Electromagnetic Fields for Soft Tissue Wound Healing : HN Mayrovitz
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Abstract

There is continued debate as to the potential role of electromagnetic fields (EMF) in their various forms as adjunctive treatments for soft tissue wound healing. In this chapter the most current facts and viewpoints are brought together with the central theme of characterizing electromagnetic connections in soft tissue wound healing. To accomplish this various rationales for such connections are introduced specifically in relationship to wound healing. As further background the major wound healing processes are described with some emphasis on the concept of stalled healing of wounds and possible EMF connections. Thereafter specific major soft tissue wounds such as venous, ischemic, diabetic and pressure ulcers are presented. For each wound type the potential efficacy of EMF therapy is critically examined and discussed. The chapter concludes with a critical examination of possible cellular and functional targets for EMF therapy as they relate to wound healing. These include cells involved in wound healing such as endothelial, keratinocytes, fibroblasts, leukocytes and macrophages and important healing processes such as blood flow augmentation and edema reduction.

1 Introduction

This chapter deals with connections between wound healing and electromagnetic fields in the form of electrotherapy with electrodes (ET) or non-contact excitation (EMF). Either form is here referred to as EMFT. Despite evidence of such connections no mechanism can as yet account for such reported effects. A broad concept underlying EMFT in relation to soft tissue healing is that applied fields and currents beneficially affect functional aspects of cells and processes involved in tissue repair. Because standard treatments exist to deal with "typical" and uncomplicated wounds, EMFT is often reserved to treat wounds or ulcers that are chronic, non- or slow-healing, or recalcitrant to standard therapy.

One rationale for EMFT use for soft tissue healing initially derived from its efficacy in bone healing. Subsequent extensions to soft tissue healing have evolved with their own plausible rationales related to the body's natural bioelectric system (Becker, 1972, Nordenstrom, 1992) and from early observed relationships between electrical events and wound repair (Burr et al., 1938) and naturally occurring 10 μA current loops measured in human legs (Grimnes, 1984). Adding to these considerations is the fact that cellular function is largely determined by membrane electrical processes. A dermal wound will interrupt the normal epithelial cell potentials at the injury site causing an injury related electric field and associated injury currents that are postulated to play an important role in the healing process (Barker et al., 1982, Foulds and Barker, 1983). The injury currents and associated electric fields arise because of disruption of the normal trans-epidermal potential (TEP) that is maintained by Na^+ and Cl^- ion fluxes through their associated channels. In unbroken skin this results in a TEP between stratum corneum (SC) and the basal layer of the epidermis of 20-50 mv with the SC relatively negative (Barker et al., 1982). When a wound is present the TEP drives currents through the low electrical resistance of

the wound causing a lateral electric field (Nuccitelli, 2003) the magnitude of which decreases as the wound heals and which is smaller with advancing age (Nuccitelli et al., 2008, Nuccitelli et al., 2011). The injury current is reported as less than 1 mA with a lateral electric field of near 200 mv/mm at the wound site that reduces to zero at about 2 cm from the wound (Jaffe and Vanable, 1984). The injury current has been measured to be up to 22 nA/cm^2 at tips of accidentally amputated fingers in children (Illingworth and Barker, 1980). Because cells involved in healing are electrically charged the endogenous bioelectricity facilitates cells to migrate to the wound (Vanable, 1989) to help the healing process.

EMFT may interact directly with wound currents or with related signal transduction processes (Lee et al., 1993), thereby re-stimulating retarded or arrested healing. Alternately, we argue that EMFT may mimic one or more intrinsic bioelectric effects and help trigger renewed healing. Accelerated healing by direct currents (200-800 μA) may be due to such a process (Carley and Wainapel, 1985). There is more recent evidence to support the notion that applied low intensity currents in the range of the injury current can enhance wound healing (Balakatounis and Angoules, 2008). Another example may be that in which low level currents of about 40 μA delivered via wearable devices reduced periwound edema from an initial depth of 1.6 mm to about 0.6 mm after 10 days of treatment (Young et al., 2011) however additional research in this area is needed. Reported benefits of EMFT on cellular and other processes involved in wound repair are manifold and include edema reduction, blood flow changes and cellular proliferation, migration, differentiation and up-regulation of various cell functions as will be discussed subsequently. Although these and other factors are pieces of the puzzle they only suggest a beneficial result. Verification needs human wound studies in a clinical setting. Such human studies are difficult due to the complexity of the wound healing process and by

logistical and practical aspects of clinical wound research. In spite of these difficulties, clinical research with EMFT has progressed with promising findings and an increasing amount of direct and indirect evidence of benefits.

EMFT healing utility has mainly been tested in skin ulcers (arterial, venous, pressure and diabetes). Some data support the concept that EMFT triggers healing of "stalled" ulcers with benefits ranging from those on a single subject with multiple wounds (Bentall, 1986) through a small number of randomized controlled trials (RCT). For example, a meta-analysis showed that EMFT was associated with a 22% weekly healing rate compared with 9% for controls (Gardner et al., 1999). An analysis of 613 patients suggested a favorable EMFT effect (Akai and Hayashi, 2002). But, not all clinical reports meet the rigorous inclusion criteria needed for the high confidence level to validate medical efficacy. Protocols that control and adequately characterize patient, wound and treatment variables are logistically difficult and expensive of both time and money. This issue has been emphasized (Vodovnik and Karba, 1992) and is now recognized. Animal experiments have also shown positive connections between EMFT and wound healing. But most animal studies use wound models quite different from human "chronic" wounds that are those in which repair is stalled and difficult to manage and the types most likely to benefit from adjunctive EMFT. Contrastingly, many EMFT-related effects on cells, tissues and processes involved in tissue repair have been convincingly shown to occur as will be described.

It may stated that the scientific case for an EMFT connection to soft tissue wound repair is not complete or fully validated. But based on clinical, experimental and cellular observations, a connection between EMFT and wound healing is strongly suggested. In 2002 the accumulated information at that time led the U.S. Centers for Medicare and Medicaid Services (CMS) to approve coverage for electrical stimulation as adjunctive therapy for various ulcers (stage III/IV

pressure, arterial, venous and diabetic) if the ulcers had not improved after 30 days of standard treatment. In 2003 CMS extended this acceptance to EMFT. More recently some private insurers have adopted a similar policy for electrical stimulation (Aetna, 2014) but their policy clearly indicates that electrical stimulation is "*electrical current via electrodes placed directly on the skin in close proximity to the ulcer" whereas they consider "high-frequency pulsed electromagnetic stimulation experimental and investigational"*. With respect to any potential EMFT-wound healing connection we believe that much remains to be learned about the factors involved, mechanisms of action, specific targets, optimal dosing and patterns and temporal strategies. These aspects need further focused research and exploration. The following sections are written with the hope that they will provide the needed background and framework to aid in this future process.

2. Wound Healing Process Synopsis

2.1 Normal Healing

Normal wound healing has three broad phases: inflammation, proliferation, and remodeling. These occur in a well-ordered functionally overlapping sequence the outcome of which depends upon interactions among many cell types, growth factors such as Fibroblast Growth Factor (FGF) and Vascular Endothelial Growth Factor (VEGF). Cells involved are vascular such as platelets, macrophages, mast, polymorphonuclear neutrophils (PMN), monocytes, endothelial, and smooth muscle, and dermal cells such as keratinocytes, melanocytes, Langerhans, fibroblasts and myofibroblasts (Yamaguchi and Yoshikawa, 2001). As part of the repair process, cells release and/or interact with many components including structural proteins, growth factors, cytokines, chemokines, adhesion molecules, nitric oxide, trace elements and proteases. Any of

the broad array of cells and interactions could, in theory be a target for adjunctive EMFT. Some of these as possible individual targets for EMFT are discussed in 5.0.

The initial inflammatory process helps limit blood loss (via clotting), promotes antibody and fibrin entry into interstitial spaces (by increased vascular permeability), and delivers needed blood flow via vasodilation. This early hyperemia increases O_2 delivery that supports antibacterial actions of accumulating neutrophils. Activated macrophages are attracted to the wound by chemotactic and/or galvanotactic signals causing them to release substances important for 1) angiogenesis, 2) granulation tissue maintenance and 3) fibroblast and keratinocyte cell proliferation. Angiogenesis involves new wound capillary formation that is stimulated by angiogenic factors released from macrophages in response to low O_2 in the wound (Knighton et al., 1983), and by growth factors from fibroblasts and endothelial cells. Nitric oxide in the wound (Lee et al., 2001) also effects macrophage, fibroblast and keratinocyte functions (Frank et al., 2002). Fibroblasts migrate to the wound and proliferate. Collagen synthesis is triggered by fibroblast-stimulating growth factors released from macrophages, and continues at a rate dependent on the adequacy of blood flow to deliver O_2 and nutrients for protein synthesis. These nutrients include amino acids and interestingly, ferrous iron. Epithelialization of open wounds depends on epithelial cell 1) migration triggered by epidermal growth factor released from macrophages and platelets, and 2) proliferation at the wound site. The epithelialization takes days to months depending on wound related factors such as keratinocyte proliferation, migration, stratification, and differentiation and features of the extracellular matrix (O'Toole, 2001). Wounds close due to active contractile forces of myofibroblasts that are provided with their energy substrates via blood flow. After wound closure healing continues as wound remodeling continues for months to years. During remodeling, wound strength increases via collagen cross-

linking and excess collagen in the wound is eliminated, and many capillaries developed during early wound healing are resorbed.

2.2 Stalled Healing and Non-Healing Wounds

A wound is an added "metabolic organ" and healing depends on the body's ability to meet the demands of this "temporary organ". If healing delay exceeds three months then it is often called "chronic", "stalled", "recalcitrant" or "non-healing". Factors impeding healing may be local or systemic. Examples include infection, and inadequate blood flow, O_2 delivery or nutrient availability to support tissue building metabolic processes. Some conditions such as diabetes mellitus (DM) have further implications: Hyperglycemia and impaired insulin signaling directly impair keratinocyte glucose utilization thereby altering proliferation and differentiation (Spravchikov et al., 2001). Inhibiting nitric oxide production reduces fibroblast and keratinocyte healing activities that delay healing (Akcay et al., 2000, Shi et al., 2001). Deficient wound concentrations of platelet activating factor impair healing of venous ulcers (Stacey and Mata, 2000). Given the many potential causes for retarded healing, no "most important" target has been defined. But, since blood supply plays a major role in healing, increases in blood flow and O_2 supply are often stated targets of EMFT and will be further discussed in section 4.2.

Beyond blood flow, evidence (Costin et al., 2012, Pesce et al., 2013) suggests EMFT can alter the wound bed cytokine profile moving it from a chronic pro-inflammatory profile to one that is anti-inflammatory thus "kick-starting" stalled wounds. There is also evidence that PEMFT increases tensile strength of experimental wounds (Strauch et al., 2007). A novel EMFT excitation pattern, based on a possible role of sensory nerves in healing, showed promise in treating a mixed etiology hard-to-heal wounds (Ricci and Afaragan, 2010). The pattern was a PEMF signal (4 ms, 4 Hz) imbedded in stochastic noise. The noise component was used based

on the assumption that it increases sensory nerve function via stochastic resonance (Kruglikov and Dertinger, 1994) and thereby improves healing. More study of this approach is warranted.

3. Methods and Strategies for EMF-related Wound Healing

EMFT may be applied at a wound site or remote to the wound so therapy may be use electric currents and fields in which the wound itself is directly or remotely treated. For ET an electrode may be placed directly in the wound bed or the wound may be in the path of electrode pairs that straddle the wound. Alternately, electro-stimulation may target nerves or tissue regions that functionally connect with, and potentially alter wound site processes, either directly or via reflex effects with EMF or ET. EMF methodologies have been reviewed (Markov, 1995, McCulloch et al., 1995) and discussed in this volume. Since with EMF devices no contact electrodes are needed they can produce effects in cases in which direct contact with skin is not advisable or possible such as when limbs and/or wounds are bandaged or otherwise covered. EMF devices use time varying excitation that may modulate a carrier frequency historically at 27.12 MHz. EMF devices differ with respect to tissue heating effects with only some specifying device power but rarely giving energy delivered to target tissues. . Tissue thermal effects can be reduced using low duty cycles in which heating of a single high power short pulse is dissipated during a much longer off-time between adjacent pulses. Pulse widths and shapes vary with some proprietary patterns claimed to be particularly effective with patents awarded for these claims. Wound treatment parameter variants include device power and magnetic field intensity, carrier frequency and pulse width, rate and duty cycle. There are also variants regarding excitation pattern specifics, *i.e.*, whether stimulation is continuous or pulsed, galvanic or frequency modulated, biphasic or monophasic, symmetrical or asymmetrical, sinusoidal or not, and whether high voltage or low voltage stimulation is used (Markov, 1995, Kloth, 2005). This wide range of

excitation parameters makes it difficult to correlate specific treatment parameters with wound healing efficacy. But, PEMFT with its inductive coupling to tissue, may provide a more uniform and predictable EMF signal in target tissues than is achieved with surface contact electrodes (Markov and Pilla, 1995) and tissue dose may be more reliably characterized. Further, the large spectral range of PEMF likely offers more chance for field coupling to produce effects in a wider range of possible (but as yet unspecified) biological processes.

4. Clinical and Related Findings Relevant to Wound Treatment using EMFT

4.1 Venous Leg Ulcers (VU)

Venous leg ulcers, (illustrated in **figure 1)**, are the most common chronic skin ulcer. They have a prevalence of near 1% (Nelzen, 2008), a open wound point prevalence of 0.1%-0.3% that increases with age. VU prevalence appears to be increasing (Lazarus et al., 2014). Venous reflux and venous hypertension due to incompetent venous valves and venous thrombosis are common findings in persons with VU. The genesis of the skin breakdown and ulceration is complex (Tassiopoulos et al., 2000). Its contributory factors include inflammation, up-regulation of intercellular and vascular adhesion molecules (Peschen et al., 1999), protein rich edema and leukocyte trapping (Smith, 2001), O_2 and microcirculatory deficits (Gschwandtner and Ehringer, 2001, Valencia et al., 2001) and PMN activation (McDaniel et al., 2013). Microvascular

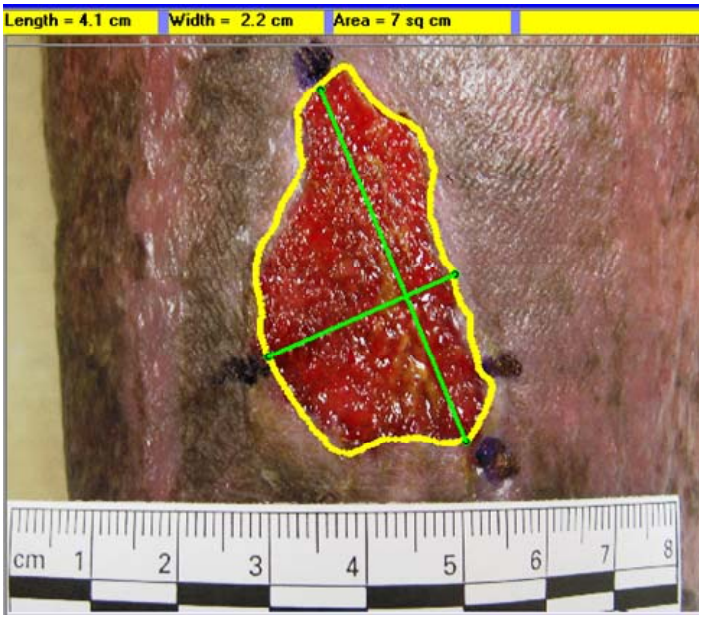

Figure 1. A typical venous ulcer (VU) located on the lateral calf. The perimeter of the VU is outlined so that its area can be determined and Changes tracked and quantified to evaluate treatment effects. In this case The area is 7 cm^2 determined by available software (www.clinsoft.org)

changes include dilated and tortuous capillaries with some capillary loss and increased capillary permeability with an increased transcapillary fluid efflux with tissue edema and altered microlymphatic function. Compression bandaging is the mainstay of standard treatment (Tang et al., 2012) that also helps normalize capillary numbers and size (Junger et al., 2000) and normalize the abnormally elevated leg blood flow (Mayrovitz and Larsen, 1994a).

In a prior review (Flemming and Cullum, 2001b), three eligible randomize controlled trials (RCT) studies were identified. A more recent review found no new additional eligible RCT studies (Aziz et al., 2013). In this latest review the authors state that "there is no high quality evidence that electromagnetic therapy increases the rate of healing of venous leg ulcers, and further research is needed". Of the studies reviewed, one (Ieran et al., 1990) compared sham vs. PEMFT (75 Hz, peak field of 2.8 mT) in 37 patients (19 sham) for 90 days. VU were present for 30 months in the actively treated group vs. 23 months in controls. PEMFT was administered over the wound by patients at their homes for 3--4 hours per day. After 90 days, 12 PEMF treated ulcers healed, compared to six in the sham group ($p<0.02$). Granulation tissue, not present prior to treatment was present in all PEMFT ulcers by day 15, whereas 7 sham group ulcers showed new granulation tissue. The other RCT (Stiller et al., 1992) investigated 27 patients with recalcitrant VU. Patients were treated for 8-weeks at home for 3 hours per day with a wearable portable EMF device that delivered a 22 Gauss bidirectional pulse of 3.5 ms at a 25% duty cycle. All received compression bandaging and daily 3-hour leg elevation. At week 8 the PEMFT group (N=17) had a 47.7% decrease in wound surface area vs. a 42.3% increase for sham ($P < 0.0002$). The investigators' global evaluations indicated that 50% of VU in the PEMFT group healed or markedly improved, vs. 0% in the sham group.

Other studies suggest benefit of EMFT of various types for VU healing. Twin 100 volt pulses (0.1 ms, 100Hz) used directly on ulcers caused healing rates superior to standard therapy alone (Franek et al., 2000). In a unique study, EMF patterns were adjusted to interact with human monocytes and then used as the sole treatment for VU patients (Canedo-Dorantes et al., 2002). Results, suggested a benefit of this treatment pattern. Improved VU healing of an ET pattern of frequency modulated short pulse sequences has also been reported (Jankovic and Binic, 2008). A recent small study used a wearable EMF device to treat VU (Rawe and Vlahovic, 2012) with reported good results while another wearable device used 40 μA currents that reduced periwound edema (Young et al., 2011) and indicated possible accelerated healing but more study is needed.

4.2 Ischemic Ulcers

A main predisposing condition for ischemic ulcers is advanced peripheral artery disease affecting arteries supplying the leg and foot. This ulcer type (example shown in **figure 2**) can be painful and difficult to treat. Improving low blood flow is key and therapies for which standard medical approaches have failed would be a most welcomed development. This ulcer type may be an important target of EMFT in the future. Pilot work (Goldman et al., 2002) using high voltage pulses to treat ischemic ulcers in diabetic patients with very poor microcirculation raised periwound O_2 sufficiently to save some legs from amputation. More recently a novel experimental wound model was used to test the efficacy of PEMF treatments in diabetic and

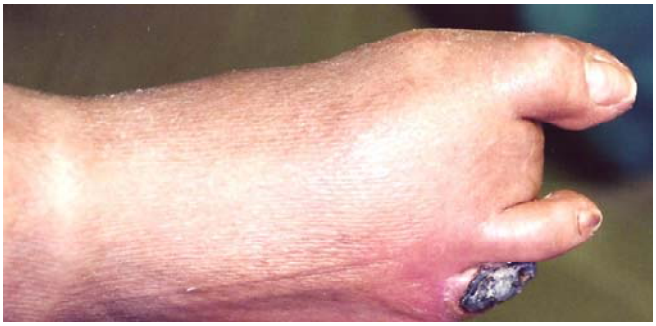

Figure 2. An ischemic ulcer on the small toe that has become necrotic. Ischemic ulcers arise due to inadequate blood flow often due to vascular disease. Their location varies but may be near bony surfaces exposed to external pressure. EMFT might be useful as a way to augment blood flow.

normal mice (Callaghan et al., 2008). They used a trapezoidal pulse (200 □s rise time and 24 □s fall time) of 4.5 ms duration and 12 Gauss peak. It was applied at 15Hz to full thickness wounds on the mice's back. Results indicate that this PEMFT reduced healing time from about 24 to 18 days in diabetic mice and from 15 to about 11 days in non-diabetic mice. From other measurements they concluded that improved healing was due to an up-regulation of FGF that via enhanced angiogenesis improved circulation and thereby caused healing acceleration.

Low blood flow impedes ischemic ulcer healing so for EMFT to be effective it must improve flow. Early work investigated flow augmentation to ischemic regions via reflex effects using pulsed radio frequency excitation (PRF-EMF) at 27.12 MHz applied to epigastric regions in healthy persons (Erdman, 1960) and patients with peripheral arterial disease (Hedenius et al., 1966). A remote site instead of the foot or ulcer was used to produce a reflexive flow increase without imposing more metabolic demand on the distant (ischemic) region. Healthy subjects (N=20) showed a dose-dependent increase in foot circulation judged by toe temperature and plethysmography (Erdman, 1960). Patients with intermittent claudication who received 12 PRF-FEMF treatments also had increased toe temperature (>3.0^{o} C) (Hedenius et al., 1966) but elevations were short-lived after 20 minute treatment. Cumulative effects appeared to be sustained judged by increased pain-free walking distance.

More direct blood flow measures used laser-Doppler (Mayrovitz and Larsen, 1994c, b, 1996) that permits skin flow to be measured before, during and after EMFT. PRF-EMF (65 μs, 600 pps, 1 G) was applied 1.5 cm above foot ulcers in diabetic patients. EMFT increased periulcer blood perfusion. Based on observed flow patterns the authors judged the increase to be mainly due to increased number of capillaries with active blood flow. This suggestion was consistent with an EMF-related capillary recruitment process (Mayrovitz and Larsen, 1996) due to

arteriolar vasodilation. Similar microcirculatory flow increases were reported for forearm skin of healthy persons (Mayrovitz and Larsen, 1992) and persons with post-mastectomy lymphedema (Mayrovitz et al., 2002c). Interestingly, no effects of static magnetic fields (500 Gauss) were observed on hands (Mayrovitz et al., 2001) or forearms (Mayrovitz et al., 2002b) or in response to vasoconstricting maneuvers (Mayrovitz et al., 2005) but a slight *reduction* in finger resting skin blood flow was found (Mayrovitz and Groseclose, 2005).

A prior pilot study suggested that EMFT in the form of high voltage pulses could increase periwound blood flow and increase ulcer healing (Goldman et al., 2004). More recently high voltage pulsed currents delivered via multiple pairs of electrodes on the leg and foot over multiple two-week cycles resulted in an acceleration of healing of arterial and mixed factor ulcers as compared to standard treatments (Magnoni et al., 2013). This method uses a treatment protocol with a pseudorandom modulation of pulse sequence parameters during the course of about a 30 minute treatment interval and is referred to as FREMS. Prior use of this method indicated a potential to increase skin blood flow (Conti et al., 2009) perhaps suggesting at least one mechanism for its reported effectiveness in this study and previously (Jankovic and Binic, 2008). Along similar lines, pulsed EMF (15 Hz, 6 mT) applied to previously ischemic myocardium of mice caused an increase in both VGEF and capillary density with improved infarction size (Yuan et al., 2010) and indications of cardiomyogenesis (2 Hz, 2 ms, 4 nA) in cellular studies (Wen et al., 2013) . The concept of a link between various forms of EMFT and blood flow is supported by other studies. For example, epidural spinal cord electrical stimulation (ESES) appears to benefit patients with severe lower extremity ischemia secondary to atherosclerotic disease. This approach, which uses implanted electrodes at the T10--T11 level and an implanted pulse generator increased microscopically measured blood velocity in

capillaries and density of skin capillaries in the foot (Jacobs et al., 1988). In patients with rest pain and ischemic ulcers, this technique resulted in immediate pain reduction, and in most patients was accompanied by microscopically verified increases in capillary blood velocity and density, and a significant increase in post-occlusive microvascular hyperemia (Jacobs et al., 1990). In more than half of these patients, the ulcers subsequently healed. Other studies using ESES have shown similar limb salvage rates and ulcer healing potential (Graber and Lifson, 1987, Mingoli et al., 1993). In patients with and without ulcers, the amount of therapeutic success depends on increased transcutaneous oxygen tension (Claeys, 1997, Kumar et al., 1997, Fromy et al., 2002), which itself depends on an increased blood flow. Further work in assessing various EMFT methods and parameters targeting treatment of arterial and ischemic ulcers is importantly needed.

4.3 Diabetes Mellitus (DM) - Related Ulcers

Persons with DM are more susceptible to skin ulcers due to neuropathy, ischemia and poor glycemic control. A higher likelihood of peripheral arterial disease and microvascular deficits increases chances for ischemia, tissue breakdown, and ulcer formation. DM skin ulcers may be difficult to heal for reasons that include reduced blood flow and wound O_2, functional deficits in cells normally involved in healing and infection. It takes much less local pressure to reduce skin blood flow inear bony prominence in persons with DM (Fromy et al., 2002). If sensory neuropathy is present normal pressure/pain signals are reduced or absent causing loss of warning sensations of impending tissue injury. Most of these ulcers are diabetic foot ulcers (DFU) with plantar ulcers (**figure 3**) a common type. For persons with DM the prevalence of DFU is reported as 4-10% (Singh et al., 2005), an

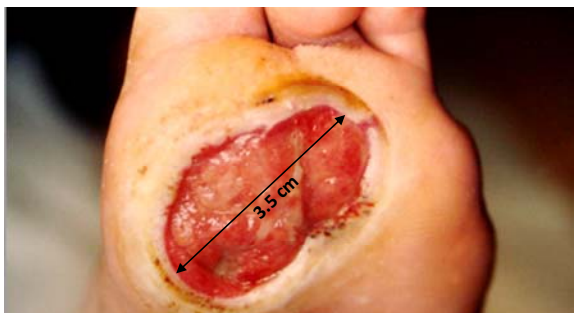

Figure 3. Diabetic plantar ulcer in a patient with sensory neuropathy. Though this ulcer appears on the bottom of the foot this type can Occur at other sites that are subject to un-sensed sustained pressure.

annual incidence of 2.5%-10.7% (Hunt, 2011) with the most common combination present reported as being neuropathy + minor foot trauma + foot deformity (Reiber et al., 1999) with edema accounting for 37% and ischemia for 35%. Persons with DM have a lifetime 10% -15% chance of getting a DFU (Gonzalez and Oley, 2000) with about half having vascular complications resulting in 0.5-0.8% of them receiving amputations (Muller et al., 2002). Treatment includes foot offloading and standard wound care (Crawford and Fields-Varnado, 2013) with a variety of supplementary and adjunctive measures being reported as potentially efficacious (Brimson and Nigam, 2013, Holmes et al., 2013, Hamed et al., 2014, Houreld, 2014).

Regarding the utility of EMFT, an earlier study (Peters et al., 2001) used pulsed-galvanic electric stimulation (50 volts, 100 μs), delivered through conductive stockings for 8 hours every night to treat 40 diabetic foot ulcers. The EMFT was given for 12 weeks to half the patients with all patients receiving standard wound care and foot offloading in this randomized, double-blind, placebo-controlled pilot study. Seventy one percent of protocol compliant patients receiving EMFT healed compared with 29% in the sham treatment group (p=.038). The authors concluded that EMFT improved wound healing. A different EMFT approach was used to treat ulcers of a group of 80 diabetic patients. Daily treatment used a biphasic stimulation pattern with either asymmetric or symmetric square-wave pulses at amplitudes to activate intact peripheral nerves in skin. Controls consisted of groups that received either very low levels of stimulation current, or no electrical stimulation. EMFT healing rates (ulcer perimeter changes) were significantly greater than controls only if asymmetric treatment was used (Baker et al., 1997). Further, a group of 64 diabetic patients with chronic ulcers, half of whom were treated with electrical nerve stimulation (80Hz, 1 ms) sufficient to induce paresthesia were reported to have significantly reduced ulcer area and more healed ulcers after 12 weeks of twice daily 20 minute treatments

(Lundeberg et al., 1992). More recently, In two interesting case studies extremely recalcitrant ulcers were reported to be healed only after the introduction of 27.12 MHz pulsed EMFT (Larsen and Overstreet, 2008) and more recent case studies reported potential efficacy of micro-current type EMFT (Lee et al., 2009, Ramadhinara and Poulas, 2013). The utility of PEMFT to heal wounds in diabetic mice with low level currents has already been described (Callaghan et al., 2008) in section 4.2. Despite the various reports citing positive outcomes of EMFT, it is felt by some that there is insufficient high level evidence of efficacy as put forward in recent reviews (Game et al., 2012, Gottrup and Apelqvist, 2012). In some ways, plantar ulcers in persons with leprosy resemble diabetic ulcers. In a pilot, randomized, double-blind, controlled clinical trial (Sarma et al., 1997), 40 leprosy patients with plantar ulcers received standard treatment and half of them also received pulsed sinusoidal magnetic fields (0.95 to 1.05 Hz, 2400 nT) for four weeks. Outcome measures changes in ulcer volume at treatment end. Control group ulcer volume of 2843 mm^3 was reduced to 1478 mm^3 at the end of treatment corresponding values in the EMFT group were 2428 $mm^3$and 337 mm^3. These data indicate that the EMFT caused significantly more rapid healing in these leprosy patients.

4.4 Pressure Ulcers (PU)

Pressure (decubitus) ulcers result from sustained or inadequately relieved pressure, often on bony prominences including heel, trochantor and sacral regions (**figure 4**). The clinical stages of pressure ulceration range from non-blanching erythema (Stage I) through full-thickness skin loss with extensive destruction and tissue necrosis involving muscle or bone (stage IV). These PU are an important clinical, humanitarian

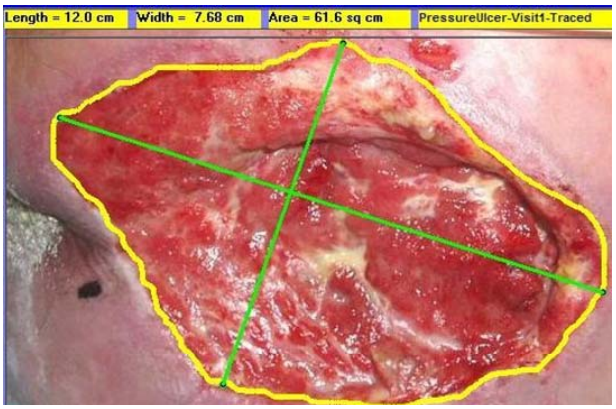

Figure 4. Large pressure ulcer located on the buttocks. Tracing outlines its perimeter and measured area is 61.6 cm^2. Pressure ulcers are often the result of blood flow deficits and tissue injury due to unrelieved pressure in the region of bony prominences.

and economic problem with a prevalence ranging from about 5%-50% depending on the type of care facility (Gottrup et al., 2013, Gunningberg et al., 2013, Aygor et al., 2014) and patient features that include such factors as age, nutritional status, mobility (Byers et al., 2000), co-existing morbidities (Amir et al., 2013, Moore et al., 2013, Scheel-Sailer et al., 2013) and general aspects of patient fragility and possibly ethnicity (Harms et al., 2014). Often a final common pathway is associated with blood flow changes within pressure-loaded tissue (Mayrovitz et al., 1997, Mayrovitz, 1998b, Mayrovitz and Smith, 1998, Mayrovitz et al., 1999, Mayrovitz and Smith, 1999, Mayrovitz and Sims, 2001, Mayrovitz et al., 2002d). These concepts may have clinical utility in persons with spinal cord injuries (Jan et al., 2013, Smit et al., 2013, Sonenblum et al., 2014). Some experimental evidence suggests that both ischemia and ischemia-reperfusion injuries are involved (Peirce et al., 2000).

Based on available RCT at the time (Sheffet et al., 2000, Flemming and Cullum, 2001a) EMFT for PU was judged to be insufficiently verified. In 2003 the CMS concluded that EMFT was an acceptable treatment modality for stage III and IV PU if healing had not progressed after 30 days of standard treatment. More recently (Smith et al., 2013) concluded that electrical stimulation was one of several adjunctive therapies that might have benefit. Some earlier studies, although not confirmatory do provide interesting and suggestive findings of potential benefits of EMFT for PU. One small study (Comorosan et al., 1993) used PRF-EMFT (27.12 MHz) on patients with long-standing PU and found significant improvement over standard treatment alone. Another study (Salzberg et al., 1995) was a randomized and double-blind and used PRF-EMFT or sham to treat a 30 spinal cord injured patients who had either stage II or III PU. Ulcers were treated for 30 minutes, twice daily, for 12 weeks, or until healed. The authors indicate that, after controlling for the baseline status of the PU, PRF-EMFT was independently

associated with a shorter median time to full healing. Use of the same PRF-EMFT method to treat patients with stage II or III long-standing PU also resulted in improved healing (Itoh et al., 1991). Similar positive results of pulsed current (300--600 μA) were reported in a double-blind placebo controlled study of long-standing stage II and III PU in which healing rates were improved with pulsed low current treatment (Wood et al., 1993). Pulsed stimulation (200 volts, 100 pps) used to treat PU in spinal cord injured patients was reported to achieve a greater reduction in ulcer area as compared to a placebo group after 20 days of treatment (Griffin et al., 1991) and treatment of 150 persons with spinal cord injury using a pulsed biphasic stimulation (0.25 msec, 40 Hz, 15--25 mA) resulted in significantly faster healing (Stefanovska et al., 1993). Based on available clinical data, it appears to this author that there is a reasonable but not conclusive case for a beneficial effect of EMFT for treating pressure ulcers. Additional studies of the role of EMFT in PU treatment and its possible prevention appears warranted.

5. Possible Cellular Targets and Mechanisms

Mechanisms by which applied EMF alter cell properties and biological processes to cause improved wound healing are unknown. Theories describing how EMF interactions might occur at cellular and subcellular levels are discussed elsewhere in this volume. Whatever the specific mechanisms turn out to be in relation to wound healing, it is this author's opinion that clinical efficacy depends on determining the proper therapeutic parameters and timing to optimally modulate cell features and their interacting processes in the context of the wound healing cascade. Specific targets for any of the postulated mechanisms could theoretically be any cell or function involved in the wound healing process. A prior review (Mayrovitz, 2004) has described some of the potential targets for EMFT in relation to wound healing. These include endothelial

cells, fibroblasts, leukocytes, macrophages, and keratinocytes. The following summarizes key aspects of these and includes progress achieved since that prior review.

5.1 Endothelial Cells (EC)

A link between EMFT and EC possibly connected to wound healing is suggested by EC proliferation (Delle Monache et al., 2008) induced by low frequency stimulation (1 mT, 50 Hz) although its specific role in granulation tissue angiogenesis is unknown. Interestingly a low intensity *static* magnetic field (120 μT) also increased EC proliferation (Martino et al., 2010). The involvement of a free radical mechanism was suggested (Martino, 2011). In vitro EC proliferation was described some years ago (Yen-Patton et al., 1988). Because endothelial cells are intimately involved in the angiogenic process the migration of endothelial progenitor cells in an electric field was carefully studied (Zhao et al., 2012). Results indicated these cells move in the field's direction in association with VGEF signaling (Bai et al., 2011). This suggests a new way in which various EMFT signals may play a role. Because many effects of VGEF on EC depend on Ca^{++} signaling (Cheng et al., 2006) this may turn out to be another example of an EMF-Ca^{++} connection.

5.2 Keratinocytes

Wound healing needs epithelial cell proliferation, migration and differentiation to re-epithelialize. Keratinocyte migration occurs during the proliferative phase and is guided by galvanotaxis whereby keratinocytes migrate to the wound and then differentiate. Reduced keratinocyte proliferation or migration can lead to impaired healing. Impaired migration may occur due to deficient lateral field gradients associated with the injury current previously described. The superimposed field strength of applied EMFT theoretically needed to overcome any such a deficit would depend on multiple intrinsic factors. Recent work indicates that

keratinocyte galvanotaxis direction and speed in the presence of combined alternating and direct electric fields depend on excitation frequency (Hart et al., 2013). Other patterns of applied EMF also indicate acceleration of keratinocyte migration in vitro (Huo et al., 2010). In addition to migration aspects, keratinocytes released nitric oxide (NO), importantly involved in the wound healing process, is increased by keratinocyte exposure to EMFT (Patruno et al., 2010), pro-inflammatory chemokines are reduced (Vianale et al., 2008) and differentiation is enhanced (Arai et al., 2013) suggesting that each of these aspects may serve as targets in the EMFT-wound healing connection. In addition, there is now evidence for a Ca^{++} connection as suggested by a DC electric field induced increase in Ca^{++} influx into undifferentiated keratinocytes (Dube et al., 2012).

5.3 Fibroblasts

Possible mechanisms whereby EMFT connects with fibroblasts in healing derive from interactions observed when fibroblasts are exposed to EMF of various types. An early suggestion was that fibroblast EMF exposure induces membrane currents that open voltage-controlled Ca^{++} channels (Biedebach, 1989) that cause changes in cell migration and proliferation. The impact of EMFT on Ca^{++} processes has been much studied. Sinusoidal EMF exposure (20 Hz, 8 mT) of human skin fibroblasts changed cellular Ca^{++} oscillation activity in a way that depended on the cell's differentiation state (Loschinger et al., 1999). Such changes in proliferation and differentiation could be triggered by transient increases in cAMP-dependent protein kinase activity (Thumm et al., 1999). Indeed, prior work showed that fibroblasts exposed to PRF-EMF (27.12 MHz) caused enhanced cell proliferation (George et al., 2002, Gilbert et al., 2002). Further, EMF stimulation (10-100 Hz, 0-130 $\mu A/cm^2$) of dermal fibroblasts in a collagen matrix showed an amplitude and frequency windowing process in cell proliferation in which an

ion-interference mechanism was involved (Binhi and Goldman, 2000). The proposed ion-interference mechanism considers effects of induced electric gradients on protein-bound substrate ions. Other evidence of a Ca^{++} connection comes from studies in which fibroblasts exposed to 2 V/cm fields at 1 and 10 Hz (but not 100 Hz) caused a six-fold increase in internal Ca^{++} (Cho et al., 2002) likely due to more Ca^{++} influx via voltage-gated Ca^{++} channels. Such channel-gating processes can be started by membrane depolarization that could be due to forced vibration of free ions on either side of the membrane that causes membrane potential changes sufficient to open the voltage-gated channels (Panagopoulos et al., 2000). More recently (Sunkari et al., 2011) in vitro migration and proliferation were enhanced when fibroblasts were exposed to a low intensity 1 GHz EMF. In addition the release of fibroblast pro-inflammatory cytokines was reduced when exposed to pulsed EMF (Gomez-Ochoa et al., 2011). Increased migration and growth was also demonstrated when fibroblasts were exposed to fields ranging from 50 to 200 mv/mm in vitro (Rouabhia et al., 2013) with the possibility that low intensity fields enhance fibroblast migration via a reactive O_2 species pathway (Tandon et al., 2014).

EMF - Ca^{++} connections in healing are ubiquitous and in this author's view are important research targets. A theoretical framework for a connection between imposed fields and Ca++ channel dynamics has recently been proposed (Sun et al., 2013). But, it must be remembered that although Ca^{++} entry into fibroblasts is associated with fibroblast stimulation (Huang et al., 1999), Ca^{++} also affects blood vessels and blood flow causing decreased flow if vascular smooth muscle is so exposed. To be effective in a wound healing sense the timing of the application of EMFT triggered Ca++ stimulations within the wound healing cycle should be considered. For now, little is known regarding optimal timing.

5.4 Leukocytes and Macrophage Involvement

Leukocyte involvement in wound healing occurs mainly when they are activated during the inflammatory phase. Activation occurs with a respiratory burst, a release of cytokines and O_2 radicals, and up-regulation of cell surface receptors that cause increased leukocyte-endothelial adhesion. This adhesion was demonstrated to increase in vivo when exposed to sinusoidal magnetic fields (50 Hz) greater than about 30 mT (Ushiyama and Ohkubo, 2004). An additional factor that may be involved in this process is myeloperoxidase (MPO) that is positively charged and is subject to the effects of external fields. MPO plays a role in polymorphonuclear neutrophils (PMN)recruitment (Klinke et al., 2011) that in the case of wounds normally move toward the wound via galvanotaxis (Rapp et al., 1988) where they are needed for their antibacterial actions. But, their continued entry and presence may cause reduced local blood flow due to capillary plugging, abnormal vasoconstriction, and tissue damage associated with PMN continued enzyme release. Evidence of such impaired healing comes from studies on diabetic mice with a prolonged inflammatory phase and retarded wound healing (Wetzler et al., 2000). The prolonged inflammatory phase appeared to be due to expression of inflammatory and leukocyte-chemo-attractive proteins released by keratinocytes that caused activated neutophils and macrophages to be sustained within the wound. If the inflammatory phase is abnormally prolonged EMFT effects on activated PMN could affect wound healing via modulations of cellular free Ca^{++} oscillations and membrane potentials that accompany PMN release of reactive O_2 metabolites. The intensity of these normal oscillations (0.05-0.1 Hz) could be increased if 20 ms pulses were delivered at the trough of these oscillations (Kindzelskii and Petty, 2000). Additionally, O_2 metabolites could be increased or decrease depending on the phase between applied field and the Ca^{++} oscillations. It is noteworthy that electrical stimulation enhanced PMN, monocyte and macrophage migration in enhanced healing (Kloth and McCulloch, 1996).

6. Blood Flow and Edema as EMF-Related Wound Healing Processes and Targets

6.1 Blood Flow

As previously described, blood flow to and within the wound are important targets in EMFT-related wound healing especially in ischemic and diabetic wounds. EMF-related blood flow changes may be induced directly via EMF effects on vascular smooth muscle, endothelial cells or blood and indirectly via neural activation, as with transcutaneous electrical nerve stimulation (Kaada and Emru, 1988). Skin vessels are innervated by sensory, sympathetic and parasympathetic fibers (Ruocco et al., 2002) and are each suitable EMF targets. Factors tending to reduce flow within the wound, such as trapped leukocytes, are also valid targets. Although blood flow deficits are involved in ischemic and in some diabetic ulcers, it is not necessarily true that more flow causes faster healing or that more tissue oxygenation is always best for the natural healing process. Effects of blood flow on healing on the timing of increases or decreases: If flow is initially too high it may affect an angiogenesis trigger (low O_2) and if too high it can increase edema. Alternatively, if flow is too low it won't support wound metabolism and may cause sustained inflammation that inhibits healing. The need to reverse polarity of some EMFT forms to cause healing may reflect a need for different flow needs (Brown et al., 1989).

Blood flow in venous ulcers illustrates the above points. Often total leg flow is increased (Mayrovitz and Larsen, 1994a) as is periulcer skin microvascular flow (Mayrovitz and Larsen, 1994b, Malanin et al., 1999). But, abnormally dilated arterioles are observed (Junger et al., 1996) and a maldistribution of flow between nutritive and non-nutritive pathways is present (Junger et al., 2000), possibly due to activated leukocytes plugging capillaries. If leukocytes are involved,

then an EMF-related reduction in neutrophil activation and adherence might be beneficial in three ways: 1) reducing local ischemia in areas served by obstructed capillaries, 2) normalizing effects of enzymes and free radicals released by activated leukocytes, and 3) reducing edema caused by their activation. Further, in patients with venous ulcers, arteriolar vasoconstriction normally induced by standing is blunted (Belcaro et al., 1995) and likely contributes to microvascular hyper-perfusion that exacerbates hypertension in capillaries and venules thereby causing more tissue edema. Thus a portrait emerges suggesting a plausible basis for delayed healing that includes an overall *hyper-perfusion* with simultaneously reduced wound blood flow and localized tissue edema. This scenario suggests that an EMF-related selective *vasoconstriction* of non-nutrient circulation may be of benefit. Alternatively, an EMF-related increase in local nutritional wound blood flow, if it overcomes the relative ischemia without causing substantial edema, might favor wound healing. Normally, edema is controlled via compression bandaging, which, among other aspects, might redistribute microcirculation and thereby to normalize a deficient nutritional capillary network. EMFT therapy for venous ulcers should always be used in conjunction with compression bandaging.

It is noteworthy that patients with chronic venous insufficiency, a frequent forerunner of venous ulcers, have increased vasomotion frequency (Chittenden et al., 1992) causing spontaneous blood flow changes in the frequency range between 0.05 to 0.5 Hz (Mayrovitz, 1998a). This suggests that EMF-related effects on vasomotion (Xu et al., 1998) may impact wound flow and healing. Such EMF effects may work via effects on intracellular Ca^{++} oscillations and other Ca^{++} signaling processes. Although not specifically studied in vascular smooth muscle cells, an EMF-related (50 Hz) reduction in total spectral power content of cytosolic Ca^{++} oscillations and specific changes in the low-frequency band (0--10^{-3} Hz), have

been demonstrated in human leukemia cells (Galvanovskis et al., 1996). An argument for the role of spectral power changes as a mode of cellular encoding has been made (Galvanovskis and J., 1998) although both amplitude and frequency may be involved. Such processes could be involved in EMF-related effects on arteriolar vasomotion and associate blood flow changes. Based on the above and other considerations, it is the author's view that effectiveness of EMFT for altering blood flow to stimulate healing may be optimized by linking field/current parameters to rhythms of healing process via feedback that detects and accommodates naturally occurring physiological and vascular dynamics.

6.2 Edema

Interstitial fluid accumulation as edema or as a protein rich lymphedema retards wound healing by decreasing blood flow, reducing O_2 diffusion to tissue (Hunt et al., 2000), and acting as a breeding ground for infection (Hunt et al., 1986). Initially, edema is due to capillary permeability changes in the inflammatory phase with damage or dysfunction of terminal lymphatics also probably involved. Edema presence is obvious under some conditions sometimes its presence is "silent," as microedema in the wound environment and its effects on healing are often not considered. Further, the physical features of sustained edema may change over time due to a progressive increase in protein concentration and fibrin cross-linking. These changes further impact healing. Because of the well established ability of EMFT to reduce gross edema, a question arises as to if EMF-related effects that may reduce microedema, either directly or by its effects on lymphatic pathways, plays a role in possible favorable effects of EMFT on wound healing. PRF-EMF may affect lymphatic channels as they do blood vessels (Mayrovitz et al., 2002a). An impact of lymphatics is further suggested by the observation that lymphatic vessels near some ulcers are reduced in number and have partially destroyed endothelium

(Eliska and Eliskova, 2001) and there potential role in angiogenesis to support granulation tissue (Paavonen et al., 2000). Earlier results (Mayrovitz et al., 2002a) with PRF-EMFT (27.1 MHz) reduced edema in patients with postmastectomy lymphedema. Since in these patients the main deficit is reduced lymphatic pathways, reduced edema with EMFT may be achieved by the development of alternate lymphatic pathways. This suggests the possibility that a promising target for EMFT might be lymphatic vessels within and surrounding the wound area. New methods are now available to assess local tissue edema at almost any body site in a non-invasive manner (Mayrovitz, 2007, Mayrovitz et al., 2013a, Mayrovitz et al., 2013b) and should aid in new research efforts to assess the possible connections between EMFT and wound related edema changes.

7. Conclusions

The cumulative substantial evidence from cellular and animal experiments and from human studies indicate positive connections between forms of electromagnetic therapy and wound healing. The composite findings provide a useful framework and underlying basis for EMF therapy when used in a thoughtful and selective manner to treat certain chronic or recalcitrant wounds. But, mechanisms are at best speculative with large gaps in our understanding of specific cellular and functional targets, therapeutic dose and regimens to achieve *optimal* treatment of specific wound types.

The complexity of the wound healing process and the differential features of specific wound types, require a selective approach to choose EMF therapy parameters, timing and targets. This means that therapeutic EMF approaches should be based on physical and physiological considerations, which then are judged on therapeutic outcomes. The EMFT-wound connections

described in this may provide a basis for continued advances in this still evolving adjunctive therapeutic modality.

8. References

Aetna IC (2014) Clinical Policy Bulletin: Electrical Stimulation for Chronic Ulcers (Number: 0680). vol. http://www.aetna.com/cpb/medical/data/600_699/0680.html.

Akai M, Hayashi K. "Effect of electrical stimulation on muscoloskeletal systems: A Meta-analysis of controlled clinical trials". Bioelectromagnetics 23 (2002):132-143

Akcay MN, Ozcan O, Gundogdu C, Akcay G, Balik A, Kose K, Oren D. "Effect of nitric oxide synthase inhibitor on experimentally induced burn wounds". J Trauma 49 (2000):327-330.

Amir Y, Halfens RJ, Lohrmann C, Schols JM. "Pressure ulcer prevalence and quality of care in stroke patients in an Indonesian hospital". J Wound Care 22 (2013):254, 256, 258-260

Arai KY, Nakamura Y, Hachiya Y, Tsuchiya H, Akimoto R, Hosoki K, Kamiya S, Ichikawa H, Nishiyama T. "Pulsed electric current induces the differentiation of human keratinocytes". Mol Cell Biochem 379 (2013):235-241

Aygor HE, Sahin S, Sozen E, Baydal B, Aykar FS, Akcicek F. "Features of pressure ulcers in hospitalized older adults". Adv Skin Wound Care 27 (2014):122-126

Aziz Z, Cullum N, Flemming K. "Electromagnetic therapy for treating venous leg ulcers". Cochrane Database Syst Rev 2 (2013):CD002933

Bai H, Forrester JV, Zhao M. "DC electric stimulation upregulates angiogenic factors in endothelial cells through activation of VEGF receptors". Cytokine 55 (2011):110-115

Baker LL, Chambers R, DeMuth SK, Villar F. "Effects of electrical stimulation on wound healing in patients with diabetic ulcers". Diabetes Care 20 (1997):405-412.

Balakatounis KC, Angoules AG. "Low-intensity electrical stimulation in wound healing: review of the efficacy of externally applied currents resembling the current of injury". Eplasty 8 (2008):e28

Barker AT, Jaffe LF, Vanable JW, Jr. "The glabrous epidermis of cavies contains a powerful battery". Am J Physiol 242 (1982):R358-366.

Becker RO. "Augmentation of regenerative healing in man. A possible alternative to prosthetic implantation". Clin Orthop 83 (1972):255-262.

Belcaro G, Laurora G, Cesarone MR, De Sanctis MT, Incandela L. "Microcirculation in high perfusion microangiopathy". J Cardiovasc Surg (Torino) 36 (1995):393-398.

Bentall RHC. "Low-level pulsed radiofrequency fields and the treatment of soft-tissue injuries". Bioelectricity and Bioenergetics 16 (1986):531-548

Biedebach MC. "Accelerated healing of skin ulcers by electrical stimulation and the intracellular physiological mechanisms involved". Acupunct Electrother Res 14 (1989):43-60

Binhi VN, Goldman RJ. "Ion-protein dissociation predicts 'windows' in electric field-induced wound-cell proliferation". Biochim Biophys Acta 1474 (2000):147-156

Brimson CH, Nigam Y. "The role of oxygen-associated therapies for the healing of chronic wounds, particularly in patients with diabetes". J Eur Acad Dermatol Venereol 27 (2013):411-418

Brown M, McDonnell MK, Menton DN. "Polarity effects on wound healing using electric stimulation in rabbits". Arch Phys Med Rehabil 70 (1989):624-627.

Burr HS, Harvey SC, Taffel M. "Bio-electric correlates of wound healing". Yale J Biol Med 11 (1938):104-107

Byers PH, Carta SG, Mayrovitz HN. "Pressure ulcer research issues in surgical patients". Adv Skin Wound Care 13 (2000):115-121

Callaghan MJ, Chang EI, Seiser N, Aarabi S, Ghali S, Kinnucan ER, Simon BJ, Gurtner GC. "Pulsed electromagnetic fields accelerate normal and diabetic wound healing by increasing endogenous FGF-2 release". Plast Reconstr Surg 121 (2008):130-141

Canedo-Dorantes L, Garcia-Cantu R, Barrera R, Mendez-Ramirez I, Navarro VH, Serrano G. "Healing of chronic arterial and venous leg ulcers with systemic electromagnetic fields". Arch Med Res 33 (2002):281-289.

Carley PJ, Wainapel SF. "Electrotherapy for acceleration of wound healing: low intensity direct current". Arch Phys Med Rehabil 66 (1985):443-446.

Cheng HW, James AF, Foster RR, Hancox JC, Bates DO. "VEGF activates receptor-operated cation channels in human microvascular endothelial cells". Arterioscler Thromb Vasc Biol 26 (2006):1768-1776

Chittenden SJ, Shami SK, Cheatle TR, Scurr JH, Coleridge Smith PD. "Vasomotion in the leg skin of patients with chronic venous insufficiency". Vasa 21 (1992):138-142

Cho MR, Marler JP, Thatte HS, Golan DE. "Control of calcium entry in human fibroblasts by frequency-dependent electrical stimulation". Front Biosci 7 (2002):a1-8.

Claeys LG. "Improvement of microcirculatory blood flow under epidural spinal cord stimulation in patients with nonreconstructible peripheral arterial occlusive disease". Artif Organs 21 (1997):201-206.

Comorosan S, Vasilco R, Arghiropol M, Paslaru L, Jieanu V, Stelea S. "The effect of diapulse therapy on the healing of decubitus ulcer". Rom J Physiol 30 (1993):41-45.

Conti M, Peretti E, Cazzetta G, Galimberti G, Vermigli C, Pola R, Scionti L, Bosi E. "Frequency-modulated electromagnetic neural stimulation enhances cutaneous microvascular flow in patients with diabetic neuropathy". J Diabetes Complications 23 (2009):46-48

Costin GE, Birlea SA, Norris DA. "Trends in wound repair: cellular and molecular basis of regenerative therapy using electromagnetic fields". Curr Mol Med 12 (2012):14-26

Crawford PE, Fields-Varnado M. "Guideline for the management of wounds in patients with lower-extremity neuropathic disease: an executive summary". J Wound Ostomy Continence Nurs 40 (2013):34-45

Delle Monache S, Alessandro R, Iorio R, Gualtieri G, Colonna R. "Extremely low frequency electromagnetic fields (ELF-EMFs) induce in vitro angiogenesis process in human endothelial cells". Bioelectromagnetics 29 (2008):640-648

Dube J, Rochette-Drouin O, Levesque P, Gauvin R, Roberge CJ, Auger FA, Goulet D, Bourdages M, Plante M, Moulin VJ, Germain L. "Human keratinocytes respond to direct current stimulation by increasing intracellular calcium: preferential response of poorly differentiated cells". J Cell Physiol 227 (2012):2660-2667

Eliska O, Eliskova M. "Morphology of lymphatics in human venous crural ulcers with lipodermatosclerosis". Lymphology 34 (2001):111-123.

Erdman WJ. "Peripheral blood flow measurements during application of pulse high frequency currents". Amer J Orthop 2 (1960):196-197

Flemming K, Cullum N. "Electromagnetic therapy for the treatment of pressure sores". Cochrane Database Syst Rev 1 (2001a):

Flemming K, Cullum N. "Electromagnetic therapy for the treatment of venous leg ulcers". Cochrane Database Syst Rev 1 (2001b):

Foulds IS, Barker AT. "Human skin battery potentials and their possible role in wound healing". Br J Dermatol 109 (1983):515-522.

Franek A, Polak A, Kucharzewski M. "Modern application of high voltage stimulation for enhanced healing of venous crural ulceration". Med Eng Phys 22 (2000):647-655.

Frank S, Kampfer H, Wetzler C, Pfeilschifter J. "Nitric oxide drives skin repair: novel functions of an established mediator". Kidney Int 61 (2002):882-888.

Fromy B, Abraham P, Bouvet C, Bouhanick B, Fressinaud P, Saumet JL. "Early decrease of skin blood flow in response to locally applied pressure in diabetic subjects". Diabetes 51 (2002):1214-1217.

Galvanovskis J, J. S. "Periodic forcing of intracellular calcium oscillators: Theoretical studies of the effects of low frequency fields on the magnitude of oscillations". Bioelectricity and Bioenergetics 46 (1998):161-174

Galvanovskis J, Sandblom J, Bergqvist B, Galt S, Hamnerius Y. "The influence of 50-Hz magnetic fields on cytoplasmic Ca2+ oscillations in human leukemia T-cells". Sci Total Environ 180 (1996):19-33.

Game FL, Hinchliffe RJ, Apelqvist J, Armstrong DG, Bakker K, Hartemann A, Londahl M, Price PE, Jeffcoate WJ. "A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes". Diabetes Metab Res Rev 28 Suppl 1 (2012):119-141

Gardner SE, Frantz RA, Schmidt FL. "Effect of electrical stimulation on chronic wound healing: a meta- analysis". Wound Repair Regen 7 (1999):495-503.

Gentzkow GD. "Electrical stimulation to heal dermal wounds". J Dermatol Surg Oncol 19 (1993):753-758.

George FR, Lukas RJ, Moffett J, Ritz MC. "In-vitro mechanisms of cell proliferation induction: A novel bioactive treatment for acceleraing wound healing". Wounds 14 (2002):107-115

Gilbert TL, Griffin N, Moffett J, Ritz MC, George FR. "The Provant Wound Closure System induces activation of p44/42 MAP kinase in normal cultured human fibroblasts". Ann N Y Acad Sci 961 (2002):168-171.

Goldman R, Brewley B, Golden M. "Electrotherapy reoxygenates inframalleolar ischemic wounds on diabetic patients". Advances in Skin and Wound Care 15 (2002):112-120

Goldman R, Rosen M, Brewley B, Golden M. "Electrotherapy promotes healing and microcirculation of infrapopliteal ischemic wounds: a prospective pilot study". Adv Skin Wound Care 17 (2004):284-294

Gomez-Ochoa I, Gomez-Ochoa P, Gomez-Casal F, Cativiela E, Larrad-Mur L. "Pulsed electromagnetic fields decrease proinflammatory cytokine secretion (IL-1beta and TNF-alpha) on human fibroblast-like cell culture". Rheumatol Int 31 (2011):1283-1289

Gonzalez ER, Oley MA. "The management of lower-extremity diabetic ulcers". Manag Care Interface 13 (2000):80-87.

Gottrup F, Apelqvist J. "Present and new techniques and devices in the treatment of DFU: a critical review of evidence". Diabetes Metab Res Rev 28 Suppl 1 (2012):64-71

Gottrup F, Henneberg E, Trangbaek R, Baekmark N, Zollner K, Sorensen J. "Point prevalence of wounds and cost impact in the acute and community setting in Denmark". J Wound Care 22 (2013):413-414, 416, 418-422

Graber JN, Lifson A. "The use of spinal cord stimulation for severe limb-threatening ischemia: a preliminary report". Ann Vasc Surg 1 (1987):578-582.

Griffin JW, Tooms RE, Mendius RA, Clifft JK, Vander Zwaag R, el-Zeky F. "Efficacy of high voltage pulsed current for healing of pressure ulcers in patients with spinal cord injury". Phys Ther 71 (1991):433-442; discussion 442-434.

Grimnes S. "Pathways of ionic flow through human skin in vivo". Acta Derm Venereol 64 (1984):93-98

Gschwandtner ME, Ehringer H. "Microcirculation in chronic venous insufficiency". Vasc Med 6 (2001):169-179

Gunningberg L, Hommel A, Baath C, Idvall E. "The first national pressure ulcer prevalence survey in county council and municipality settings in Sweden". J Eval Clin Pract 19 (2013):862-867

Hamed S, Bennett CL, Demiot C, Ullmann Y, Teot L, Desmouliere A. "Erythropoietin, a novel repurposed drug: an innovative treatment for wound healing in patients with diabetes mellitus". Wound Repair Regen 22 (2014):23-33

Harms S, Bliss DZ, Garrard J, Cunanan K, Savik K, Gurvich O, Mueller C, Wyman JF, Eberly L, Virnig B. "Prevalence of pressure ulcers by race and ethnicity for older adults admitted to nursing homes". J Gerontol Nurs 40 (2014):20-26

Hart FX, Laird M, Riding A, Pullar CE. "Keratinocyte galvanotaxis in combined DC and AC electric fields supports an electromechanical transduction sensing mechanism". Bioelectromagnetics 34 (2013):85-94

Hedenius P, Odeblad E, Wahlstrom L. "Some prelimnary investigations on the therapeutic effect of pulsed short waves in intermittent claudication". Current Therapeutic Research 8 (1966):317-321

Holmes C, Wrobel JS, Maceachern MP, Boles BR. "Collagen-based wound dressings for the treatment of diabetes-related foot ulcers: a systematic review". Diabetes Metab Syndr Obes 6 (2013):17-29

Houreld NN. "Shedding light on a new treatment for diabetic wound healing: a review on phototherapy". ScientificWorldJournal 2014 (2014):398412

Huang JS, Mukherjee JJ, Chung T, Crilly KS, Kiss Z. "Extracellular calcium stimulates DNA synthesis in synergism with zinc, insulin and insulin-like growth factor I in fibroblasts". Eur J Biochem 266 (1999):943-951.

Hunt DL. "Diabetes: foot ulcers and amputations". Clin Evid (Online) 2011 (2011):

Hunt TK, Hopf H, Hussain Z. "Physiology of wound healing". Adv Skin Wound Care 13 (2000):6-11.

Hunt TK, Rabkin J, von Smitten K. "Effects of edema and anemia on wound healing and infection". Curr Stud Hematol Blood Transfus 53 (1986):101-113

Huo R, Ma Q, Wu JJ, Chin-Nuke K, Jing Y, Chen J, Miyar ME, Davis SC, Li J. "Noninvasive electromagnetic fields on keratinocyte growth and migration". J Surg Res 162 (2010):299-307

Ieran M, Zaffuto S, Bagnacani M, Annovi M, Moratti A, Cadossi R. "Effect of low frequency pulsing electromagnetic fields on skin ulcers of venous origin in humans: a double-blind study". J Orthop Res 8 (1990):276-282.

Illingworth CM, Barker AT. "Measurement of electrical currents emerging during the regeneration of amputated finger tips in children ". Clin Phys Physiol Meas 1 (1980):87

Itoh M, Montemayor JS, Jr., Matsumoto E, Eason A, Lee MH, Folk FS. "Accelerated wound healing of pressure ulcers by pulsed high peak power electromagnetic energy (Diapulse)". Decubitus 4 (1991):24-25, 29-34.

Jacobs MJ, Jorning PJ, Beckers RC, Ubbink DT, van Kleef M, Slaaf DW, Reneman RS. "Foot salvage and improvement of microvascular blood flow as a result of epidural spinal cord electrical stimulation". J Vasc Surg 12 (1990):354-360.

Jacobs MJ, Jorning PJ, Joshi SR, Kitslaar PJ, Slaaf DW, Reneman RS. "Epidural spinal cord electrical stimulation improves microvascular blood flow in severe limb ischemia". Ann Surg 207 (1988):179-183.

Jaffe LF, Vanable JW, Jr. "Electric fields and wound healing". Clin Dermatol 2 (1984):34-44.

Jan YK, Liao F, Rice LA, Woods JA. "Using reactive hyperemia to assess the efficacy of local cooling on reducing sacral skin ischemia under surface pressure in people with spinal cord injury: a preliminary report". Arch Phys Med Rehabil 94 (2013):1982-1989

Jankovic A, Binic I. "Frequency rhythmic electrical modulation system in the treatment of chronic painful leg ulcers". Arch Dermatol Res 300 (2008):377-383

Junger M, Klyscz T, Hahn M, Rassner G. "Disturbed blood flow regulation in venous leg ulcers". Int J Microcirc Clin Exp 16 (1996):259-265.

Junger M, Steins A, Hahn M, Hafner HM. "Microcirculatory dysfunction in chronic venous insufficiency (CVI)". Microcirculation 7 (2000):S3-12.

Kaada B, Emru M. "Promoted healing of leprous ulcers by transcutaneous nerve stimulation". Acupunct Electrother Res 13 (1988):165-176

Kindzelskii AL, Petty HR. "Extremely low frequency pulsed DC electric fields promote neutrophil extension, metabolic resonance and DNA damage when phase-matched with metabolic oscillators". Biochim Biophys Acta 1495 (2000):90-111.

Klinke A, Nussbaum C, Kubala L, Friedrichs K, Rudolph TK, Rudolph V, Paust HJ, Schroder C, Benten D, Lau D, Szocs K, Furtmuller PG, Heeringa P, Sydow K, Duchstein HJ, Ehmke H, Schumacher U, Meinertz T, Sperandio M, Baldus S. "Myeloperoxidase attracts neutrophils by physical forces". Blood 117 (2011):1350-1358

Kloth LC. "Electrical stimulation for wound healing: a review of evidence from in vitro studies, animal experiments, and clinical trials". Int J Low Extrem Wounds 4 (2005):23-44

Kloth LC, McCulloch JM. "Promotion of wound healing with electrical stimulation". Adv Wound Care 9 (1996):42-45.

Knighton DR, Hunt TK, Scheuenstuhl H, Halliday BJ, Werb Z, Banda MJ. "Oxygen tension regulates the expression of angiogenesis factor by macrophages". Science 221 (1983):1283-1285.

Kruglikov IL, Dertinger H. "Stochastic resonance as a possible mechanism of amplification of weak electric signals in living cells". Bioelectromagnetics 15 (1994):539-547

Kumar K, Toth C, Nath RK, Verma AK, Burgess JJ. "Improvement of limb circulation in peripheral vascular disease using epidural spinal cord stimulation: a prospective study". J Neurosurg 86 (1997):662-669.

Larsen JA, Overstreet J. "Pulsed radio frequency energy in the treatment of complex diabetic foot wounds: two cases". J Wound Ostomy Continence Nurs 35 (2008):523-527

Lazarus G, Valle MF, Malas M, Qazi U, Maruthur NM, Doggett D, Fawole OA, Bass EB, Zenilman J. "Chronic venous leg ulcer treatment: future research needs". Wound Repair Regen 22 (2014):34-42

Lee BY, Al-Waili N, Stubbs D, Wendell K, Butler G, Al-Waili T, Al-Waili A. "Ultra-low microcurrent in the management of diabetes mellitus, hypertension and chronic wounds: report of twelve cases and discussion of mechanism of action". Int J Med Sci 7 (2009):29-35

Lee RC, Canaday DJ, Doong H. "A review of the biophysical basis for the clinical application of electric fields in soft-tissue repair". J Burn Care Rehabil 14 (1993):319-335.

Lee RH, Efron D, Tantry U, Barbul A. "Nitric oxide in the healing wound: a time-course study". J Surg Res 101 (2001):104-108.

Loschinger M, Thumm S, Hammerle H, Rodemann HP. "Induction of intracellular calcium oscillations in human skin fibroblast populations by sinusoidal extremely low-frequency magnetic fields (20 Hz, 8 mT) is dependent on the differentiation state of the single cell". Radiat Res 151 (1999):195-200

Lundeberg TC, Eriksson SV, Malm M. "Electrical nerve stimulation improves healing of diabetic ulcers". Ann Plast Surg 29 (1992):328-331.

Magnoni C, Rossi E, Fiorentini C, Baggio A, Ferrari B, Alberto G. "Electrical stimulation as adjuvant treatment for chronic leg ulcers of different aetiology: an RCT". J Wound Care 22 (2013):525-526, 528-533

Malanin K, Kolari PJ, Havu VK. "The role of low resistance blood flow pathways in the pathogenesis and healing of venous leg ulcers". Acta Derm Venereol 79 (1999):156-160.

Markov M. "Electric current and electromagnetic field effects on soft tissue: Implications for wound healing". Wounds 7 (1995):94-110

Markov M, Pilla AA. "Electromagnetic stimulation of soft tissues:pulsed radio frequency treatment of postoperative pain and edema". Wounds 7 (1995):143-151

Martino CF. "Static magnetic field sensitivity of endothelial cells". Bioelectromagnetics 32 (2011):506-508

Martino CF, Perea H, Hopfner U, Ferguson VL, Wintermantel E. "Effects of weak static magnetic fields on endothelial cells". Bioelectromagnetics 31 (2010):296-301

Mayrovitz H, Sims N, Macdonald J. "Effects of Pulsed Radio Frequency Diathermy on Postmastectomy Arm Lymphedema and Skin Blood Flow: A Pilot Investigation". Lymphology in press (2002a):

Mayrovitz HN (1998a) Assessment of Human Microvascular Function. In: Analysis of Cardiovascular Function(Drzewiecki, G. and Li, J., eds), pp 248-273 New York: Springer.

Mayrovitz HN. "Pressure and blood flow linkages and impacts on pressure ulcer development". Adv Wound Care 11 (1998b):4

Mayrovitz HN (2004) Electromagentic Linkages in Soft Tissue Wound Healing. (Markov, M., ed), pp 461-483.

Mayrovitz HN. "Assessing local tissue edema in postmastectomy lymphedema". Lymphology 40 (2007):87-94

Mayrovitz HN, Bernal M, Brlit F, Desfor R. "Biophysical measures of skin tissue water: variations within and among anatomical sites and correlations between measures". Skin Res Technol 19 (2013a):47-54

Mayrovitz HN, Groseclose EE. "Effects of a static magnetic field of either polarity on skin microcirculation". Microvasc Res 69 (2005):24-27

Mayrovitz HN, Groseclose EE, King D. "No effect of 85 mT permanent magnets on laser-Doppler measured blood flow response to inspiratory gasps". Bioelectromagnetics 26 (2005):331-335

Mayrovitz HN, Groseclose EE, Markov M, Pilla AA. "Effects of permanent magnets on resting skin blood perfusion in healthy persons assessed by laser Doppler flowmetry and imaging". Bioelectromagnetics 22 (2001):494-502

Mayrovitz HN, Groseclose EE, Sims N. "Assessment of the short-term effects of a permanent magnet on normal skin blood circulation via laser-Doppler flowmetry". The Scientific Review of Alternative Medicine 6 (2002b):5-9

Mayrovitz HN, Larsen PB. "Effects of pulsed electromagnetic fields on skin microvascular blood perfusion". Wounds 4 (1992):197-202

Mayrovitz HN, Larsen PB. "Leg blood flow in patients with venous ulcers: relationship to site and ulcer area". Wounds 6 (1994a):195-200

Mayrovitz HN, Larsen PB. "Periwound skin microcirculation of venous leg ulcers". Microvasc Res 48 (1994b):114-123

Mayrovitz HN, Larsen PB. "Standard and near-surface laser-Doppler perfusion in foot dorsum skin of diabetic and nondiabetic subjects with and without coexisting peripheral arterial disease". Microvasc Res 48 (1994c):338-348

Mayrovitz HN, Larsen PB. "Functional microcirculatory impairment: a possible source of reduced skin oxygen tension in human diabetes mellitus". Microvasc Res 52 (1996):115-126

Mayrovitz HN, Macdonald J, Sims N. "Effects of pulsed radio frequency diathermy on postmastectomy arm lymphedema and skin blood flow: A pilot investigation.". Lymphology (2002c):

Mayrovitz HN, Macdonald J, Smith JR. "Blood perfusion hyperaemia in response to graded loading of human heels assessed by laser-Doppler imaging". Clin Physiol 19 (1999):351-359

Mayrovitz HN, McClymont A, Pandya N. "Skin tissue water assessed via tissue dielectric constant measurements in persons with and without diabetes mellitus". Diabetes Technol Ther 15 (2013b):60-65

Mayrovitz HN, Sims N. "Biophysical effects of water and synthetic urine on skin". Adv Skin Wound Care 14 (2001):302-308

Mayrovitz HN, Sims N, Taylor MC. "Sacral skin blood perfusion: a factor in pressure ulcers?". Ostomy Wound Manage 48 (2002d):34-38, 40-32

Mayrovitz HN, Smith J. "Heel-skin microvascular blood perfusion responses to sustained pressure loading and unloading". Microcirculation 5 (1998):227-233

Mayrovitz HN, Smith J, Delgado M, Regan MB. "Heel blood perfusion responses to pressure loading and unloading in women". Ostomy Wound Manage 43 (1997):16-20, 22, 24 passim

Mayrovitz HN, Smith JR. "Adaptive skin blood flow increases during hip-down lying in elderly women". Adv Wound Care 12 (1999):295-301

McCulloch JM, Kloth LC, Feedar JA (1995) Wound healing alternatives in management. In: Contemporay Perspectives in Rehabilitation(Wolf, S. E., ed), pp 275-310 Philadelphia: F. A. Davis.

McDaniel JC, Roy S, Wilgus TA. "Neutrophil activity in chronic venous leg ulcers--a target for therapy?". Wound Repair Regen 21 (2013):339-351

Mingoli A, Sciacca V, Tamorri M, Fiume D, Sapienza P. "Clinical results of epidural spinal cord electrical stimulation in patients affected with limb-threatening chronic arterial obstructive disease". Angiology 44 (1993):21-25.

Moore Z, Johanssen E, van Etten M. "A review of PU prevalence and incidence across Scandinavia, Iceland and Ireland (Part I)". J Wound Care 22 (2013):361-362, 364-368

Muller IS, de Grauw WJ, van Gerwen WH, Bartelink ML, van Den Hoogen HJ, Rutten GE. "Foot ulceration and lower limb amputation in type 2 diabetic patients in dutch primary health care". Diabetes Care 25 (2002):570-574.

Nelzen O. "Prevalence of venous leg ulcer: the importance of the data collection method". Phlebolymphology 15 (2008):143-150

Nordenstrom BE. "Impact of biologically closed electric circuits (BCEC) on structure and function". Integr Physiol Behav Sci 27 (1992):285-303.

Nuccitelli R. "A role for endogenous electric fields in wound healing". Curr Top Dev Biol 58 (2003):1-26

Nuccitelli R, Nuccitelli P, Li C, Narsing S, Pariser DM, Lui K. "The electric field near human skin wounds declines with age and provides a noninvasive indicator of wound healing". Wound Repair Regen 19 (2011):645-655

Nuccitelli R, Nuccitelli P, Ramlatchan S, Sanger R, Smith PJ. "Imaging the electric field associated with mouse and human skin wounds". Wound Repair Regen 16 (2008):432-441

O'Toole EA. "Extracellular matrix and keratinocyte migration". Clin Exp Dermatol 26 (2001):525-530.

Paavonen K, Puolakkainen P, Jussila L, Jahkola T, Alitalo K. "Vascular endothelial growth factor receptor-3 in lymphangiogenesis in wound healing". Am J Pathol 156 (2000):1499-1504.

Panagopoulos DJ, Messini N, Karabarbounis A, Philippetis AL, Margaritis LH. "A mechanism for action of oscillating electric fields on cells". Biochem Biophys Res Commun 272 (2000):634-640.

Patruno A, Amerio P, Pesce M, Vianale G, Di Luzio S, Tulli A, Franceschelli S, Grilli A, Muraro R, Reale M. "Extremely low frequency electromagnetic fields modulate expression of inducible nitric oxide synthase, endothelial nitric oxide synthase and cyclooxygenase-2 in the human keratinocyte cell line HaCat: potential therapeutic effects in wound healing". Br J Dermatol 162 (2010):258-266

Peirce SM, Skalak TC, Rodeheaver GT. "Ischemia-reperfusion injury in chronic pressure ulcer formation: a skin model in the rat". Wound Repair Regen 8 (2000):68-76.

Pesce M, Patruno A, Speranza L, Reale M. "Extremely low frequency electromagnetic field and wound healing: implication of cytokines as biological mediators". Eur Cytokine Netw 24 (2013):1-10

Peschen M, Lahaye T, Hennig B, Weyl A, Simon JC, Vanscheidt W. "Expression of the adhesion molecules ICAM-1, VCAM-1, LFA-1 and VLA-4 in the skin is modulated in progressing stages of chronic venous insufficiency". Acta Derm Venereol 79 (1999):27-32.

Peters EJ, Lavery LA, Armstrong DG, Fleischli JG. "Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial". Arch Phys Med Rehabil 82 (2001):721-725.

Ramadhinara A, Poulas K. "Use of wireless microcurrent stimulation for the treatment of diabetes-related wounds: 2 case reports". Adv Skin Wound Care 26 (2013):1-4

Rapp B, de Boisfleury-Chevance A, Gruler H. "Galvanotaxis of human granulocytes. Dose-response curve". Eur Biophys J 16 (1988):313-319

Rawe IM, Vlahovic TC. "The use of a portable, wearable form of pulsed radio frequency electromagnetic energy device for the healing of recalcitrant ulcers: a case report". Int Wound J 9 (2012):253-258

Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA, Boulton AJ. "Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings". Diabetes Care 22 (1999):157-162

Ricci E, Afaragan M. "The effect of stochastic electrical noise on hard-to-heal wounds". J Wound Care 19 (2010):96-103

Rouabhia M, Park H, Meng S, Derbali H, Zhang Z. "Electrical stimulation promotes wound healing by enhancing dermal fibroblast activity and promoting myofibroblast transdifferentiation". PLoS One 8 (2013):e71660

Ruocco I, Cuello AC, Parent A, Ribeiro-da-Silva A. "Skin blood vessels are simultaneously innervated by sensory, sympathetic, and parasympathetic fibers". J Comp Neurol 448 (2002):323-336.

Salzberg CA, Cooper-Vastola SA, Perez F, Viehbeck MG, Byrne DW. "The effects of non-thermal pulsed electromagnetic energy on wound healing of pressure ulcers in spinal cord-injured patients: a randomized, double-blind study". Ostomy Wound Manage 41 (1995):42-44, 46, 48 passim.

Sarma GR, Subrahmanyam S, Deenabandhu A, Babu CR, Madhivathanan S, Kesavaraj N. "Exposure to pulsed magnetic fields in the treatment of plantar ulcers in leprosy patients--a pilot, randomized, double-blind, controlled clinical trial". Indian J Lepr 69 (1997):241-250

Scheel-Sailer A, Wyss A, Boldt C, Post MW, Lay V. "Prevalence, location, grade of pressure ulcers and association with specific patient characteristics in adult spinal cord injury patients during the hospital stay: a prospective cohort study". Spinal Cord 51 (2013):828-833

Sheffet A, Cytryn AS, Louria DB. "Applying electric and electromagnetic energy as adjuvant treatment for pressure ulcers: a critical review". Ostomy Wound Manage 46 (2000):28-33, 36-40, 42-24

Shi HP, Most D, Efron DT, Tantry U, Fischel MH, Barbul A. "The role of iNOS in wound healing". Surgery 130 (2001):225-229.

Singh N, Armstrong DG, Lipsky BA. "Preventing foot ulcers in patients with diabetes". JAMA 293 (2005):217-228

Smit CA, Zwinkels M, van Dijk T, de Groot S, Stolwijk-Swuste JM, Janssen TW. "Gluteal blood flow and oxygenation during electrical stimulation-induced muscle activation versus pressure relief movements in wheelchair users with a spinal cord injury". Spinal Cord 51 (2013):694-699

Smith ME, Totten A, Hickam DH, Fu R, Wasson N, Rahman B, Motu'apuaka M, Saha S. "Pressure ulcer treatment strategies: a systematic comparative effectiveness review". Ann Intern Med 159 (2013):39-50

Smith PD. "Update on chronic-venous-insufficiency-induced inflammatory processes". Angiology 52 Suppl 1 (2001):S35-42.

Sonenblum SE, Vonk TE, Janssen TW, Sprigle SH. "Effects of Wheelchair Cushions and Pressure Relief Maneuvers on Ischial Interface Pressure and Blood Flow in People With Spinal Cord Injury". Arch Phys Med Rehabil (2014):

Spravchikov N, Sizyakov G, Gartsbein M, Accili D, Tennenbaum T, Wertheimer E. "Glucose effects on skin keratinocytes: implications for diabetes skin complications". Diabetes 50 (2001):1627-1635.

Stacey MC, Mata SD. "Lower levels of PAI-2 may contribute to impaired healing in venous ulcers - a preliminary study". Cardiovasc Surg 8 (2000):381-385.

Stefanovska A, Vodovnik L, Benko H, Turk R. "Treatment of chronic wounds by means of electric and electromagnetic fields. Part 2. Value of FES parameters for pressure sore treatment". Med Biol Eng Comput 31 (1993):213-220

Stiller MJ, Pak GH, Shupack JL, Thaler S, Kenny C, Jondreau L. "A portable pulsed electromagnetic field (PEMF) device to enhance healing of recalcitrant venous ulcers: a double-blind, placebo-controlled clinical trial". Br J Dermatol 127 (1992):147-154

Strauch B, Patel MK, Navarro JA, Berdichevsky M, Yu HL, Pilla AA. "Pulsed magnetic fields accelerate cutaneous wound healing in rats". Plast Reconstr Surg 120 (2007):425-430

Sun GX, Wang LJ, Xiang C, Qin KR. "A dynamic model for intracellular calcium response in fibroblasts induced by electrical stimulation". Math Biosci 244 (2013):47-57

Sunkari VG, Aranovitch B, Portwood N, Nikoshkov A. "Effects of a low-intensity electromagnetic field on fibroblast migration and proliferation". Electromagn Biol Med 30 (2011):80-85

Tandon N, Cimetta E, Villasante A, Kupferstein N, Southall MD, Fassih A, Xie J, Sun Y, Vunjak-Novakovic G. "Galvanic microparticles increase migration of human dermal fibroblasts in a wound-healing model via reactive oxygen species pathway". Exp Cell Res 320 (2014):79-91

Tang JC, Marston WA, Kirsner RS. "Wound Healing Society (WHS) venous ulcer treatment guidelines: what's new in five years?". Wound Repair Regen 20 (2012):619-637

Tassiopoulos AK, Golts E, Oh DS, Labropoulos N. "Current concepts in chronic venous ulceration". Eur J Vasc Endovasc Surg 20 (2000):227-232.

Thumm S, Loschinger M, Glock S, Hammerle H, Rodemann HP. "Induction of cAMP-dependent protein kinase A activity in human skin fibroblasts and rat osteoblasts by extremely low-frequency electromagnetic fields". Radiat Environ Biophys 38 (1999):195-199.

Ushiyama A, Ohkubo C. "Acute effects of low-frequency electromagnetic fields on leukocyte-endothelial interactions in vivo". In Vivo 18 (2004):125-132

Valencia IC, Falabella A, Kirsner RS, Eaglstein WH. "Chronic venous insufficiency and venous leg ulceration". J Am Acad Dermatol 44 (2001):401-421; quiz 422-404.

Vanable JW, Jr. (1989) Integumentary potentials and wound healing. In: Electric Fields in Vertebrate Repair, pp 171-224: Alan R. Liss, Inc.

Vianale G, Reale M, Amerio P, Stefanachi M, Di Luzio S, Muraro R. "Extremely low frequency electromagnetic field enhances human keratinocyte cell growth and decreases proinflammatory chemokine production". Br J Dermatol 158 (2008):1189-1196

Vodovnik L, Karba R. "Treatment of chronic wounds by means of electric and electromagnetic fields. Part 1. Literature review". Med Biol Eng Comput 30 (1992):257-266.

Wen L, Zhang C, Nong Y, Yao Q, Song Z. "Mild electrical pulse current stimulation upregulates S100A4 and promotes cardiogenesis in MSC and cardiac myocytes coculture monolayer". Cell Biochem Biophys 65 (2013):43-55

Wetzler C, Kampfer H, Stallmeyer B, Pfeilschifter J, Frank S. "Large and sustained induction of chemokines during impaired wound healing in the genetically diabetic mouse: prolonged persistence of neutrophils and macrophages during the late phase of repair". J Invest Dermatol 115 (2000):245-253.

Wood JM, Evans PE, 3rd, Schallreuter KU, Jacobson WE, Sufit R, Newman J, White C, Jacobson M. "A multicenter study on the use of pulsed low-intensity direct current for healing chronic stage II and stage III decubitus ulcers". Arch Dermatol 129 (1993):999-1009.

Xu S, Okano H, Ohkubo C. "Subchronic effects of static magnetic fields on cutaneous microcirculation in rabbits". In Vivo 12 (1998):383-389.

Yamaguchi Y, Yoshikawa K. "Cutaneous wound healing: an update". J Dermatol 28 (2001):521-534.

Yen-Patton GP, Patton WF, Beer DM, Jacobson BS. "Endothelial cell response to pulsed electromagnetic fields: stimulation of growth rate and angiogenesis in vitro". J Cell Physiol 134 (1988):37-46

Young S, Hampton S, Tadej M. "Study to evaluate the effect of low-intensity pulsed electrical currents on levels of oedema in chronic non-healing wounds". J Wound Care 20 (2011):368, 370-363

Yuan Y, Wei L, Li F, Guo W, Li W, Luan R, Lv A, Wang H. "Pulsed magnetic field induces angiogenesis and improves cardiac function of surgically induced infarcted myocardium in Sprague-Dawley rats". Cardiology 117 (2010):57-63

Zhao Z, Qin L, Reid B, Pu J, Hara T, Zhao M. "Directing migration of endothelial progenitor cells with applied DC electric fields". Stem Cell Res 8 (2012):38-48