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Corresponding Author: Mr Leon Poltawski,

Corresponding Author's Institution: University of Hertfordshire

First Author: Leon Poltawski

Order of Authors: Leon Poltawski; Tim Watson

Abstract: Microcurrent therapy is unique amongst the electrophysical modalities in applying electric fields and currents of similar form and magnitude to those produced naturally by the body. The therapy involves application of electric currents of the order of millionths of an amp, and there is evidence that it can promote healing in a variety of damaged tissues. Clinical trial evidence indicates that the therapy may be effective with non-uniting fractures, spinal fusions and a skin ulcers of varying aetiology, particularly where other forms of treatment have not been successful. In vitro, animal and human studies also suggest that there is unexplored potential for the application of microcurrent to a variety of musculoskeletal disorders. However, higher quality and more comprehensive clinical trial data may be required before musculoskeletal clinicians consider adding this modality to their electrotherapy repertoire.

BIOELECTRICITY AND MICROCURRENT THERAPY FOR TISSUE HEALING – A NARRATIVE REVIEW

Leon Poltawski

School of Health & Emergency Professions, University of Hertfordshire, Hatfield, AL10 9AB, UK.

Tel +44 1707 284968. Email: L.Poltawski@herts.ac.uk (Corresponding author)

Tim Watson

School of Health & Emergency Professions, University of Hertfordshire, Hatfield, AL10 9AB, UK

ABSTRACT

Microcurrent therapy is unique amongst the electrophysical modalities in applying electric fields and currents of similar form and magnitude to those produced naturally by the body. The therapy involves application of electric currents of the order of millionths of an amp, and there is evidence that it can promote healing in a variety of damaged tissues. Clinical trial evidence indicates that the therapy may be effective with non-uniting fractures, spinal fusions and a skin ulcers of varying aetiology, particularly where other forms of treatment have not been successful. In vitro, animal and human studies also suggest that there is unexplored potential for the application of microcurrent to a variety of musculoskeletal disorders. However, higher quality and more comprehensive clinical trial data may be required before musculoskeletal clinicians consider adding this modality to their electrotherapy repertoire.

KEYWORDS

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INTRODUCTION

Contemporary accounts of tissue healing are typically expressed entirely in terms of biochemistry¹⁻⁴. The actions of substances such as cytokines and growth factors are said to initiate and mediate the various stages of inflammation and repair that normally follow tissue damage⁵. Yet evidence has accumulated over many decades that a full description of the physiology of healing must also include the role of bioelectricity, accumulations and flows of charge that are generated endogenously - within the body. The importance of bioelectricity in functions such as nervous system signalling and muscle contraction has been long recognised, but it is involved in many other physiological processes. These include the development, adaptation, repair and regeneration of tissues throughout the body⁶⁻⁹.

Recognition of bioelectricity's role in tissue healing provides a rationale for the therapeutic application of electrical stimulation, particularly in cases where natural repair processes have broken down. Microcurrent therapy (MCT) is an example of this. Uniquely amongst the various electrotherapeutic modalities, MCT involves application of voltages and currents of similar magnitude to those generated endogenously during normal tissue healing. Although relatively unknown and currently little used by physiotherapists, MCT has been shown to be of benefit in several types of tissue healing and it may be effective in others. It has advantages of stimulating healing generally, and not just one element of the process; it has very few side effects; and it may offer an effective treatment for musculoskeletal disorders such as tendinopathies where endogenous healing appears to be dysfunctional.

This paper outlines current thinking on the role of bioelectricity in healing, presents empirical evidence regarding MCT for the promotion of tissue healing, and suggests implications for both clinical and research communities. The majority of published research in this area is concerned with bone and skin lesions, but patterns and mechanisms of healing in these tissues share features with those seen in damaged tendons, ligaments and other musculoskeletal structures¹⁰⁻¹². Therefore the evidence presented here is of relevance to researchers and clinicians concerned with a variety of musculoskeletal disorders.

Bioelectricity and healing

The human body, in common with other living organisms, expends a significant proportion of its energy generating electricity¹³. In fact the body is a conglomeration of electric batteries. Every cell maintains a voltage across its external membrane, and across the membranes of its organelles^{14, 15}. This is achieved by the active transport of ions, particularly sodium (Na^+) and Potassium (K^+), against their concentration gradients, establishing charge separations that constitute a potential difference or voltage across the membrane¹⁶. Aggregates of cells also set up voltages across various tissue layers, cutaneous and corneal epithelium, vascular and intestinal walls, and the cortex and periosteum of long bones^{14, 15, 17-21}. These voltages are of the order of millivolts (mV) in magnitude, and where there is a conducting pathway they cause the movement of ions within tissue, constituting a bioelectric current, typically in the microamp (μA) range¹⁴.

At the cellular level, bioelectricity is involved in the transport through the membrane of ions that can mediate cell behaviour. Even in non-excitable cells there are voltage-gated channels controlling the passage of ions that mediate cell behaviour²². At the tissue level, endogenous fields are intrinsic to a number of metabolic processes, including development, adaptation and repair. They can influence cell morphology and the growth of body parts during foetal development^{13, 23, 24}; they are generated when connective tissues such as bone and tendon are stressed and can influence adaptive modifications in the extracellular matrix²⁵⁻²⁸; and when tissue is damaged they set up currents that appear to drive elements of the healing response^{17, 29-32}. The currents diminish as healing progresses, with normal values being re-established once healing is complete^{17, 23, 32, 33}.

That bioelectricity is intrinsic to such processes – rather than mere by-products – has been established by a wealth of experimental evidence. Perhaps the most convincing is that setting up a voltage in opposition to the endogenous one, or blocking the passage of biocurrents in wounds, can slow or abolish the healing response in a variety of tissue types^{15, 33-35}. In vitro studies have also demonstrated that application of electric fields and currents similar to those generated within the body can cause significant changes in the structure and behaviour of cells. Application of microcurrent to tissue has been found to boost the number of organelles responsible for cellular activities, and to increase concentrations of ATP, the cellular currency of energy^{36, 37}. These changes can facilitate cell proliferation and protein synthesis, which have been found to increase when microcurrents are applied to the constituent cells of skin^{38, 39}, tendons^{40, 41}, cartilage⁴² and bone⁴³. Such effects are highly parameter-dependent, however. Larger currents or alternating microcurrents at certain frequencies have been found to reduce cell proliferation or induce cell death in some cases^{44, 45}.

Ion channels in cell membranes may migrate under the influence of an applied field, resulting in cytoskeletal modifications, including creation of membrane projections that cause cell movement^{24, 37}. Directed movement of cells within an electric field – known as galvanotaxis – has been observed with many cell types. These include leukocytes and macrophages, which are key mediators in different stages of healing⁴⁶, as well as a variety of cells responsible for tissue formation, such as keratinocytes, vascular endothelial cells, osteoblasts, osteoclasts, chondrocytes and fibroblasts^{24, 37, 47, 48}. Different cell types have been found to move in opposite directions, and reversing the field reverses the direction of migration^{37, 49}.

At the tissue level, unidirectional fields and direct currents (DC) can promote vascular permeability⁵⁰ angiogenesis⁵¹ and neural sprouting^{31, 52} as well as formation of new skin, bone, cartilage and soft tissue formation^{39, 53-57}. Such findings are significant because they suggest that applying fields and currents with similar parameters to bioelectricity may be used to stimulate tissue healing. Cell migration, proliferation and synthesis of new tissue are all essential components of the healing process^{1, 46}. If applied electricity can mimic endogenous electrical signals that guide cellular behaviour, then a therapeutic option may be available where natural healing has failed.

Therapeutic Microcurrent

There are various forms of electrotherapy that may deliver average currents in the microamp range, such as high voltage pulsed current (HVPC) and high frequency alternating currents induced by electric or electromagnetic fields (e.g. Pulsed Short-wave Therapy). However, the waveforms produced by these modalities are quite unlike those of any observed endogenous currents and voltages, which tend to be unidirectional, and of constant or slowly varying amplitude¹⁴. Since MCT is predicated on the basis that it mimics endogenous bioelectric signals, the main focus here is on those studies that use electrical stimulation with similar parameters. A good deal of evidence regarding the effects of microcurrent on tissue healing has accumulated over recent decades. Where clinical trials have been reported, they are presented, though reference to in vitro and animal studies is also made where clinical trial data is scarce.

BONE

Electrical stimulation was used for promotion of bone healing in the early 19th century. English physician John Birch applied direct current to the ends of a 13 month-old non-uniting tibial fracture via percutaneous electrodes⁵⁸. After 6 weeks of treatment the fracture had consolidated. Other historical examples of electricity being used in this way era are recorded, but the therapy later fell into disuse. It was revived in the mid 20th century, when a scientific rationale for its application was developed on the basis of in vitro and animal experiments. In the 1950s several workers found that application of microcurrent to bone could initiate osteogenesis in both normal and damaged bone^{59,60}. Later studies investigated the effects of parameters such as current size, polarity and electrode material and configuration on the process⁶¹⁻⁶³. New bone could be laid down by direct currents of about 20 μA , with maximal formation occurring at the cathode (the negative electrode). Currents above 30 μA could cause bone resorption or osteonecrosis^{55,62,64}. Such data provide a convincing rationale for the use of microcurrent to stimulate bone healing, and subsequent in vivo animal studies suggested that it might be beneficial for several clinical applications, including fresh fractures, delayed and non-uniting fractures, osteotomies and spinal fusions, although parameter choices varied considerably and not all applications were successful⁶⁵⁻⁷⁰. For reviews of such studies, see^{71,72}.

Clinical studies

The earliest modern application of MCT for human bone healing was to non-uniting fractures. In 1971, Friedenbergs and colleagues published a case study in which a malleolar fracture, which had failed to unite after more than a year, was healed by treatment with direct current of 10 μA via a cathode inserted into the fracture site⁷³. Several larger studies followed, in which MCT was applied to delayed or non-uniting fractures. Delayed unions are those that take longer than would be expected for the particular fracture site and patient characteristics; non-union is said to occur when healing stops and union is not achieved after 6 – 8 months⁷⁴. In 1977 Brighton and colleagues reported a study involving treatment of 57 lower and upper limb non-unions with 10 - 20 μA , delivered to the site by 2 - 4 cathodes for 12 weeks, followed by 12 weeks further immobilisation⁷⁵. Of those treated, 76% went on to develop full union, with most failures accounted for by insufficient current delivery or breakage of electrodes. In a follow-up multi-centre study 84% of 178 non-unions treated using a similar protocol achieved union. Complications were reported as minor⁷⁶. Another multicentre trial in a different country used the same current but delivered through a single cathode to 84 patients with either delayed or non-union⁷⁷, mostly of the tibia or femur. Time to achieve union varied between 12 and 36 weeks. A ten-year follow-up assessment of 37 of the patients enrolled in this trial found normal bone remodelling, continued union and no side effects of the electrodes that were left in situ (the remaining participants were unavailable for review)⁷⁸.

Microcurrent pulsed at 20 Hz has also been evaluated and found beneficial with a mixed caseload of non-uniting fractures, congenital pseudarthroses, osteotomies and leg-lengthening procedures. DC of pulse amplitude 20 – 25 μ A and duration 30 ms was applied via a cathode wrapped around or threaded through the fracture site and with the anode implanted in the medulla (as opposed to the subcutaneous positioning used in other trials). Treatment times varied according to case until union was observed radiographically, and varied between 2 and 12 months. The overall success rate was 87% although adjunctive treatments and individual characteristics varied considerably. Authors of one of the earlier studies⁷⁵ reported that they found that constant DC always produced superior outcomes to pulsed current, although they presented no relevant parameter or outcome data.

Some of these studies are rather dated and do not meet contemporary reporting standards for clinical trials. The absence of a formal control group is justified by the fact that usually no bone healing had been observed for months, and spontaneous recovery in such cases is rare, so participants were considered to be acting as their own controls⁷⁶. However placebo and time effects cannot be ruled out when evaluating their evidence. The lack of more recent studies may reflect the greater popularity of less invasive electrotherapeutic modalities⁷⁹, although MCT may give superior results in selected cases. A comparison with capacitative and inductive coupling as adjuncts for bone graft treatment of tibial non-unions reported in 1995 found that microcurrent was more effective with high risk cases such as those with atrophic non-unions or previous graft failure⁸⁰. Where there were no identified risk factors, none of the electrotherapies was superior to graft alone.

Although non-invasive forms of electrotherapy have superseded MCT for some applications, it has continued to be employed in selected cases of lumbar spinal fusions, where there is evidence of its superiority over other modalities. Lumbar spinal fusions are used in cases of disabling joint instability or disc degeneration, and normally involve a bone graft and instrumentation. Failure rates can be as high as 40%⁸¹, but may be reduced substantially by the application of MCT. After its first clinical use was reported in 1974⁸², direct current application, typically of 20 μ A applied by a single or multiple cathodes to the fusion site for 5-6 months, was subject to evaluation in several trials⁸³⁻⁸⁵. In these studies patients receiving MCT in addition to standard treatment had successful fusion rates of 81 – 96%, compared to 54 – 81% for those on standard treatment alone, as assessed by radiographic and clinical criteria. Results for methodologically sound controlled trials consistently indicate statistically significant outcomes in favour of DC MCT compared with control groups⁸⁶. It is particularly effective when used in high risk cases such as those with previous failed fusions, multiple level surgery, smokers and those with co-morbidities such as diabetes and obesity⁸⁷⁻⁸⁹, and has a stronger evidence base in its favour than either CC or IC, particularly for posterior fusions⁹⁰. An economic evaluation of the therapy as an adjunct in spinal fusion surgery⁹¹ also found that it provided significant cost savings and shorter in-patient stays.

Other small studies have suggested that DC MCT may be useful in other bone lesions, including high risk ankle and hind-foot fusions^{92, 93} and selected congenital pseudarthroses⁹⁴⁻⁹⁷. Their findings have yet to be confirmed in larger trials. Two controlled trials have suggested that MCT may also accelerate healing in fresh fractures^{98, 99}, though this application is still largely unexplored.

Systematic reviews of trials have concluded that the best evidence for promotion of bone healing by application of small electric currents is in cases of non-uniting lower limb fractures and spinal fusions^{71, 86, 88, 90, 100-105}. Meta-analyses have been weakened by pooling data from trials using heterogeneous groups and treatment parameters, and even different forms of electrotherapy^{86, 101}. Nevertheless, consideration of the evidence regarding MCT in particular suggests that its application, usually for several months, may enhance tissue healing in a variety of bone lesions.

SKIN

Since it is easily accessible for study, skin is the tissue in which the bioelectrics of healing have perhaps been subject to the greatest scrutiny. Several reviews providing accounts of in vitro and animal studies are available^{53, 72, 106}, and only the human and clinical studies are dealt with here. Several authors have identified the seventeenth century use of charged gold leaf for resolution of smallpox lesions as the first example of electrotherapy for human skin healing^{53, 107, 108}. In fact there is no mention of electric charge in the cited source¹⁰⁹. Charged gold leaf, which would deliver small and diminishing currents to adjacent tissue, was used successfully in the 1960s to assist healing in surgical vascular wounds and cutaneous ulcers^{110, 111}. However, charging appears to have been considered an aid to adherence of the leaf rather than an agent of healing in itself. Nevertheless, more recent studies have consistently concluded that electrical stimulation, including MCT, can indeed promote healing in various types of human skin wounds, particularly ulcers. The first of these was reported in 1968 by Assimacopoulos who, following successful use of microcurrent to accelerate healing of surgical scars on rabbit ears¹¹², tried the treatment with recalcitrant leg ulcers in three patients¹¹³. Direct current between 50 and 100 μA was delivered continuously for several weeks via a stainless steel mesh cathode soaked in saline and placed on a moist dressing on the wound, and an anode affixed to the thigh or abdominal wall. All the wounds healed within 6 weeks and no side effects of treatment were reported.

In a larger study, Wolcott and colleagues used MCT with 83 ulcers of varying aetiology in 67 patients¹¹⁴. A measure of control was introduced by assessing but not treating additional ulcers in eight of the sample patients. "About three quarters" of the patients had failed to respond to other conservative treatment. Direct current between 400 and 800 μA was applied via a copper mesh cathode over the wound and anode on skin 15cm proximal. The current level was determined individually, adjusted so as to avoid bleeding or excess exudate production, and was delivered for 2 hours, thrice daily for several weeks, in some cases months, until healing occurred (a full breakdown of durations was not given). The protocol involved a polarity-swapping element, based on early experience that healing would often plateau after a few days and could be restarted by reversing the polarity of the electrodes. Over a mean treatment time of 7.7 weeks, there was a mean volume reduction in treated wounds of 82%, with a mean healing rate of 13.4% per week. 34 lesions (40%) healed completely. These figures mask a wide range of individual and group responses, with paraplegic patients (presumably mostly spinal cord injured) consistently responding less well to treatment. Of the eight patients (mostly paraplegic) with microcurrent-treated and control ulcers, mean volume reductions were 93 (range 75 – 100) % in the MCT ulcers and 33 (range 0 – 75) % in the control ulcers. The study evidence is weakened by the lack of information on duration of ulcers, the inclusion of patients for whom standard treatments had not been tried, early termination of electrotherapy protocol in more than half of the sample, and the small size of the control group. Even so, it began to build the case that MCT could assist healing in a variety of skin ulcer types.

MCT using similar protocols – and various alternatives - were later used in several larger controlled trials by other groups¹¹⁵⁻¹²¹. These involved a variety of skin ulcer types including those due to venous and arterial insufficiency, secondary to diabetes, and pressure ulcers following spinal cord injury. MCT typically involved currents of the order of several hundred microamps, often continuous DC but sometimes pulsed or low frequency biphasic. Where currents were unidirectional, the anode was normally placed on the wound, within a moist dressing. Treatment times were usually an hour or more each day for several weeks or even months. Healing was measured in terms of percentage reductions in wound surface area or volume over a defined time, and in the majority of cases ulcers receiving MCT as an adjunct to conventional treatment healed more quickly and completely than those receiving conventional treatment alone.

More recent studies have suggested that MCT may also be effective with other types of skin wounds. In a trial involving 30 patients, microcurrent was found more effective than conventional treatment in promoting skin graft healing following thermal injury¹²². A DC current between 50 and 100 μA was applied continuously

for several days via an anodal dressing on the wound. Stimulated wounds closed in an average 4.6 days compared to 7.2 days for controls. A series of case studies involving application of monophasic microcurrent to pressure sores, an infected venous ulcer and a recalcitrant pilonidal sinus also found evidence of benefit in terms of ¹²³ accelerated healing and reduction of bacterial load. The novelty of these cases was that the current (of unspecified magnitude) was provided by a proprietary dressing with an integrated circuit and battery and electrodes.

Reviews of electrical stimulation for skin wound healing have consistently concluded that the weight of evidence is in its favour when it is used as adjunctive treatment with other conservative management strategies ^{53, 86, 108, 124-128}. In the USA, government and private medical insurers pay for its use with recalcitrant ulcers due to pressure, arterial or venous insufficiency and diabetes ¹²⁷. However most reviews have not considered the different modalities separately, because the numbers would not justify subgroup analysis. Where MCT studies are considered alone, the range of protocols employed means that optimum parameters cannot yet be identified. Both continuous and pulsed, monophasic and biphasic, anodal and cathodal stimulation seem capable of promoting healing. The parameters that are supported by a majority of studies are current size (in the hundreds of microamps), treatment time (typically several weeks, for hours rather than minutes each day) and application directly to the wound bed. Monophasic or “unbalanced” currents (those with a net delivery of charge) are more common in the studies indicating MCT effectiveness.

TENDONS AND OTHER TISSUES

Data from in vitro and animal studies, and a small number of human trials, suggest that there may be unexplored potential for microcurrent treatment of soft connective tissue lesions, particularly in tendons and ligaments. In these structures, the extracellular matrix (ECM) is laid down by various phenotypes of the fibroblast, a cell that has been shown to migrate, proliferate and increase synthesis of ECM proteins under the influence of applied electric fields and currents ^{40, 41, 129-132}.

Tissue and animal studies

By using explants, whole tissue samples taken from animals and maintained in laboratory cultures, investigators have been able to conduct well-controlled studies of the effects of applied current on tendons and ligaments. Nessler and Mass reported using these methods in 1987, when they applied continuous 7 μA current for up to 6 weeks to surgically transected and sutured rabbit flexor tendon explants ¹³³. Bioassay and histological analysis showed greater and more rapid fibroblast proliferation, protein synthesis and collagen deposition consistent with normal tendon healing in stimulated explants compared to their controls. These changes were observed distant from the cathode, which had been placed into the lesion, and the authors speculated that the current density was too great close to the cathode. Soon after, Cleary and colleagues investigated the influence of various microcurrent parameters by applying pulsed monophasic microcurrent to chicken flexor tendon explants for three days, varying current amplitude, direction and pulsing frequency ¹³⁰. They found that levels of fibroblast proliferation, protein synthesis and collagen fibroplasia at the cut surfaces of stimulated explants were significantly greater than those of unstimulated controls. Effect sizes were greatest at current densities of near 1 $\mu\text{A}/\text{cm}^2$, and at pulse frequency 1 Hz, and dropped off at higher values. Applying the current longitudinally maximised the effects, whilst no significant differences between treated and control explants were found with transverse application. This observation was explained by other studies showing that fibroblasts lay down collagen fibres parallel to the direction of the applied field ^{134, 135}.

In a study using explants of rabbit flexor tendons and their sheaths, longitudinal stimulation with various DC microcurrent levels was applied for up to 2 weeks ⁴¹. Investigation of the cut surfaces revealed evidence of cell proliferation and collagen deposition in both treated and control samples, with adhesions forming in the

epitenon-sheath as a result. Application of microcurrent caused different effects according to current size. Above 1 μA there was evidence of tissue degeneration and cell death, but at 0.5 μA proliferation continued in the tendon substance but was significantly reduced in the sheath. This observation rather astonishingly suggests that microcurrent can selectively inhibit proliferation that would lead to counterproductive adhesion formation during sheathed-tendon healing.

In the first reported in vivo animal study, low level current was applied to surgically wounded flexor tendons of 6 ponies via a cathode implanted in the wound and an anode 3cm distal¹³⁶. No gross or histological differences were seen between treated and contralateral control tendons at 4, 5 and 6 weeks post-injury. The author speculated that the (unmonitored) current, provided by a bimetallic strip, may have been too low to affect healing. Later studies were more encouraging, though a wide range of parameters was adopted, making generalisation from their results problematic. Stanish and colleagues transected the medial portion of the patellar tendons of nine dogs and divided them into three groups, receiving plaster immobilisation, brief compression bandaging or constant 20 μA current applied via a cathode wrapped around the tendon¹³⁷. After six weeks the dogs were killed and the tendons removed with their contralateral counterparts for comparison. Breaking strengths as a percentage of the normal tendon values were 47% and 50% for the first two groups, and 92% for the MCT group. Though the sample sizes were small, the difference is striking.

In a larger study¹³⁸, the patellar tendons of 45 rabbits were transected bilaterally and cathodes sutured into the lesions, anodes mounted on the tissue surface. One limb was left untreated, the other given 10 μA DC continuously, with tendons removed at for three, five or seven weeks for evaluation. Mechanical strength was found to increase more rapidly in the early weeks in stimulated tendons, whilst mature collagen formation was greater in the later weeks, compared to controls. This suggested that MCT could accelerate healing in both proliferative and remodelling phases of healing.

Subsequent studies with rat Achilles tendons, knee ligaments and joint capsules have consistently suggested that MCT with a range of parameters can accelerate repair and result in stronger tissue and reduced contracture formation after injury, compared to unstimulated controls^{56, 139-143}. Microcurrent has also been observed to promote rabbit cartilage growth⁵⁷ and repair¹⁴⁴, as well as rat peripheral nerve regeneration⁵². DC or unbalanced biphasic current was used in all the tendon studies, but AC was also successfully employed with other tissues. Treatment times varied between one and 24 hours a day for between one and four weeks. Where currents were modulated, their amplitudes were of the order of 100 μA (with considerably lower average values), and electrodes were implanted, usually delivering current parallel to fibre orientation. The strength of the studies is in their use of contralateral controls, allowing a cause-effect relationship to be established. However their findings cannot be aggregated because of heterogeneity in their treatment parameters. They all used surgical means to create lesions and animal models that are imperfect analogues of human tissue disorders. The lack of histological data also means that conclusions cannot be drawn about repair processes. Despite these limitations, they provide evidence that microcurrent can promote resolution of tissue damage, and have justified progression to clinical trials of MCT.

Human studies

Following their work with surgically wounded canine tendons, Stanish and colleagues reported on a series of more than 100 patients in which MCT was used after surgical repair of torn Achilles and patellar tendons and anterior cruciate ligaments. A direct current of 20 μA was applied (for an unreported time, presumably several weeks) via a cathode wrapped around the lesion and a subcutaneous anode and power-pack. The authors reported accelerated return to full weight-bearing and function, and histological analysis of 45 reconstructed ligaments 9 months after surgery showed the tissue to be revascularised with mature and well organised collagen. This was not a formally controlled trial, however, and little numerical data is provided for scrutiny.

MCT has been subject to trial with several examples of chronic tendinopathy. One involved 48 people with Achilles tendinopathy of at least 3 months system duration, randomly assigned to receive either microcurrent or conventional conservative treatment¹⁴⁵. A monophasic square wave of amplitude 40 μ A and frequency 10Hz was applied via surface electrodes placed transversely across the lesion. Treatment was for 30 minutes daily over 14 days, followed by a regime of eccentric exercises. Numerical measures of patient-rated pain and stiffness and clinician-rated clinical status were recorded at baseline and at 3, 6 and 12 months after treatment. Statistically significant differences in favour of the MCT group were found in these measures. Sonography, which can be used to image changes associated with tendinopathy^{146, 147}, was also employed. The authors reported that sonographic findings were "in agreement" with these outcomes, though specific data are not given. Improvements were most marked in the first three months after treatment. The study is weakened by non-standardisation of the conventional treatment and a complex and unvalidated scoring system used with the outcome measures. However, the data are encouraging.

A more recent pilot controlled trial has used MCT for chronic tennis elbow¹⁴⁸. Sixteen people with symptoms lasting at least 3 months were randomly assigned to receive either a 6-week standardised exercise programme or exercise plus MCT. Biphasic square wave current with a variety of parameters including amplitudes 40 μ A or 300 μ A and frequencies of 0.3, 3 and 30 Hz. Treatment was administered via probes contacting the skin at various points on the elbow and forearm for several minutes, ten times over three weeks. Outcome measures were pressure pain threshold at the tendon, grip strength and pain on gripping, recorded at baseline and 1, 2, 3 and 6 weeks later. All participants improved but no significant differences between groups were seen in any of the outcome measures. The conclusions may have been affected by the small sample size of the study, but in any case it was hampered at the outset by the use of MCT with very short duration and methods of application that were given no scientific justification by the authors.

Trials using microcurrent have been reported for a range of other soft tissue lesions, including plantar fasciitis¹⁴⁹, delayed-onset muscle soreness (DOMS)¹⁵⁰⁻¹⁵², radiation-induced fibrosis¹⁵³ and osteoarthritis¹⁵⁴. The outcomes of these trials suggest – though not unequivocally - the MCT may have an analgesic effect that is not due to sensory stimulation, since the treatment is normally sub-sensory. Pain relief may account for the improvement in other outcome measures such as range of movement and function. In one study there was also evidence of mediation of the healing process. Serum creatine kinase (CK) levels, which elevate following muscle damage, were found to be lower in DOMS-induced muscles after MCT than in an untreated control group. The microcurrent was delivered by a skin-mounted charged dielectric pad, providing an average 20 μ A over 48 hours, and the CK level differences were significantly lower in the treated group 4-7 days after injury¹⁵¹.

Drawing firm conclusions from these human studies is hampered by various factors. In particular, the use of proprietary devices delivering microcurrent whose parameters are based on little if any scientific rationale. The outcome measured they adopt often give only indirect information about tissue status, and some studies are poorly constructed or reported. Nevertheless they suggest that MCT may have potential in promoting the resolution of various musculoskeletal soft tissue disorders, and indicate the need for well-conducted clinical trials. The normally sub-sensory nature of microcurrent means that double-blind placebo-controlled trials, which could provide convincing evidence, are practicable. However, at least for the present, the most robust evidence in favour of MCT for soft tissue lesions is provided by cellular and animal studies.

CONCLUSIONS

The evidence in support of MCT has been convincing enough to justify its inclusion in the clinician's repertoire for treatment of several examples of recalcitrant bone and skin lesions. Indeed federal and private health

insurance providers in the USA have accepted its use (along with other forms of electrical stimulation) for spinal fusions and hard to heal skin ulcers for some years^{53, 83}. In contrast, the lack of substantial and robust human trial evidence for the use of MCT with musculoskeletal soft tissue lesions is frustrating. Clinicians are justifiably cautious when presented with yet another form of electrotherapy, especially when the case for more familiar and well-used modalities such as therapeutic ultrasound has been questioned in several reviews¹⁵⁵⁻¹⁵⁷.

Yet MCT has several significant features in its favour: there is already substantial evidence that it can promote healing in a variety of tissue types and disorders, especially where other approaches have failed; it may help redress an underlying physiological dysfunction as well as reducing its symptoms; its mechanism of action appears to be as a trigger or facilitator of the healing process, unlike some new approaches such as exogenous growth factors, which have specific targets in the healing cascade. Reported side-effects of MCT are few and minor, and it can be provided by a small, portable generator, over an extended period where necessary, requiring minimal therapist supervision once initiated. The therapy has been shown to be most beneficial when it is used as part of a broader management strategy. Given these characteristics, the potential for MCT in a range of recalcitrant musculoskeletal disorders is worthy of closer attention by both research and clinical communities.

REFERENCES

Most important papers are marked with an asterisk.

1. Kalfas, I.H., *Principles of bone healing*. Neurosurg Focus, 2001. **10**(4): p. E1.
2. Liu, S.H., R.S. Yang, R. al-Shaikh, and J.M. Lane, *Collagen in tendon, ligament, and bone healing. A current review*. Clin Orthop Relat Res, 1995(318): p. 265-78.
3. Agren, M.S. and M. Werthen, *The extracellular matrix in wound healing: a closer look at therapeutics for chronic wounds*. Int J Low Extrem Wounds, 2007. **6**(2): p. 82-97.
4. Hunt, T.K., H. Hopf, and Z. Hussain, *Physiology of wound healing*. Adv Skin Wound Care, 2000. **13**(2 Suppl): p. 6-11.
5. Werner, S. and R. Grose, *Regulation of wound healing by growth factors and cytokines*. Physiol Rev, 2003. **83**(3): p. 835-70.
6. Bassett, C.A.L., *Bioelectromagnetism in the services of medicine*, in *Electroagnetic Fields: Biological Interactions and Mechanisms*, M. Blank, Editor. 1995, American Chemical Society: Washington DC.
7. Kloth, L.C. and J.A. Feedar, *Electrical stimulation in tissue repair*. Contemp Perspect Rehabil, 1990. **5 Wound Healing - Alternatives in Management**: p. 221-58.
8. Becker, R.O. and G. Selden, *The body electric: Electromagnetism and the foundation of life*. 1985, New York: William Morrow.
- *9. Black, J., *Electrical stimulation: Its role in growth, repair and remodelling of the musculoskeletal system*. 1987, New York: Prager.
10. Mast, B.A., *Healing in other tissues*. Surg Clin North Am, 1997. **77**(3): p. 529-47.
11. Platt, M.A., *Tendon repair and healing*. Clin Podiatr Med Surg, 2005. **22**(4): p. 553-60, vi.
12. Molloy, T., Y. Wang, and G. Murrell, *The roles of growth factors in tendon and ligament healing*. Sports Med, 2003. **33**(5): p. 381-94.
- *13. Nuccitelli, R., *Endogenous electric fields in embryos during development, regeneration and wound healing*. Radiat Prot Dosimetry, 2003. **106**(4): p. 375-83.
14. Nuccitelli, R., *Endogenous ionic currents and DC electric fields in multicellular animal tissues*. Bioelectromagnetics, 1992. **Suppl 1**: p. 147-57.
15. Friedenberg, Z.B., M.C. Harlow, R.B. Heppenstall, and C.T. Brighton, *The cellular origin of bioelectric potentials in bone*. Calcif Tissue Res, 1973. **13**(1): p. 53-62.
16. Wright, S.H., *Generation of resting membrane potential*. Adv Physiol Educ, 2004. **28**(1-4): p. 139-42.
17. Borgens, R.B., *Endogenous ionic currents traverse intact and damaged bone*. Science, 1984. **225**(4661): p. 478-82.
18. Friedenberg, Z.B. and C.T. Brighton, *Bioelectric potentials in bone*. J Bone Joint Surg Am, 1966. **48**(5): p. 915-23.
19. Foulds, I.S. and A.T. Barker, *Human skin battery potentials and their possible role in wound healing*. Br J Dermatol, 1983. **109**(5): p. 515-22.
20. Trumbore, D.C., W.J. Heideger, and K.W. Beach, *Electrical potential difference across bone membrane*. Calcif Tissue Int, 1980. **32**(2): p. 159-68.

21. Gustke, R.F., P. McCormick, H. Ruppin, et al., *Human intestinal potential difference: recording method and biophysical implications*. J Physiol, 1981. **321**: p. 571-82.
22. Wu, W.K., G.R. Li, T.M. Wong, et al., *Involvement of voltage-gated K⁺ and Na⁺ channels in gastric epithelial cell migration*. Mol Cell Biochem, 2008. **308**(1-2): p. 219-26.
23. Borgens, R.B., *Natural and applied currents in limb regeneration and development*, in *Electric Fields in Vertebrate Repair*, R.B. Borgens, et al., Editors. 1984, Alan R Liss Inc: New York.
24. McCaig, C.D., A.M. Rajniecek, B. Song, and M. Zhao, *Controlling cell behavior electrically: current views and future potential*. Physiol Rev, 2005. **85**(3): p. 943-78.
25. Chen, C.T., R.P. McCabe, A.J. Grodzinsky, and R. Vanderby, Jr., *Transient and cyclic responses of strain-generated potential in rabbit patellar tendon are frequency and pH dependent*. J Biomech Eng, 2000. **122**(5): p. 465-70.
26. Spadaro, J.A., *Mechanical and electrical interactions in bone remodeling*. Bioelectromagnetics, 1997. **18**(3): p. 193-202.
27. Fukada, E. and I. Yasuda, *On the Piezoelectric Effect of Bone*. Journal of the Physical Society of Japan, 1957. **12**(10): p. 1158-1162.
28. Anderson, J.C. and C. Eriksson, *Electrical properties of wet collagen*. Nature, 1968. **218**(5137): p. 166-8.
29. Vanables, J.W.J., *Integumentary potentials and wound healing*, in *Electric Fields in Vertebrate Repair*, R.B. Borgens, et al., Editors. 1984, Alan R Liss Inc: New York.
30. Borgens, R.B., *What is the role of naturally produced electric current in vertebrate regeneration and healing*. Int Rev Cytol, 1982. **76**: p. 245-98.
31. Song, B., M. Zhao, J. Forrester, and C. McCaig, *Nerve regeneration and wound healing are stimulated and directed by an endogenous electrical field in vivo*. J Cell Sci, 2004. **117**(Pt 20): p. 4681-90.
32. Kappel, D., S. Zilber, and L. Ketchum, *In vivo electrophysiology of tendons and applied current during tendon healing*, in *Biologic and clinical effects of low-frequency magnetic and electric fields*, J.G. Llaurodo, A. Sances, and J.H. Battocletti, Editors. 1974, C C Thomas: Illinois. p. 252-260.
33. Jaffe, L.F. and J.W. Vanable, Jr., *Electric fields and wound healing*. Clin Dermatol, 1984. **2**(3): p. 34-44.
34. Song, B., M. Zhao, J.V. Forrester, and C.D. McCaig, *Electrical cues regulate the orientation and frequency of cell division and the rate of wound healing in vivo*. Proc Natl Acad Sci U S A, 2002. **99**(21): p. 13577-82.
35. Zhao, M., B. Song, J. Pu, et al., *Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-gamma and PTEN*. Nature, 2006. **442**(7101): p. 457-60.
36. Cheng, N., H. Van Hoof, E. Bockx, et al., *The effects of electric currents on ATP generation, protein synthesis, and membrane transport of rat skin*. Clin Orthop Relat Res, 1982(171): p. 264-72.
37. Funk, R.H. and T.K. Monsees, *Effects of electromagnetic fields on cells: physiological and therapeutical approaches and molecular mechanisms of interaction. A review*. Cells Tissues Organs, 2006. **182**(2): p. 59-78.
38. Cheng, K. and R.J. Goldman, *Electric fields and proliferation in a dermal wound model: cell cycle kinetics*. Bioelectromagnetics, 1998. **19**(2): p. 68-74.

39. Leffman, D.J., D.A. Arnall, P.R. Holman, and M.W. Cornwall, *Effect of microamperage stimulation on the rate of wound healing in rats: a histological study*. Phys Ther, 1994. **74**(3): p. 195-200.
40. Lin, Y.L., H. Moolenaar, P.R. van Weeren, and C.H. van de Lest, *Effect of microcurrent electrical tissue stimulation on equine tenocytes in culture*. Am J Vet Res, 2006. **67**(2): p. 271-6.
41. Fujita, M., S. Hukuda, and Y. Doida, *The effect of constant direct electrical current on intrinsic healing in the flexor tendon in vitro. An ultrastructural study of differing attitudes in epitenon cells and tenocytes*. J Hand Surg [Br], 1992. **17**(1): p. 94-8.
42. Okihana, H. and Y. Shimomura, *Effect of direct current on cultured growth cartilage cells in vitro*. J Orthop Res, 1988. **6**(5): p. 690-4.
43. Wang, Q., S. Zhong, J. Ouyang, et al., *Osteogenesis of electrically stimulated bone cells mediated in part by calcium ions*. Clin Orthop Relat Res, 1998(348): p. 259-68.
44. Cucullo, L., G. Dini, K.L. Hallene, et al., *Very low intensity alternating current decreases cell proliferation*. Glia, 2005. **51**(1): p. 65-72.
45. Blumenthal, N.C., J. Ricci, L. Breger, et al., *Effects of low-intensity AC and/or DC electromagnetic fields on cell attachment and induction of apoptosis*. Bioelectromagnetics, 1997. **18**(3): p. 264-72.
46. Wong, M.E., J.O. Hollinger, and G.J. Pinero, *Integrated processes responsible for soft tissue healing*. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1996. **82**(5): p. 475-92.
47. Zhao, M., A. Agius-Fernandez, J.V. Forrester, and C.D. McCaig, *Directed migration of corneal epithelial sheets in physiological electric fields*. Invest Ophthalmol Vis Sci, 1996. **37**(13): p. 2548-58.
48. Chao, P.H., R. Roy, R.L. Mauck, et al., *Chondrocyte translocation response to direct current electric fields*. J Biomech Eng, 2000. **122**(3): p. 261-7.
49. Ferrier, J., S.M. Ross, J. Kanehisa, and J.E. Aubin, *Osteoclasts and osteoblasts migrate in opposite directions in response to a constant electrical field*. J Cell Physiol, 1986. **129**(3): p. 283-8.
50. Vanable, J.W.J., *Integumentary potentials and wound healing*, in *Electric Fields in Vertebrate Repair*, R.B. Borgens, et al., Editors. 1984, Alan R Liss Inc: New York.
51. Bai, H., C.D. McCaig, J.V. Forrester, and M. Zhao, *DC electric fields induce distinct preangiogenic responses in microvascular and macrovascular cells*. Arterioscler Thromb Vasc Biol, 2004. **24**(7): p. 1234-9.
52. Mendonca, A.C., C.H. Barbieri, and N. Mazzer, *Directly applied low intensity direct electric current enhances peripheral nerve regeneration in rats*. J Neurosci Methods, 2003. **129**(2): p. 183-90.
- *53. Kloth, L.C., *Electrical stimulation for wound healing: a review of evidence from in vitro studies, animal experiments, and clinical trials*. Int J Low Extrem Wounds, 2005. **4**(1): p. 23-44.
54. Supronowicz, P., K. Ullmann, P. Ajayan, et al. *Electrical stimulation promotes osteoblast functions pertinent to osteogenesis*. in *Transactions Orthopaedic Research Society*. 2001.
55. Brighton, C.T., Z.B. Friedenberg, J. Black, et al., *Electrically induced osteogenesis: relationship between charge, current density, and the amount of bone formed: introduction of a new cathode concept*. Clin Orthop Relat Res, 1981(161): p. 122-32.

- *56. Enwemeka, C.S. and N.I. Spielholz, *Modulation of tendon growth and regeneration by electrical fields and currents*, in *Dynamics of human biologic tissues*, D.P. Currier and R.M. Nelson, Editors. 1992, FA Davis Company: Philadelphia. p. 231-254.
57. Takei, N. and M. Akai, *Effect of direct current stimulation on triradiate physal cartilage. In vivo study in young rabbits*. Arch Orthop Trauma Surg, 1993. **112**(4): p. 159-62.
58. Peltier, L.F., *A brief historical note on the use of electricity in the treatment of fractures*. Clin Orthop Relat Res, 1981(161): p. 4-7.
59. Yasuda, I., *Fundamental aspects of fracture treatment* J. Kyoto Med. Soc., 1953. **4**: p. 395-406.
60. Percy, E.C. and C.L. Wilson, *Experimental studies on epiphyseal stimulation*. J Bone Joint Surg Am, 1956. **38-A**(5): p. 1096-104.
61. Bassett, C.A., R.J. Pawluk, and R.O. Becker, *Effects of Electric Currents on Bone in Vivo*. Nature, 1964. **204**: p. 652-4.
62. Friedenberg, Z.B., L.M. Zemsky, R.P. Pollis, and C.T. Brighton, *The response of non-traumatized bone to direct current*. J Bone Joint Surg Am, 1974. **56**(5): p. 1023-30.
63. Rubinacci, A. and L. Tessari, *A correlation analysis between bone formation rate and bioelectric potentials in rabbit tibia*. Calcif Tissue Int, 1983. **35**(6): p. 728-31.
64. McGinnis, M.E., *The Nature and Effects of Electricity in Bone*, in *Electric Fields in Vertebrate Repair*, R.B. Borgens, et al., Editors. 1989, Alan R. Liss: New York. p. 225-284.
65. Friedenberg, Z.B., P.G. Roberts, Jr., N.H. Didizian, and C.T. Brighton, *Stimulation of fracture healing by direct current in the rabbit fibula*. J Bone Joint Surg Am, 1971. **53**(7): p. 1400-8.
66. Zorlu, U., M. Tercan, I. Ozyazgan, et al., *Comparative study of the effect of ultrasound and electrostimulation on bone healing in rats*. Am J Phys Med Rehabil, 1998. **77**(5): p. 427-32.
67. Kleczynski, S., *Electrical stimulation to promote the union of fractures*. Int Orthop, 1988. **12**(1): p. 83-7.
68. Chakkalakal, D.A., L. Lippiello, R.L. Shindell, and J.F. Connolly, *Electrophysiology of direct current stimulation of fracture healing in canine radius*. IEEE Trans Biomed Eng, 1990. **37**(11): p. 1048-58.
69. Marino, A.A., B.D. Gross, and R.D. Specian, *Electrical stimulation of mandibular osteotomies in rabbits*. Oral Surg Oral Med Oral Pathol, 1986. **62**(1): p. 20-4.
70. France, J.C., T.L. Norman, R.D. Santrock, et al., *The efficacy of direct current stimulation for lumbar intertransverse process fusions in an animal model*. Spine, 2001. **26**(9): p. 1002-8.
71. Lavine, L.S. and A.J. Grodzinsky, *Electrical stimulation of repair of bone*. J Bone Joint Surg (Am), 1987. **69A**(4): p. 626-30.
72. Black, J., *Electrical stimulation of hard and soft tissues in animal models*. Clin Plast Surg, 1985. **12**(2): p. 243-57.
73. Friedenberg, Z.B., M.C. Harlow, and C.T. Brighton, *Healing of nonunion of the medial malleolus by means of direct current: a case report*. J Trauma, 1971. **11**(10): p. 883-5.
74. Rodriguez-Merchan, E.C. and F. Forriol, *Nonunion: general principles and experimental data*. Clin Orthop Relat Res, 2004(419): p. 4-12.
75. Brighton, C.T., Z.B. Friedenberg, E.I. Mitchell, and R.E. Booth, *Treatment of nonunion with constant direct current*. Clin Orthop Relat Res, 1977(124): p. 106-23.
76. Brighton, C.T., J. Black, Z.B. Friedenberg, et al., *A multicenter study of the treatment of non-union with constant direct current*. J Bone Joint Surg Am, 1981. **63**(1): p. 2-13.

77. Paterson, D.C., G.N. Lewis, and C.A. Cass, *Treatment of delayed union and nonunion with an implanted direct current stimulator*. Clin Orthop Relat Res, 1980(148): p. 117-28.
78. Cundy, P.J. and D.C. Paterson, *A ten-year review of treatment of delayed union and nonunion with an implanted bone growth stimulator*. Clin Orthop Relat Res, 1990(259): p. 216-22.
79. Evans, R.D.L., D. Foltz, and K. Foltz, *Electrical stimulation with bone and wound healing*. Clinics in Podiatric Medicine and Surgery, 2001. **18**(1): p. 79-95.
80. Brighton, C.T., P. Shaman, R.B. Heppenstall, et al., *Tibial nonunion treated with direct current, capacitive coupling, or bone graft*. Clin Orthop Relat Res, 1995(321): p. 223-34.
81. Kahanovitz, N., *Spine update: the use of adjunctive electrical stimulation to enhance the healing of spine fusions*. Spine, 1996. **21**(21): p. 2523-5.
82. Dwyer, A.F. and G.G. Wickham, *Direct current stimulation in spinal fusion*. Med J Aust, 1974. **1**(3): p. 73-5.
83. Kane, W.J., *Direct current electrical bone growth stimulation for spinal fusion*. Spine, 1988. **13**(3): p. 363-5.
84. Meril, A.J., *Direct current stimulation of allograft in anterior and posterior lumbar interbody fusions*. Spine, 1994. **19**(21): p. 2393-8.
85. Rogozinski, A. and C. Rogozinski, *Efficacy of implanted bone growth stimulation in instrumented lumbosacral spinal fusion*. Spine, 1996. **21**(21): p. 2479-83.
86. Akai, M. and K. Hayashi, *Effect of electrical stimulation on musculoskeletal systems; a meta-analysis of controlled clinical trials*. Bioelectromagnetics, 2002. **23**(2): p. 132-43.
87. Gan, J.C. and P.A. Glazer, *Electrical stimulation therapies for spinal fusions: current concepts*. Eur Spine J, 2006. **15**(9): p. 1301-11.
88. Akai, M., N. Kawashima, T. Kimura, and K. Hayashi, *Electrical stimulation as an adjunct to spinal fusion: a meta-analysis of controlled clinical trials*. Bioelectromagnetics, 2002. **23**(7): p. 496-504.
89. Kucharzyk, D.W., *A controlled prospective outcome study of implantable electrical stimulation with spinal instrumentation in a high-risk spinal fusion population*. Spine, 1999. **24**(5): p. 465-8; discussion 469.
90. Morone, M.A. and H. Feuer, *The use of electrical stimulation to enhance spinal fusion*. Neurosurg Focus, 2002. **13**(6): p. e5.
91. Kahanovitz, N. and C. Pashos, *The role of implantable direct current electrical stimulation in the critical pathway for lumbar spinal fusion*. J Care Manage, 1996. **6**: p. 2-8.
92. Midis, N. and S.F. Conti, *Revision ankle arthrodesis*. Foot Ankle Int, 2002. **23**(3): p. 243-7.
93. Donley, B.G. and D.M. Ward, *Implantable electrical stimulation in high-risk hindfoot fusions*. Foot Ankle Int, 2002. **23**(1): p. 13-8.
94. Brighton, C.T., Z.B. Friedenberg, L.M. Zemsky, and P.R. Pollis, *Direct-current stimulation of non-union and congenital pseudarthrosis. Exploration of its clinical application*. J Bone Joint Surg Am, 1975. **57**(3): p. 368-77.
95. Lavine, L.S., I. Lustrin, and M.H. Shamos, *Treatment of congenital pseudarthrosis of the tibia with direct current*. Clin Orthop Relat Res, 1977(124): p. 69-74.
96. Paterson, D.C., G.N. Lewis, and C.A. Cass, *Treatment of congenital pseudarthrosis of the tibia with direct current stimulation*. Clin Orthop Relat Res, 1980(148): p. 129-35.
97. Paterson, D.C. and R.B. Simonis, *Electrical stimulation in the treatment of congenital pseudarthrosis of the tibia*. J Bone Joint Surg Br, 1985. **67**(3): p. 454-62.

98. Jorgensen, T.E., *Electrical stimulation of human fracture healing by means of a slow pulsating, asymmetrical direct current*. Clin Orthop Relat Res, 1977(124): p. 124-7.
99. Masureik, C. and C. Eriksson, *Preliminary clinical evaluation of the effect of small electrical currents on the healing of jaw fractures*. Clin Orthop Relat Res, 1977(124): p. 84-91.
100. Driban, J.B., *Bone stimulators and microcurrent: clinical bioelectrics*. Athletic Therapy Today, 2004. **9**(5): p. 22-7, 36-7, 72.
101. Mollon, B., V. da Silva, J.W. Busse, et al., *Electrical stimulation for long-bone fracture-healing: a meta-analysis of randomized controlled trials*. J Bone Joint Surg Am, 2008. **90**(11): p. 2322-30.
102. Chao, E.Y. and N. Inoue, *Biophysical stimulation of bone fracture repair, regeneration and remodelling*. Eur Cell Mater, 2003. **6**: p. 72-84; discussion 84-5.
103. Cochran, G.V., *Experimental methods for stimulation of bone healing by means of electrical energy*. Bull N Y Acad Med, 1972. **48**(7): p. 899-911.
104. Lavine, L., I. Lustrin, R. Rinaldi, and M. Shamos, *Clinical and ultrastructural investigations of electrical enhancement of bone healing*. Ann N Y Acad Sci, 1974. **238**: p. 552-63.
- *105. Aaron, R.K., D.M. Ciombor, and B.J. Simon, *Treatment of nonunions with electric and electromagnetic fields*. Clin Orthop Relat Res, 2004(419): p. 21-9.
106. Lampe, K.E., *Electrotherapy in tissue repair*. J Hand Ther, 1998. **11**(2): p. 131-9.
107. Markov, M.S. and A.A. Pilla, *Review: electromagnetic field stimulation of soft tissues: pulsed radio frequency treatment of post-operative pain and edema*. Wounds: A Compendium of Clinical Research and Practice, 1995. **7**(4): p. 143-51.
108. Ojingwa, J.C. and R.R. Isseroff, *Electrical stimulation of wound healing*. J Invest Dermatol, 2003. **121**(1): p. 1-12.
109. Aitchison Robertson, W.G., *Digby's Receipts*. Ann Med Hist, 1925. **7**(3): p. 216-219.
110. Kanof, N.M., *Gold Leaf in the Treatment of Cutaneous Ulcers*. J Invest Dermatol, 1964. **43**: p. 441-2.
111. Gallagher, J.P. and F. Geschickter, *The Use of Charged Gold Leaf in Surgery*. Jama, 1964. **189**: p. 928-33.
112. Assimacopoulos, D., *Wound healing promotion by the use of negative electric current*. Am Surg, 1968. **34**(6): p. 423-31.
113. Assimacopoulos, D., *Low intensity negative electric current in the treatment of ulcers of the leg due to chronic venous insufficiency. Preliminary report of three cases*. Am J Surg, 1968. **115**(5): p. 683-7.
114. Wolcott, L.E., P.C. Wheeler, H.M. Hardwicke, and B.A. Rowley, *Accelerated healing of skin ulcer by electrotherapy: preliminary clinical results*. South Med J, 1969. **62**(7): p. 795-801.
115. Gault, W.R. and P.F. Gatens, Jr., *Use of low intensity direct current in management of ischemic skin ulcers*. Phys Ther, 1976. **56**(3): p. 265-9.
116. Carley, P.J. and S.F. Wainapel, *Electrotherapy for acceleration of wound healing: low intensity direct current*. Arch Phys Med Rehabil, 1985. **66**(7): p. 443-6.
117. Stefanovska, A., L. Vodovnik, H. Benko, and R. Turk, *Treatment of chronic wounds by means of electric and electromagnetic fields*. Med Biol Eng Comput, 1993. **31**(3): p. 213-20.
118. Baker, L.L., R. Chambers, S.K. DeMuth, and F. Villar, *Effects of electrical stimulation on wound healing in patients with diabetic ulcers*. Diabetes Care, 1997. **20**(3): p. 405-12.

119. Wood, J.M., P.E. Evans, 3rd, K.U. Schallreuter, et al., *A multicenter study on the use of pulsed low-intensity direct current for healing chronic stage II and stage III decubitus ulcers*. Arch Dermatol, 1993. **129**(8): p. 999-1009.
120. Barron, J.J., W.E. Jacobson, and G. Tidd, *Treatment of decubitus ulcers. A new approach*. Minn Med, 1985. **68**(2): p. 103-6.
121. Karba, R., D. Semrov, L. Vodovnik, et al., *DC electrical stimulation for chronic wound healing enhancement Part 1. Clinical study and determination of electrical field distribution in the numerical wound model*. Bioelectrochemistry and Bioenergetics 1997. **43**(2): p. 265-270.
122. Huckfeldt, R., A.B. Flick, D. Mikkelsen, et al., *Wound closure after split-thickness skin grafting is accelerated with the use of continuous direct anodal microcurrent applied to silver nylon wound contact dressings*. J Burn Care Res, 2007. **28**(5): p. 703-7.
123. Moore, K., *Electric stimulation of chronic wounds*. Journal of Community Nursing, 2007. **21**(1): p. 20-22.
124. Watson, T., *Electrical stimulation for wound healing*. Physical Therapy Reviews, 1996. **1**(2): p. 89-103.
125. Ramadan, A., M. Elsaidy, and R. Zyada, *Effect of low-intensity direct current on the healing of chronic wounds: a literature review*. J Wound Care, 2008. **17**(7): p. 292-6.
126. Gardner, S.E., R.A. Frantz, and F.L. Schmidt, *Effect of electrical stimulation on chronic wound healing: a meta-analysis*. Wound Repair Regen, 1999. **7**(6): p. 495-503.
127. Balakatounis, K.C. and A.G. Angoules, *Low-intensity Electrical Stimulation in Wound Healing: Review of the Efficacy of Externally Applied Currents Resembling the Current of Injury*. Eplasty, 2008. **8**: p. e28.
128. Vodovnik, L. and R. Karba, *Treatment of chronic wounds by means of electric and electromagnetic fields. Part 1. Literature review*. Med Biol Eng Comput, 1992. **30**(3): p. 267-76.
129. Chao, P.H., H.H. Lu, C.T. Hung, et al., *Effects of applied DC electric field on ligament fibroblast migration and wound healing*. Connect Tissue Res, 2007. **48**(4): p. 188-97.
130. Cleary, S.F., L.M. Liu, R. Graham, and R.F. Diegelmann, *Modulation of tendon fibroplasia by exogenous electric currents*. Bioelectromagnetics, 1988. **9**(2): p. 183-94.
131. McLeod, K.J., R.C. Lee, and H.P. Ehrlich, *Frequency dependence of electric field modulation of fibroblast protein synthesis*. Science, 1987. **236**(4807): p. 1465-9.
132. Sun, S., J. Wise, and M. Cho, *Human fibroblast migration in three-dimensional collagen gel in response to noninvasive electrical stimulus. I. Characterization of induced three-dimensional cell movement*. Tissue Eng, 2004a. **10**(9-10): p. 1548-57.
133. Nessler, J.P. and D.P. Mass, *Direct-current electrical stimulation of tendon healing in vitro*. Clin Orthop Relat Res, 1987(217): p. 303-12.
134. Lee, R.C., D.J. Canaday, and H. Doong, *A review of the biophysical basis for the clinical application of electric fields in soft-tissue repair*. J Burn Care Rehabil, 1993. **14**(3): p. 319-35.
135. Erickson, C.A. and R. Nuccitelli, *Embryonic fibroblast motility and orientation can be influenced by physiological electric fields*. J Cell Biol, 1984. **98**(1): p. 296-307.
136. Norrie, R.D., *A preliminary report on regenerative healing in the equine tendon*. Am J Vet Res, 1975. **36**(10): p. 1523-4.
137. Stanish, W., *The use of electricity in ligament and tendon repair*. Physician Sportsmed, 1985. **13**: p. 108-116.

138. Akai, M., H. Oda, Y. Shirasaki, and T. Tateishi, *Electrical stimulation of ligament healing. An experimental study of the patellar ligament of rabbits*. Clin Orthop Relat Res, 1988(235): p. 296-301.
139. Chan, H.K., D.T. Fung, and G.Y. Ng, *Effects of low-voltage microamperage stimulation on tendon healing in rats*. J Orthop Sports Phys Ther, 2007. **37**(7): p. 399-403.
140. Kenney, T.G. and L.E. Dahners, *The effect of electrical stimulation on ligament healing in a rat model*, in *Orthopaedic Research Society, 3rd annual meeting*. 1988: Atlanta, GA.
141. Akai, M., Y. Shirasaki, and T. Tateishi, *Electrical stimulation on joint contracture: an experiment in rat model with direct current*. Arch Phys Med Rehabil, 1997. **78**(4): p. 405-9.
142. Litke, D.S. and L.E. Dahners, *Effects of different levels of direct current on early ligament healing in a rat model*. J Orthop Res, 1994. **12**(5): p. 683-8.
143. Tart, R.P. and L.E. Dahners, *Effects of electrical stimulation on joint contracture in a rat model*. J Orthop Res, 1989. **7**(4): p. 538-42.
144. Lippiello, L., D. Chakkalakal, and J.F. Connolly, *Pulsing direct current-induced repair of articular cartilage in rabbit osteochondral defects*. J Orthop Res, 1990. **8**(2): p. 266-75.
- *145. Chapman-Jones, D. and D. Hill, *Novel microcurrent treatment is more effective than conventional therapy for chronic Achilles tendinopathy: randomised comparative trial*. Physiotherapy, 2002. **88**(8): p. 471-480.
146. Reiter, M., N. Ulreich, A. Dirisamer, et al., *Colour and power Doppler sonography in symptomatic Achilles tendon disease*. Int J Sports Med, 2004. **25**(4): p. 301-5.
147. Connell, D., F. Burke, P. Coombes, et al., *Sonographic examination of lateral epicondylitis*. AJR Am J Roentgenol, 2001. **176**(3): p. 777-82.
148. Ho, L.O., W.L. Kwong, and G.L. Cheing, *Effectiveness of Microcurrent Therapy in the Management of Lateral Epicondylitis: A Pilot Study* Hong Kong Physiotherapy Journal, 2007. **25**: p. 14-20.
149. Cho, M.S., R.J. Park, S.H. Park, et al., *The Effect of Microcurrent-Inducing Shoes on Fatigue and Pain in Middle-Aged People with Plantar Fasciitis*. J Phys Ther Sci, 2007. **19**(2).
150. Allen, J.D., C.G. Mattacola, and D.H. Perrin, *Effect of microcurrent stimulation on delayed-onset muscle soreness: a double-blind comparison*. Journal of Athletic Training, 1999. **34**(4): p. 334-7.
151. Lambert, M.I., P. Marcus, T. Burgess, and T.D. Noakes, *Electro-membrane microcurrent therapy reduces signs and symptoms of muscle damage*. Med Sci Sports Exerc, 2002. **34**(4): p. 602-7.
152. Denegar, C.R., A.P. Yoho, A.J. Borowicz, and N. Bifulco, *The effects of low-volt, microamperage stimulation on delayed onset muscle soreness*. Journal of Sport Rehabilitation, 1992. **1**(2): p. 95-102.
153. Lennox, A.J., J.P. Shafer, M. Hatcher, et al., *Pilot study of impedance-controlled microcurrent therapy for managing radiation-induced fibrosis in head-and-neck cancer patients*. Int J Radiat Oncol Biol Phys, 2002. **54**(1): p. 23-34.
154. Zizic, T.M., K.C. Hoffman, P.A. Holt, et al., *The treatment of osteoarthritis of the knee with pulsed electrical stimulation*. J Rheumatol, 1995. **22**(9): p. 1757-61.
155. Robertson, V.J. and K.G. Baker, *A review of therapeutic ultrasound: effectiveness studies*. Phys Ther, 2001. **81**(7): p. 1339-50.

156. van der Windt, D.A., G.J. van der Heijden, S.G. van den Berg, et al., *Ultrasound therapy for musculoskeletal disorders: a systematic review*. *Pain*, 1999. **81**(3): p. 257-71.
157. Falconer, J., K.W. Hayes, and R.W. Chang, *Therapeutic ultrasound in the treatment of musculoskeletal conditions*. *Arthritis Care Res*, 1990. **3**(2): p. 85-91.