the wound. However, two supplementary criteria may stratify best-suited patients, or the patients who are most in need of treatment with HOT, including glycaemic control and comorbid contraindications and possible complications for HOT.[69]

13.1. Glycaemic control

It has been found that poor glycaemic control is a predisposing and perpetuating factor for DFU's. Further, high HcA1c values prior to HOT treatment have been found to lead to worse outcomes when undergoing HOT, including slower wound healing.[70] In one study by Karadurmus et al., they reported a reduction in HbA1c levels after 30 sessions of HOT, which started at 9.1 % and dropped to 8 % following HOT treatment. Moreover, a study by Aydin et al. showed a reduction in HbA1c from 8.13 % to 7.04 % following 30 sessions. When considering this relationship, Irawan et al. also found that short term HOT significantly reduced leukocyte count, serum creatinine and HbA1c.[71] These studies show a reciprocal relationship between glycaemic control and HOT outcomes, therefore, HOT may present an opportunity as both a glycaemic modulator for treatment resistant hyperglycaemia, and as a DFU treatment in patients stable and low HbA1c (<60), as wound healing has been shown to be faster in these individuals.

13.2. Contraindications and complications for HOT

HOT is not an option open to all and contraindications include untreated pneumothorax, recent ear trauma or surgery, current upper respiratory tract infection, allergic rhinitis, chronic sinusitis and claustrophobia.[12] Whilst Kranke et al. reported no evidence of major adverse outcomes in their systematic review of healthy patients with DFU's, these comorbidities may lead to major adverse outcomes when treating patients with HOT.[56] There are some risks of major adverse effects,

including sinus, lung and dental-filling-related barotraumas, but these appear to be very rare, as Plafki et al. could not identify any cases in a study of over 11,000 patients. A very low risk (about 0.03 % of treatments) exists of acute cerebral oxygen toxicity, leading to seizures, as air-breathing 'breaks' are used as a precaution during HOT.[64] There is also a very low, but potentially life-threatening, risk of fire in a high-oxygen environment, so strict precautions must be followed.[65] Finally, Gupta and Somasundaram also found that patients with pacemakers or implantable devices, recent eye or thoracic surgery, obstructive lung disease, history of seizures, perilymph fistulas, tuberculosis and untreated cancer also displayed a risk for HOT treatment.[72] As the rates of these illnesses can be higher in diabetic populations, especially at the point of presenting with a DFU, then special care must be taken depending on the type of comorbidity the patient has presented with. In addition, out with specific conditions - the age and frailty of the patient must be considered, as patients who are not able to tolerate high pressures and high oxygen concentrations due to physiological processes of ageing may not meet criteria for HOT therapy, due to an increased risk of barotrauma and hyperoxic injury.[64]

Minor complications are, however, more common. The principal complication of extended courses of HOT (affecting up to half of those undergoing over 30 sessions), is a temporary loss of visual acuity (mean −0.5 dioptres), secondary to changes in the shape of the lens.[66] This typically resolves soon after cessation of treatment, but a very small number (approximately 1 in 50–60,000 treatments) experience ongoing problems, requiring corrective lenses.[56] The second most common adverse effect is stimulation of acute confinement anxiety, which can often be managed with low-dose anxiolytics.[12] Additionally, around 4 % of patients experience middle ear barotrauma during the procedure.[64] Although painful, most cases of aural barotrauma are mild and recover spontaneously over a few weeks, allowing therapy to be resumed.[56]

13.3. Wound severity and pervasiveness

In countries where HOT is considered in clinical management of DFU's, such as the United States, suitability for treatment decisions are influenced by the Wagner Grading of the ulcer.[73] Wagner Grading ranges from zero to five, depending on severity of the DFU, and is used across several countries to provide an objective and standardised measurement for DFU classification. A zero on the scale represents a high risk foot without an ulcer, five represents extensive gangrene that covers the entire foot. The Undersea and Hyperbaric Medical Society guidelines suggest that HOT should be administered in patients whose symptoms have not resolved with standard treatment, with a Wagner Grade 3 or above (deep ulcer and abscess with associated bony infiltration or evidence of abnormal pulse at the location of ulcer, ischemic rubor or distal cyanosis).[74]

13.4. Conventional treatment resistance

In many countries where HOT is recommended for DFUs, guidelines state that first and second line treatments should be trialled first. Amongst first line treatments, the American Diabetes Association suggests wound debridement and management of infections, off-loading and glycaemic control. Second line interventions require secondary care in the UK, and include surgical revascularization and topical negative pressure wound therapy.[75]

14. Conclusion

Wound healing is a particularly complex process, involving many cells and signalling molecules, and it remains incompletely understood. The current evidence suggests that hyperglycaemia, hypoxia, chronic inflammation (due to infection, immune-cell dysfunction or other causes), peripheral neuropathy, and macro- and micro-vascular dysfunction may all adversely affect DFU healing.[23]

The current standard DFU treatment approach of glycaemic control, nutritional support, smoking cessation, off-loading, debridement, moist dressings, infection control and, if appropriate, revascularisation, is successful in many patients, but cannot prevent poor healing outcomes and amputations in a minority of cases.[31]

HOT, with its potential to address DFU hypoxia, shows theoretical promise and has been successfully used in the treatment of individual DFUs for several decades. Despite this, there remains a lack of strong clinical evidence of benefits to encourage HOT's wider adoption. The lack of clarity in the evidence is, in part, likely because DFUs are complex wounds and their presentation is variable in terms of severity, detectable ischaemia, co-morbidities and secondary infection.[3,67] Future studies should attempt to ascertain the nature of pathogenesis of DFUs and compare these as independent variables, to better understand the difference in effectiveness of HOT.[58]

Overall, it appears that HOT is a safe option for DFU treatment, although there are some important risks of minor adverse side-effects, related to the pressure changes involved. There are also clear issues around its global accessibility.

Further high-quality clinical research is needed, including RCTs and meta-analyses, to improve the evidence base for HOT, and research into cost effectiveness of HOT, or RCT's into the effectiveness of cheaper alternatives, such as topical oxygen therapy could be conducted. In the meantime, many leading world centres of hyperbaric medicine, such as the DDRC in Plymouth, continue to offer HOT for DFUs, as an adjunct to other treatment approaches, even if they are not endorsed by current clinical guidelines for these conditions.[47,68]

CRediT authorship contribution statement

Ken Mackay: Writing – review & editing, Writing – original draft. **Rhiannon Thompson:** Writing – original draft. **Matthew Parker:** Writing – review & editing, Writing – original draft, Project administration. **James Pedersen:** Writing – original draft. **Hayden Kelly:** Writing – original draft. **Mairi Loynd:** Writing – original draft. **Emily Giffen:** Writing – original draft. **Angus Baker:** Writing – original draft.

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Declaration of competing interest

None.

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