Direct Energy Therapeutics and Its Role in Chronic Wound Healing

These alternate therapies may improve outcomes.

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Chronic wounds impact the quality of life of nearly 2.5% of the total population in the United States and roughly 8.2 million Medicare beneficiaries.[1] Chronic non-healing wounds tend to be correlated with co-morbid conditions such as vascular deficits, hypertension, chronic kidney disease, and diabetes.[1] In the United States diabetes is the eighth leading cause of death.[2] It is estimated that the condition has led to $327 billion in medical costs in the U.S. alone.[2] In 2019, 37.3 million people were diagnosed with the condition, and 96 million individuals older than eighteen were diagnosed with pre-diabetes.[3]

Patients with diabetes are at risk for development of foot infections, with a yearly risk of up to 7%,[4] and a 25% lifetime risk of developing a diabetic foot ulceration (DFU).[3,5] The annual incidence of DFU worldwide is between 9.1 and 26.1 million.[6] One in six DFU patients experiences a limb amputation leading to a 5-year mortality rate of up to 77%.[5] It is therefore imperative to address management and treatment of chronic wounds, including DFUs, to prevent limb loss and/or loss of life.

Standard of Care for Chronic Wounds

Standard of care for chronic wounds consists of ensuring adequate vascularity to the wound area, bio-burden control, moist wound healing, and debridement of the wound, along with offloading for DFUs and compression for venous leg ulcers.[7] In addition to standard of care there is a plethora of specialized dressings, cellular, acellular and matrix-like products, advanced modalities, and technologies to facilitate the closure of chronic wounds. One of the advanced technologies consists of direct energy conversion devices. A direct energy conversion device converts one form of energy to another. Energy can be converted between electrical, magnetic, kinetic, optical, and chemical forms.[8] These devices are commonly found in everyday items including laptops and cell phones.[8] In the automotive industry they are found in car parts including batteries, optical cameras, and hall sensors.[8] The human body can also be considered an energy conversion device. For example, photoreceptors of the retina in the eye convert optical energy of photons to electrical energy of neurons.[8]

Energy conversion is a fundamental concept applied in many disciplines including branches of science and engineering.[8] Medical application of direct energy conversion can be seen in light therapy, radiofrequency, microcurrent, and extracorporeal shockwave therapy devices. This article will focus on the potential utilization of various direct energy technologies in the healing of chronic wounds.

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Light Therapy

Early origins of light therapy root back from Egypt, India, and Greece.[9] Medicinal use of light progressed into the 19th Century where it was referred to as “light as therapy” by Florence Nightingale.[9] In 1903, light therapy had been incorporated into medical practice in regions such as Scandinavia, America, and Australia.[9] In the 19th century, Dr. Niels Finsen was awarded a Nobel prize for the use of ultraviolet (UV) light in the treatment of lupus vulgaris and application of red light for the treatment of small pox.[10,11]

By the 1950s, light therapy, specifically UVB light, was being used in the treatment of dermatological conditions.[9] In the 1980s, other medical specialties, including ophthalmology

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and cardiology, had started implementing its use.[9] Since the 1990s light has been used globally in the form of photobiomodulation for management of conditions such as: lymphedema, cancer, depression, oral mucositis, retinopathy, and wounds.[9]

Photobiomodulation, also known as low-level light therapy (LLLT),[12] has been shown to alter cellular function.[5] Light therapy works by use of power laser or light emitting diodes where function is dependent on absorptive properties of the skin.[5] Absorption of light through photoreceptors of chromophores in tissue results in increased synthesis of collagen, cytokines, and growth factors, and initiates proliferative processes in wound healing.[5] Tissue that is exposed to LLLT absorbs the specific wavelength of light transmitted through the mitochondrial respiratory chain enzyme, cytochrome C oxidase (COX).[12] Photobiomodulation can activate a cascade of cellular events stimulating intracellular signaling pathways including the MAPK, PI3K, JAK/STAT pathways, which are responsible for tissue restoration in wound healing.[12] Device-setting parameters for therapeutic use of LLLT are dependent on the power density, wavelength, fluence, irradiation time, and treatment duration.[5] Therapeutic use of LLLT has been assessed in the literature for wound healing, in particular with diabetic foot ulcers.[13]

In a meta-analysis performed by Huang, et al.,[13] the effects of LLLT were assessed in treatment for DFUs. Thirteen randomized controlled trials with a total of 413 patients were analyzed. There were 227 participants in the intervention group and 186 participants in the control group. Severity of the ulcerations ranged from stage one to stage three on the Wagner scale, and duration of ulceration varied between one week to 95 months.

The patient follow-up time ranged between 15 days to 20 weeks. The wavelength was 400-904nm, power density of 50mW/cm2, fluence of 2J/cm2, irradiation time of 30 seconds, and a distance of 1 cm away from the wound. Results from this meta-analysis focused on three outcome measures: complete healing rate, ulcer area reduction percentage, and mean healing time. Nine studies provided data on the complete healing rate, five studies provided data on ulcer area reduction percentage, and two studies reported on the mean healing time.

All results were statistically significant and demonstrated that in comparison to the control group, LLLT had an increase in complete healing rate ($P < .00001$), reduction in the ulcer area ($P = .0002$),and decrease in mean healing time ($P < .00001$). The authors suggest that based on the findings of this meta-analysis, LLLT may have a potential for healing DFUs, and is a non-invasive, non-pharmacologic therapy that may be considered in promoting wound closure.

Radiofrequency devices create an electromagnetic field (EMF) that can interact with the electronegative and electropositive charges in skin.

Radiofrequency Devices

Application of radiofrequency energy for medicinal use dates back to more than 120 years ago.[14] It was first introduced by Nicola Tesla in 1891. He discovered that it was possible to produce heat in a human body, but it could also cause electric shock.[14] In 1892, Jacques Arsene d'Arsonval, a French physician and biophysicist, discovered that frequencies above 10kHz caused warming instead of shock to the human body.[14,15] R. Von Zaynek, an Austrian chemist, suggested use of radiofrequency heating for deep tissues, a concept later to be known as diathermy.[14,15] Currently, application of radiofrequency electromagnetic field (RF-EMF) has been integrated into medical devices to further evaluate therapeutic effects in wound healing.[16]

Radiofrequency devices create an electromagnetic field (EMF) that can interact with the electronegative and electropositive charges in skin. The transepithelial potential (TEP) in the stratum corneum of skin is electronegative, whereas in the subepithelial layer, it's electropositive.[17] In epithelial injury, disruption of the epithelial barrier collapses the TEP at the wound edge.[18] This results in the establishment of an endogenous wound electric field of about 100mV/mm that is directed towards the center of the wound.[18] The wound electric field guides epithelial cells to migrate directionally towards the cathode, the direction of the wound center.[18]

This phenomenon is known as galvanotaxis or electrotaxis.[19] These charges can then generate electrical signals to initiate repair following wound formation and stimulate tissue regeneration.[17] Most chronic wounds do not progress past the inflammatory phase.[20] For chronic hard-to-heal wounds, the use of EMF can potentially promote a shift out of the inflammatory phase to progress into the re-epithelialization phase.[16]

An in vitro study focused on wound healing evaluated cell migration and cytokine expression changes under a radiofrequency electromagnetic field.[16] The authors noted that time-varying exposure to an electromagnetic field can affect biological systems differently. The experimental design consisted of three different protocols (protocol A, B and C) to identify the specific pattern of exposure needed to improve wound healing.

Protocol A consisted of 30 minutes of RF-EMF exposure, followed by 6 hours of sham exposure, and another 30 minutes of RF-EMF exposure. Protocol B consisted of 6 hours of RF-EMF exposure, and protocol C consisted of 24 hours of RF-EMF exposure. The sham-exposed conditions for each protocol consisted of keeping the cells for the same duration of time without any radiation exposure. The results showed that RF-EMF contributed to progressive wound closure in a time-dependent manner in all three protocols, with protocol B demonstrating complete wound closure by 24 hours.

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Use of RF-EMF also promoted keratinocyte migration, regulated expression of genes involved in wound healing, such as matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases, and pro/anti-inflammatory cytokines. In this study, prolonged or decreased exposure to RF influenced changes in signal duration, protein expression, and cell migration in wound closure. The authors concluded that evaluation of different timing applications of RF may provide a better understanding of biostimulatory or bioinhibitory reactions in wound healing.

Microcurrent

In 1781, Luigi Galvani found that frog legs contracted when exposed internal crural nerves were touched by a scalpel.[21] He referred to his discovery as "animal electricity."[21] Alessandro Volta followed Galvani's work on frog legs where he concluded that electricity is produced by contact between different metals, and the frog was acting as a passive conductor.[21] In 1843, Dubois Raymond created a galvanometer based on the works of Galvani and Volta.[21] The galvanometer could detect currents of injury of approximately 1 μA for the first time.[21]

By the 1970s, non-invasive externally generated subsensory current therapy, known as microcurrent therapy, was developed.[22] Health-based application of microcurrent therapy can be explained by the Arndt-Schulz law, which states that weak electrical stimulation can increase physiological activities, whereas strong electrical stimuli can inhibit them.[22]

By the 1970s, non-invasive externally generated subsensory current therapy, known as microcurrent therapy, was developed.[22]

In unbroken skin layers, the skin battery is maintained by the epidermis and dermis, where movement of Na^{+}, K^{+}, Ca^{2+}, and Cl^{-} generate a polarity with positive and negative poles.[23] When an injury has taken place in the epithelium, an electric leak forms that short-circuits the skin battery.[23] This allows current to flow out of the wound, a principle known as the current of injury.[23,24] The current of injury is measurable 2-3mm around the wound and creates an electric potential.[23]

The current is sustained in a moist environment but shuts off when a wound dries out.[23] Since healing is arrested when the flow of current is disturbed,[23] microcurrent devices can mimic the current of injury to re-stimulate healing processes in wounds.[25]

In a study performed by Kurz, et al.,[25] microcurrent electrical stimulation therapy was applied in patients with hard-to-heal wounds. In total, 40 wounds and 39 patients

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were analyzed. Wound types analyzed were classified into the following categories: post-surgical, traumatic, diabetic foot ulcer, pressure injuries, and venous and/or arterial. Single use microcurrent devices were applied every 48 hours for a course of twelve days; thus six devices were supplied per box. The device automatically delivered low voltage biphasic and monophasic pulsed current (LVBMPC) for 30 minutes every two hours in the first 24 hours, and then every four hours during the next 24 hours, before the device needed to be replaced.

The parameters for the device were set to application of the current in a fixed pattern with biphasic components changing from 50 to 500 μA at pulse frequencies between

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50 and 900 Hz, and a monophasic component operating at 40 μA. Electrodes were placed on healthy skin on either side of the wound, so that the wound could still be dressed. Pain was assessed on a VAS scale at 48 hours, seven days, and fourteen days. Across all wound types, sixty eight percent (27/40) were considered painful. The results showed that 96% of patients with a painful wound experienced pain reduction within the first 48 hours of treatment, and at the seven- and fourteen-day mark. It was also noted that 78% of the wounds displayed reductions in peri-wound edema, inflammation, wound depth and area. Based on the results of this study, the authors suggest that potential benefits of microcurrent electrical stimulation use may include wound healing and pain relief.

Extracorporeal Shock Wave Therapy (ESWT)

Extracorporeal shockwave therapy (ESWT) first emerged around the 1980s as extracorporeal shockwave lithotripsy to disintegrate kidney stones.[26] In the early 1990s, effects of extracorporeal shockwave were seen on bone and soft tissues, which led to use in musculoskeletal disorders.[27] In 1995, guidelines on use of ESWT were established at a German consensus meeting.[27] The German Society for Orthopaedics and Traumatology contributed to further development of the device.[28] During this time period, shockwave was actively being used for sport orthopedic soft tissue indications.[27] Currently, ESWT is used for conditions such as tendonitis, epicondylitis, plantar fasciitis, and chronic diabetic ulcers.[26]

Shockwaves are a form of pressure waves, an oscillating mechanical wave that can propagate through solids, liquids, and gases.[26] Shockwaves have positive and negative phases that exert certain effect on interfaces between tissues and

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their varying densities.[26] In the positive phase, high pressure shockwaves may hit an interface and be reflected, or they may be gradually absorbed.[26] In the negative phase, or tensile phase, the shock wave generates cavitations at the tissue interface.[26] This results in the formation of air bubbles. Air bubbles can implode with high speed, producing a second wave of shockwaves or microjets of fluid.[26]

ESWT can be administered in different forms such as focused or radial shockwave therapies.[26] Focused shockwaves reach maximum pressure at increased depths of tissue and can be generated as electrohydraulic, electromagnetic, and piezoelectric forms.[26] These forms of focused shockwaves are similar in that they are generated in water.[26] Radial shockwaves have a diverging pressure field and reach maximum pressure at the source, targeting superficial structures.[26] Hypothesized theories on therapeutic use of ESWT suggest that biological effects of ESWT are a result of mechanotransduction, where the ultrasonic vibrations on tissues may lead to regeneration and healing.[26] ESWT may facilitate the generation of various growth factors and subsequently promote neovascularization of tissue, improving blood perfusion.[29]

In a meta-analysis performed by Zhang, et al.,[30] the effects of ESWT and conventional wound therapy were compared in acute and chronic soft tissue wounds. Ten randomized controlled trials with 473 patients were assessed. Age range of patients was between 45-69 years old. Conventional wound therapy (CWT) was applied in all studies, but in two of the studies, CWT was performed with hyperbaric oxygen treatment.

Frequency of shock wave treatment varied from 0.5 to 2 sessions per week for a duration of 1 to 8 weeks. Parameters for use of ESWT included impulses ranging from 25-500 pulses/cm2 with energy density between .03 and .23 mJ/mm2. Six studies used wound healing rates as an outcome measure and found that ESWT was more effective than CWT alone in the treatment of various wounds ($P < .0001$).

Five studies used percentage of the wound area to compare the effects of ESWT and CWT. The results demonstrated that ESWT statistically significantly increased the wound healing area and had a more significant treatment effect when compared with CWT ($P < .0001$). Four studies evaluated wound healing time and the results showed that on average the healing time was 11 days shorter in the ESWT groups than in the CWT groups ($P = .003$).

In a subgroup analysis, ESWT statistically significantly shortened the healing time of acute wounds by 3 days ($P < .0001$) and chronic wounds by 19 days ($P < .0001$) compared to CWT. Six studies reported wound infection after ESWT or CWT. The meta-analysis showed a statistically significantly lower incidence of wound infection after ESWT (53% reduction) when compared with CWT. The authors suggest that based on the data from the meta-analysis, ESWT may be an easily applied device with good therapeutic effects on acute and chronic soft tissue wounds of different etiologies.

Application of direct energy conversion devices such as light therapy, radiofrequency, microcurrent, and extracorporeal shockwave, as adjunctives to standard of care therapies may potentially improve patient outcomes in wound healing.

Conclusion

Chronic non-healing wounds, including diabetic foot ulcers, may pose many health challenges and risks to patients. Chronic lower extremity ulcerations can last on average between 12 to 13 months, and recurrence of these ulcerations occur in 60-70% of patients.[31] This may lead to significant loss of function and decreased quality of life.[31] Due to the detrimental effects of these ulcerations causing impairment, it may be of significance to explore advanced technologies and modalities that may improve health outcomes in these patients.

Wound care is generally managed with standard of care practices, but adjunctive advanced wound healing therapies may demonstrate promising results in wound closure. Application of direct energy conversion devices such as light therapy, radiofrequency, microcurrent, and extracorporeal shockwave, as adjunctives to standard of care therapies may potentially improve patient outcomes in wound healing. However, more studies are needed to further explore the benefits and risks of these direct energy conversion devices. **PM**

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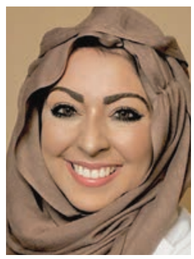

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