Alternative Therapeutic Approaches in Skin Ulcers Due to Systemic Sclerosis

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Alternative Approaches

Among the main principles of medical treatment, it has become evident that the use of alternative non-pharmaceutical therapies should play a more significant role in management. We present and discuss the various modalities and their mechanisms in this chapter aiming to highlight their efficacy and current evidence base in the treatment of digital ulcerations in scleroderma.

Hyperbaric Oxygen Therapy

The concept of hyperbaric oxygen therapy (HBOT) aims to raise the partial pressure of oxygen in plasma alongside saturating haemoglobin. By confining the patient within a compression chamber and raising atmospheric pressures to 2–2.5 atmospheric absolute units (ATA), a partial pressure of oxygen (PO_2) at or greater than 100 kPa [1, 2] can be established.

Plasma becomes highly oxygenated, and oxygen diffusion into tissues increases, thereby addressing the cellular hypoxia. Furthermore, the effects of HBOT have been shown to reduce postischaemic oedema, ameliorating tissue perfusion and the microcirculation [3]. Physiologically, the effect of raising the partial pressure of oxygen induces vasoconstriction though with compensatory higher oxygenation [4, 5]. Additionally, the delivery of high concentration of oxygen tends to increase the formation of free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) that in turn upregulates antioxidants [6]. As shown in the diagram below (Fig. 23.1), the overall therapeutic effects of HBOT can be explained by the anti-inflammatory and pro-regenerative mechanisms mediated via cellular signalling pathways [1].

Currently, the National Health Service of England has commissioned the use of HBOT for use in decompression illness, gas embolism and acute carbon monoxide poisoning [2]. However, the potential for its use in other disease states has also been extensively investigated [5, 7]. A Cochrane review regarding chronic diabetic ulcers illustrated an improvement in wound healing with supplementary HBOT, at least in the short term [8]. Table 23.1 shows HBOT applied in DU of scleroderma and its outcome. The studies shown identified patients with intractable peripheral ulcers associated with scleroderma. In all cases where HBOT was considered, patients' healing potential was assessed in terms of perfusion indices using transcutaneous oximetry. A reading greater than 300 mmHg under hyperbaric oxygen delivery

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satisfied the criteria for HBOT. As results showed, the outcomes were variable at 6 months post-HBOT with complete healing of some ulcers but not others, though consistently tissue perfusion had improved.

Such case reports shed light on the potential of HBOT in treating ulcers of scleroderma. The technicalities of such modality of treatment involve patients committing significant time in the chamber as well as being able to tolerate the confined space. Logistically, hyperbaric chambers are still not widely available; with various chambers of different treatment capabilities scattered across the United Kingdom and Northern Ireland [11] and over 500 across North America [12]. Additionally, the side effects of hyperbaric treatment include barotrauma of cavities, such as the ears, sinuses, teeth, eyes, gastrointestinal tract and lungs [13]. Careful monitoring of patients and pre-procedure assessments to identify any risk of barotrauma as well as appropriate reversal of atmospheric pressures require qualified and trained staff to manage the process.

In summary, HBOT has the potential to become a vital adjunct in treating digital ulcers associated with scleroderma. However, more studies and research is required, especially randomised controlled trials, as we have only seen sparse evidence published.

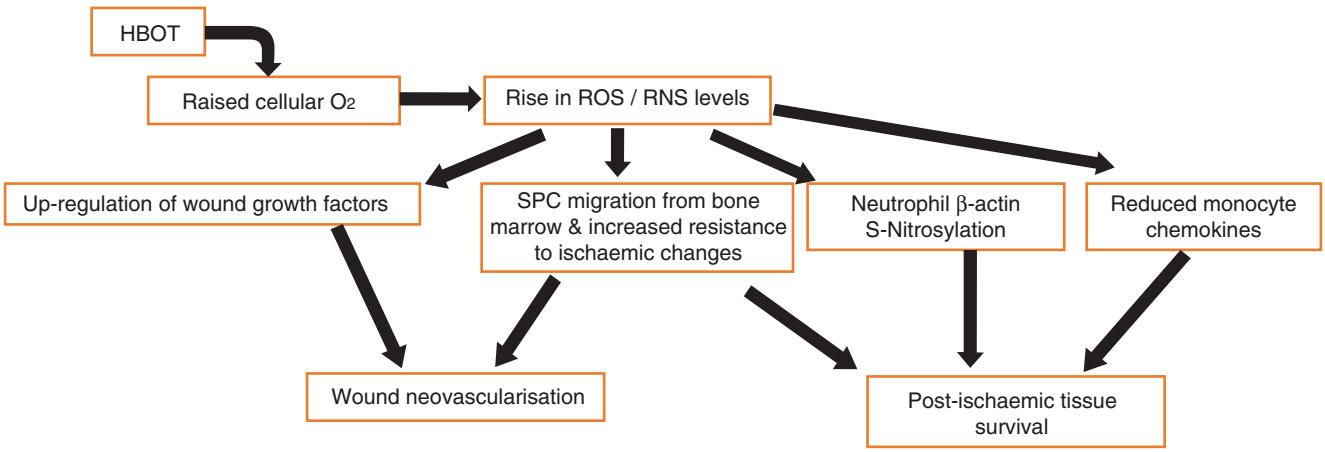

Fig. 23.1 Signalling pathways involved in tissue neovascularisation and tissue viability as induced by HBOT. At the centre of these pathways are ROS/RNS that act as signalling molecules, leading to various signalling cascades and promoting growth factors, stem cells recruitment and reduction in inflammatory mediators. SDF-1 stromal-derived factor-1, TGFβ1 transforming growth factor β1, VEGF vascular endothelial growth factor, SPC stem/progenitor cells, HIF-1/2 hypoxia inducible factor 1/2, HO-1 haem oxygenase-1, HSP heat shock proteins. (Modified from Thom [1])

Table 23.1 HBOT used for DU of scleroderma [9, 10]

Study		Patient	Methods	Outcomes
Markus et al. (2006) [9]	Case 1.	Bilateral medial malleoli ulcers in a patient with scl-70 antibodies positive scleroderma	HBOT at 2.4 ATA for 90 minutes per session, 5 days a week for 6 weeks	6 months post-HBOT: Complete healing with no recurrence
	Case 2.	Bilateral symmetrical ulcers of the third digits in a patient with overlap syndrome [systemic lupus erythematosus and limited scleroderma]	HBOT at 2.4 ATA for 90 minutes per session, 5 days a week for 6 weeks	6 months post-HBOT: Complete healing of right-sided ulcer Left sided digit remained ulcerated Overall perfusion improvement
Gerodimos et al. (2013) [10]	Case 1.	Ulcers at the left medial malleolus and right first toe in a patient with limited cutaneous scleroderma	HBOT at 2.4 ATA for 90 minutes per session for 34 sessions + regular debridement	Complete healing of the left ankle ulcer Right toe ulcer incompletely healed; though tissue perfusion improved (avoided amputation)

Botox

The botulinum toxin (Botox) is a neurotoxin derived from the gram-positive anaerobic bacterium *Clostridium botulinum.* Historically it has been described as the 'sausage poison' due to its association with an episode of mass poisoning following a feast on contaminated sausage and ham (not due to its morphology) [14]. Ever since, it has been developed to treat many conditions, as listed in Table 23.2.

Of the seven toxins produced by *Clostridium botulinum* (types A, B, C1, D, E, F, G), the neurotoxins A (or Botox-A), B and E are the most potent to humans with a potential to cause fatal botulism, particularly the former. The main targets of the botulinum toxin are acetylcholine systems at the neuromuscular junctions (NMJ), autonomic ganglia, postganglionic parasympathetic nerve endings and postganglionic sympathetic nerve endings. The toxin polypeptide itself comprises a heavy and a light chain. The combined mechanisms of the toxins include blocking neurotransmitter release at cholinergic nerve terminals [15–20], resulting in depressed endplate potentials at the NMJ and subsequent muscle paralysis [21]. At other sites of action, cholinergic mechanisms are also inhibited, such as at eccrine epithelia driven by acetylcholine (explaining its use in hyperhidrosis) and at smooth muscle structures [15]. One study [22] addressed the effects of Botox-A on different classes of cotransmitters at autonomic neurovasculature. Their findings implicated Botox-A in the partial inhibition of noradrenergic systems of vasoconstriction as well as eliminating cholinergic presynaptic inhibition of vasodilator neurones, conferring a state of vasodilatation independent of nitric oxide-mediated vasodilation. Animal studies have also shown that surgical flaps treated with Botox-A exhibited an increase in survival rate due to improved circulation and increased expression of vascular endothelial growth factor (VEGF) [23–26].

Further, recent studies illustrated the role of Botox-A, which also protected against endothelial damage in vitro by reducing the oxidative damage elicited during ischaemia-reperfusion injury [27]. In the study, episodes of ischaemia were induced as intermittent hypoxia to tissue, in an attempt to mimic ischaemia-reperfusion injury, the putative causal mechanism of Raynaud's phenomenon (RP). Altogether, these properties of Botox have made it a potential candidate in the management of digital ischaemia seen in Raynaud's phenomenon and associated ulceration. Subjectively and objectively, symptoms of RP such as pain, numbness, digital stiffness and perfusion as well as ulcer healing seem to improve by administration of Botox-A [28–34]. From local experience at the Royal Free London NHS Foundation Trust, an established scleroderma centre in London, Botox has been observed to provide symptomatic relief, mostly for ulcers occurring at or around the proximal and distal interphalangeal joints of digits (Fig. 23.2). The drawbacks of using Botox-A, however, include lack of standardised injection protocols and the potential side effects of botulinum at the target site. Local muscle weakness, albeit transient, has been reported [30]. Nonetheless, randomised controlled trials with Botox-A for RP and specifically addressing ulcerations are needed to substantiate the long-term effects and efficacy of such treatment.

Table 23.2 The established role of Botox in other conditions [15–19]

Domain						
Neuromuscular	Idiopathic focal dystonia	Craniocervical spasms and dystonias	Facial dystonias	Tardive dystonia	Chronic migraines	Primary hyperhidrosis
Pelvic floor	Detrusor-related overactive bladder					
Ocular	Primary/secondary eso/exotropia	Nonconcomitant misalignment	Paralytic strabismus	Restrictive or myogenic strabismus		
Cosmetic/ dermatologic	Glabellar lines	Facial and neck wrinkles, creases and lines				

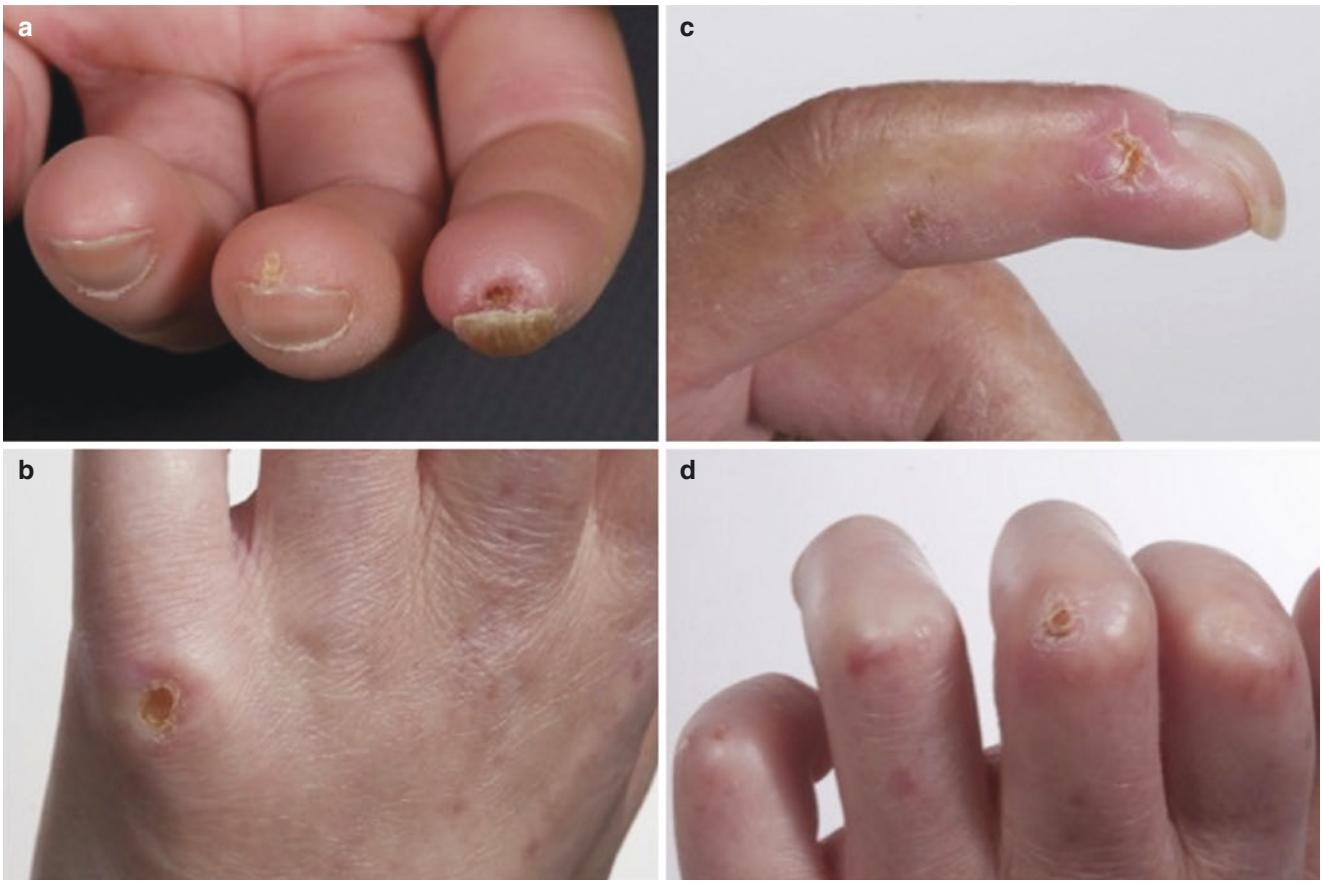

Fig. 23.2 Collection of images taken from patients with scleroderma with associated digital ulcerations due to trauma. From local clinical experience, ulcers occurring at the pulps (**a**) and the metacarpophalangeal (MCP) (**b**) region have not yielded much success when treated with Botox. However, symptomatic relief may be obtained when treating ulcers occurring around or at the distal (**c**) and proximal (**d**) interphalangeal joints. (Images from Salford Royal NHS Foundation Trust hospital, England, UK)

Vitamin E

Though technically an umbrella term for the various isomers of tocopherols and tocotrienols, vitamin E (the nutritional term) has become synonymous with the biologically active form, α-tocopherol. As a lipophilic molecule, it enters from the diet in chylomicrons and is carried in plasma as very low-density lipoproteins (VLDL). This essential vitamin plays a significant role in scavenging lipid peroxyl radicals terminating chain reactions of lipid peroxidation. Oxygen free radicals initiate the chain peroxidation of lipids, be it at the terminals of phospholipid membranes or low-density lipoproteins. α-Tocopherol evidently plays an important role in erythrocyte membrane stability by breaking this chain reaction. Upon scavenging free radicals, the oxidised form of vitamin E requires ascorbic acid (vitamin C) to regenerate and regain potency [35]. Evaluation of vitamin E has implicated it in maintaining endothelial integrity, inhibiting inflammatory adhesion molecules and pro-inflammatory cytokine release, as well as vasodilation and reducing platelet aggregation via prostaglandin pathways [36–40]. The following figure depicts the mechanisms of action elicited by α-tocopherol that may help protect the endothelium and cellular membranes (Fig. 23.3).

Patients with scleroderma exhibit low levels of vitamin E [41]. Clinical experience and case reports have shown the potential of this antioxidant in promoting beneficial skin changes, whether administered systemically or topically [42, 43]. Fiori and colleagues enrolled a group of 27 patients with known scleroderma-associated digital ulcers and studied the effects of a locally formulated vitamin E gel on topical application (Table 23.3).

The results showed that administration of vitamin E achieved more rapid wound healing, with better pain control, in turn reducing costs of any supplementary medications. However, the study did not address the long-term effects of such management. Further research with a larger sample size and prospective long-term follow-up is necessary to comprehensively ascertain the benefits of vitamin E as an alternative therapy for digital ulcers in scleroderma.

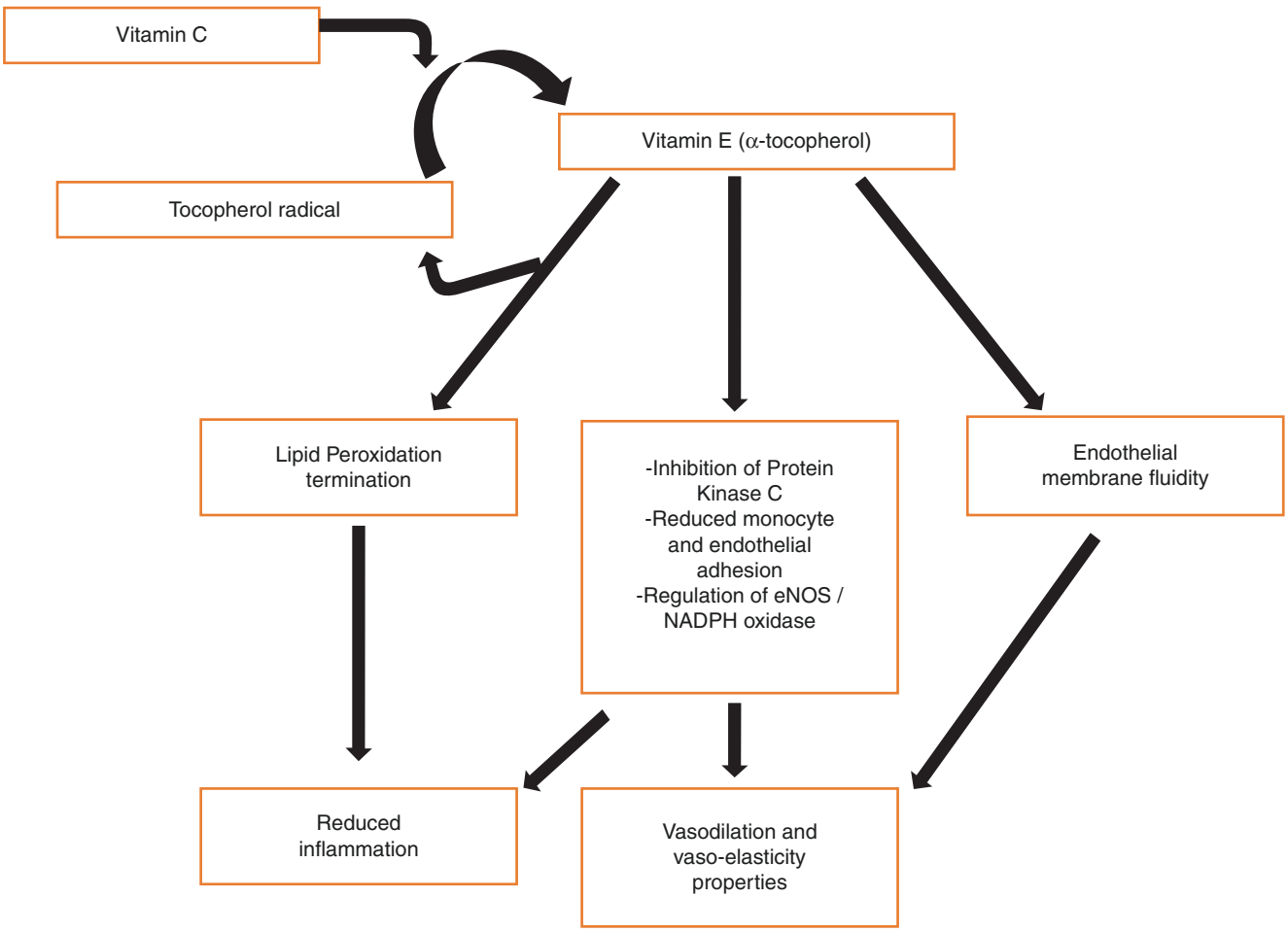

Fig. 23.3 Overview of the proposed wound healing and endothelial functions of vitamin E. Its actions involve maintaining cellular membrane stability as well as reducing inflammation while preventing damage to the elasticity of the endothelium. Recycling of vitamin E requires adequate presence of ascorbic acid (vitamin C). *eNOS* endothelial nitric oxide synthase, *NADPH* nicotinamide adenine dinucleotide phosphate

Table 23.3 Effect of vitamin E on digital ulcers of scleroderma

Study	Numbers	Methods	Outcomes	Potential
Fiori et al. (2009) [44]	27 patients with scleroderma digital ulcers	15 on experimental arm – topical vitamin E gel alongside wound care protocol	Mean time to healing: 7 weeks faster wound healing than controls	Faster healing, reduction in pain, reduction in consumption of other medications (including analgesics)
		vs.		
		12 on wound care protocol only	Reduction of pain at 18 sessions vs. 26 sessions for controls	

Topical Nitric Oxide Agents

Nitric oxide-generating agents can act as potent vasodilators via the metabolite nitrogen monoxide – or nitric oxide (NO). This is achieved by the formation of *S-nitrosothiols* intermediates as effective donors of NO [45]. NO binds the haem group of guanylate cyclase, activating this enzyme and releasing cyclic guanosine monophosphate (cGMP). The increasing number of cGMP lowers intracellular calcium and at the level of the endothelium relaxes smooth muscle cells. Moreover, the role of NO extends beyond its vasodilatory effects. Other functions include inhibition of platelet aggregation, killing of pathogens, bladder control and mediation of neurologic pathways [46]. Production of NO endogenously is derived from the nitric oxide synthase enzymes (NOS), comprising three recognised isoforms (Table 23.4).

Several literature reports have described increased levels of NO [47–52] in patients with scleroderma, while others have described the contrary [53]. The pattern, however, seems to show a tendency towards increased NO with higher levels of iNOS. Certainly, iNOS expression seems to correlate with worsening grades of disease progression at the digits [51, 52].

Regarding digital ulceration, however, Tucker and colleagues trialled topical sodium nitrite containing gels and tested these on the forearms and digits of patients with severe RP. The vasodilatory effects of NO were elicited in both patients with RP and healthy controls, though more so at the forearms than at the fingers [54]. They suggested a potential role for the use of this agent in the acute onset of RP. Further trials, using a customised formulation of a topical nitrate agent (namely MQX 503), also showed improvement in RP subjectively in terms of RP episodes and duration, pain, stiffness and hand disability, with better blood flow at the digits [55, 56]. Application of a preparation of glyceryl trinitrate (GTN) at the digits was also objectively shown to improve perfusion confirmed by laser Doppler ultrasonography [57].

Despite the raised NO levels that may be observed in scleroderma patients, it seems exogenous NO application may benefit these patients with RP symptoms and its sequelae. Conversely, the above-mentioned trials only investigated short-term effects of topical nitrite agents. Reported side effects of topical applications included headaches, dizziness, light headedness and local paraesthesia/skin irritation. Randomised controlled studies looking at long-term effects, dosages and standardisation of a topical regime are necessary. Nonetheless, this modality seems to offer a potential avenue in tackling RP and possibly preventing associated ulceration of the digits.

Table 23.4 The various types of NOS and their expression and effects physiologically [45, 46]

Isoform	Sites	Expression	Effects
Neuronal NOS (nNOS)	Neuronal	Constitutive, but levels inducible	Response to excitatory amino acids Neurotransmission/neuromodulation Synaptic plasticity (including long-term memory)
Inducible NOS (iNOS)	Inflammation (organs, endothelium or immune cells) Lung epithelium	Inducible	Free radical damage to pathogens Excess implicated in disease states
Endothelial NOS (eNOS)	Endothelium Some neuronal tissue	Constitutive, but levels inducible	Vasodilation Inhibition of platelet aggregation

External Compressions

Mechanical force to improve tissue perfusion is a simple yet effective modality. Applying external pneumatic pressure to limbs can improve blood flow, be it by continuous or intermittent compressions [58–60]. Pneumatic pressure creates a favourable arteriovenous gradient that allows perfusion of capillaries, vasodilation due to effects of sheer stress and loss of venous pressure leading to an inhibition of the autoregulation of the vasculature [61].

Many case series have identified intermittent pneumatic compressions (IPC) as having beneficial therapeutic outcomes in managing critical limb ischaemia. Limb salvage, wound healing, relief of pain at rest, increased blood flow to the affected limb, improved limb mobility, avoidance of limb amputation and an improved quality of life were among the positive outcomes reported in such studies [62–65]. A similar potential was observed in the context of scleroderma ulcers. Filho and co-workers looked at the effects of IPC in 17 patients with ulcers associated with scleroderma. Using IPC allowed for frequent healing of ulcers in the fingers and toes [66]. Confirmation of such healing in scleroderma was observed in a study where 5 h a day of IPC achieved healing of digital ulcers after 21 weeks, with a reduction in pain after commencing therapy [58].

As of yet, no large prospective and randomised controlled trials have been published regarding external pneumatic compressions. Nonetheless, the concept of compressions to alleviate distal ischaemia holds much promise. Many pneumatic devices have been marketed for other purposes, for example, for deep vein thromboprophylaxis [67]. Should enough evidence arise that favours their use in ulcers of scleroderma, then a rapid expansion in provision is conceivable.

Ultrasound Therapy

Ultrasonography has become a mainstay across various medical and surgical specialties, including therapeutic applications (such as physical therapy, lithotripsy, tissue ablation, bone fracture healing, transdermal drug delivery enhancement, thrombus dissolution and others) [68]. There has also been an increasing interest in the use of ultrasound in the treatment of chronic wounds.

One study looked at the effects of using non-contact, low frequency ultrasound therapy on venous ulcers [69]. In the randomised and controlled trial, it was observed that supplementing standard wound care with ultrasound therapy provided significant relief in pain after 4 weeks. Furthermore, ulcer area showed a significant reduction for patients receiving ultrasound adjunct compared to standard wound care alone, with twice the number of ulcers achieving complete healing after 7 weeks into treatment compared to the control arm. In another retrospective study looking at chronic wounds below the knee of various aetiologies, non-contact ultrasound therapy delivered by means of a saline mist intermediate also achieved more healing of wounds with a higher rate of healing compared to controls [70]. The mechanisms by which ultrasound seems to supplement better healing can be attributed to its debridement effects. It has been shown to destroy bacterial biofilms at wound sites through transient cavitation and bubble dynamics. Further, it promotes neovascularisation and favourable granulation tissue modification [71–74]. The Food and Drug Administration have recently approved this technique of non-contact low frequency ultrasound delivered with saline mist for ‘wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates and bacteria’ [75].

A case report of a 68-year-old male with a painful ulcer on his left second finger associated with limited cutaneous sclerosis highlighted the benefits of ultrasound therapy. Unable to tolerate regular debridement due to pain, the authors opted for ultrasound therapy along with standard daily dressings. After 6 weeks of 5 min application of ultrasonography, three times a week, the patient reported being pain-free from the ulcer and complete closure of the wound site was seen at 10 weeks [76]. This case report highlights the importance of trialling alternative therapies and can be a foundation stone for further research into digital ulcers. Prospective follow-up studies are required to determine the long-term effects of this modality of treatment. Certainly, the use of ultrasound requires competency and is highly operator-dependent. As with many treatment modalities involving chronic lesions, adherence to a strict and well-designed management protocol is crucial.

Iontophoresis

Iontophoresis is the process of delivering electric currents at microampere (μA) amplitude to aid and enhance the transfer of ionised compounds, such as medicines or chemicals, into the skin. Figure 23.4 illustrates this concept in a simplistic manner.

The idea is to be able to tolerate committing the affected skin area into a solution that aids in the ionisation of the drug to be delivered and close the electrical circuit for the system to function. Closure of the circuit could be done either by using one limb (or the affected area) in the iontophoresis device while on the same limb attaching the return cathode, or by using the contralateral limb also submersed in a solution (such as saline) as the downstream electrode.

Some uses of iontophoresis include treatment of hyperhidrosis (particularly of the palms and soles), where patients are required to undergo two to four sessions a week using tap water as the ionising solution only, though glycopyrronium bromide (an antimuscarinic agent) may be used with caution [77]. Delivery of vasodilatory agents with iontophoresis has also been studied. Circulatory enhancement, as observed using laser Doppler, was achieved when using iontophoresis to deliver acetylcholine (Ach) and sodium nitroprusside (NaNP) in patients with scleroderma [78, 79]. A later study examined the effect of iontophoresis in healthy subjects and the use of vasodilatory Ach and NaNP on a single finger and compared that blood flow to the adjacent finger. Their results confirmed an improved perfusion of the affected digit only [80]. A couple of years later, another study examined eight patients with scleroderma, but no ulcerations, and the response to finger-only iontophoresis at a current of 200 μA using Ach and NaNP solutions. The study found an improvement in blood flow in the fingers, with no systemic side effects [81].

The evidence is there that perfusion is ameliorated when using iontophoresis to deliver Ach and NaNP. However, results confirming whether this would prevent or help in the management of scleroderma ulcers are yet to be published.

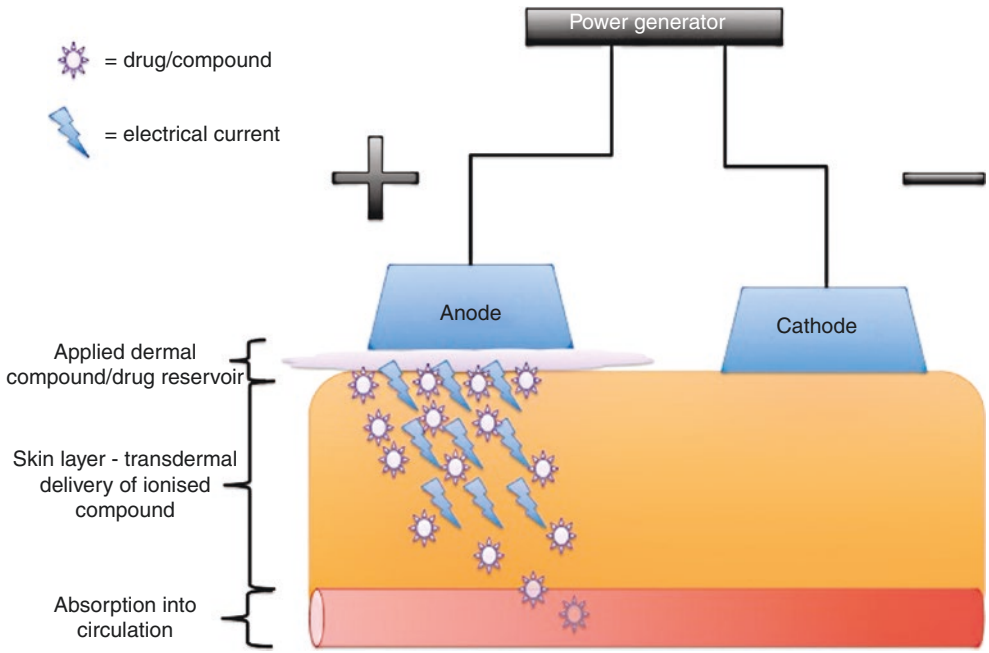

Fig. 23.4 Illustration of the mechanism of iontophoresis: a closed circuit current is required to ensure flow of ionised matter across the target area

Maggot Debridement Therapy (MDT)

Biodebridement, biosurgery, wound myiasis, larval therapy or maggot debridement therapy (MDT) refer to the use of living larvae of the greenbottle fly, *Lucilia sericata*, for the treatment of wounds. Historically, ancient tribal paintings from the Maya of Central America as well as from Australia's aboriginals depict the use of larvae for medicinal purposes. However, following the introduction of antibiotics, the popularity of larval therapy suffered [82].

Though an unpleasant thought for some, MDT is becoming more widely looked into as it has shown therapeutic benefits for pressure sores, decubitus ulcers, diabetic ulcers, neurovascular and vascular ulcers, osteomyelitis, necrotising fasciitis, postsurgical wound infections and burns [83]. The means by which maggots promote wound debridement include mechanical and enzymatic mechanisms. The maggot's mouth acts as a hook that latches onto necrotic tissue and along with their rough body surface allow for mechanical debridement as they crawl. Additionally, the excretions and secretions derived from maggots include enzymes and compounds (such as allantoin, sulfhydryl radicals, calcium cysteine, glutathione, collagenases and serine proteases, among others) that digest necrotic tissue and bacterial biofilms. Maggots have also been shown to ingest and kill bacteria in their guts as well as producing ammonia and altering environmental pH, inhibiting further bacterial growth [84]. Other maggot secretions have been shown to reduce complement proteins as well as enhancing growth factors from macrophages [82]. The use of MDT in chronic ulcers and wounds confirmed that healing time was shortened and improved the healing rate, which can potentially reduce the use of antibiotics while stimulating earlier onset tissue regeneration [84, 85]. Though no study has yet shown the use of MDT in the ulcers associated with scleroderma, this could be a promising new avenue for research.

Herbal Remedies

One cannot mention alternative medicine without delving into the realms of herbal remedies. To date, no herbal remedy has been identified or researched that may help in the treatment of scleroderma-associated ulcers, as per the authors' literature review. One study based in China looked into the cellular and molecular benefits of using Yiqihuoxue formula (Yqx), a traditional Chinese medication whose two main components are derived from the *Astragalus membranaceus* and *Salvia miltiorrhiza* plants [86]. *Astragalus membranaceus* is a perennial plant, native to the North and East of China, Mongolia and Korea. Its root is extracted and dried then used as the medicinal entity [87]. *Salvia miltiorrhiza* (red sage/Chinese sage) is a deciduous perennial plant, indigenous to Japan and commonly found in grassy forests and along streams in the West and Southwest of China. Its root is the main medicinal component [88]. The study identified a role for Yqx as being anti-fibrotic when applied to skin cells harvested from bleomycin-induced mice models (daily bleomycin subcutaneous injections for 3 weeks leading to skin fibrosis) as well as cultured fibroblasts from the skin of patients with scleroderma. It was postulated that the active ingredient of *Salvia miltiorrhiza* – salvianolic acid B (SAB) – acted against the cytokine transformation growth factor beta (TGF-β) signalling pathway involved in collagen production by fibroblasts, a process that is abnormally augmented in scleroderma [89, 90]. The immunomodulatory effects of *Astragalus membranaceus* were highlighted as its main contributing effect [86].

Another plant that has been studied is the *Capparis spinosa* – a green spiny shrub that naturally grows along the Mediterranean basin as well as the North-West of China. Its methanol extract has been shown to act as an antioxidant [91]. When applied to fibroblasts derived from scleroderma lesions, there was significant protection from free radical damage as well as exhibiting fibrotic-modulatory effects [92].

The studies discussed above only addressed the microbiologic effects of the herbal medications. Though potentially they exhibit anti-fibrotic effects, their application at a clinical level is yet to be determined. Further research in the uses of such remedies in patients with scleroderma ulcers is required.

Conclusion

Our experience suggests that alternative therapies may complement mainstream treatment in carefully selected cases. As we have seen, there are many potential alternative therapies that are being researched and applied at a preliminary clinical level. Research into the efficacy of most of these therapies is in its embryonic stages with some holding much promise. However, they are far from supplanting established treatments. Large-scale clinical trials with robust study methodologies are required to prove efficacy of most of the alternative treatments. We have seen hyperbaric oxygen therapy and topical vitamin E gels showing much potential, though only backed by case reports. There remains a lack of evidence addressing the long-term benefits and side effects of the therapies discussed. As such, alternative therapies may only provide a provisional complementary aid until further trials and studies prove otherwise.

Early disease recognition, basic wound care and preventative lifestyle measures are the cornerstone of managing digital ulcers. The importance of patient education and multidisciplinary team work cannot be overstated.

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