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REVIEW ARTICLE PEER-REVIEWED

Do Magnetic Fields Have a Place in the Treatment of Diabetic Conditions?

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Abstract

The use of electromagnetic field therapy (EMFT) is a non-invasive, potential alternative or complementary choice in the treatment of wounds, chronic pain, neuropathy, and other medical conditions including tissue repair and cell proliferation. Static Magnetic Fields (SMF) have been reported to increase microcirculatory blood flow by mediating vasodilation via nitric oxide. Studies report that SMF exposure causes homeostatic, normalizing effects on vascular tone that may have beneficial effects in situations where tissue perfusion is limited, such as may be present in diabetes. Pulsed Electromagnetic Fields (PEMF) have also shown promise in treating diabetic wounds by improving wound healing rates and other attributes. Our purpose was to critically review prior applications of EMFT for relevancy and effectiveness in treating diabetic complications. The goal was to provide information to allow for informed decisions on the possible use of these modalities in the treatment of persons with diabetic complications. The focus was on the following major areas; wound healing, neuropathy, blood glucose control, blood flow, inflammation and oxidative stress.

Introduction & Background

Over the past 40 years, the number of diabetes mellitus diagnoses has nearly quadrupled from 108 million in 1980 to 422 million in 2014 [1]. Complications of diabetes include neuropathy, foot wounds, delayed or nonhealing wounds and microvascular deficits and other organ system issues [2-4]. Diabetic foot ulcers can be a serious complication of the condition, and if left untreated, can lead to severe infection, gangrene, and in some instances death [5]. More than one million diabetic patients undergo lower limb amputation per year, which totals to nearly 50-70% of all limb amputations performed [6]. As global cases of diabetes continue to rise, its complications follow this trend and continue to worsen morbidity and mortality. Diabetic wounds are sometimes challenging to treat and control and as such, there is an important need for adjunctive and efficient management protocols. Electromagnetic field therapy (EMFT) is a non-invasive possible alternative or complementary choice to treat wounds, chronic pain, diabetic neuropathy, and other medical conditions including tissue repair and cell proliferation [7-10]. Static Magnetic Fields (SMF), derived either from magnets or from electrical devices carrying non-time varying currents, are one form of EMFT that has been reported to have a variety of effects including an increase in microcirculatory blood flow by mediating vasodilation via nitric oxide (NO). Diabetic neuropathy, a major risk factor for diabetic foot ulceration, is associated with impaired blood flow causing inadequate tissue perfusion potentially causing ischemia [11]. Studies have reported that SMF exposure may also have homeostatic, normalizing effects on vascular tone that may have beneficial effects in situations where tissue perfusion is limited, such as in diabetic neuropathy [11].

While wound debridement, antibiotics, revascularization, and off-loading of plantar ulcers are

current standard of care treatments, costs and other factors sometimes cause delayed treatment and it has been suggested that SMF might be a non-invasive, affordable diabetic wound treatment tool that works by suppressing inflammatory cytokines and accelerating wound closure and revascularization [6]. Pulsed Electromagnetic Fields (PEMF) have also been suggested to be a possible treatment for diabetic wounds [12, 13]. Thus, there is sufficient preliminary information to further investigate the potential role of such EMFT types with respect to diabetes complications.

Review

Our purpose was to critically review and evaluate prior applications of EMFT with respect to relevancy and effectiveness in treating complications of diabetes with the overall goal of providing information that will allow for informed decisions as to the use of these modalities.

Search strategy

The following databases were searched for peer reviewed published articles in the English language: PubMed, Biomed Reference Collection: Comprehensive, CINAHL Complete, Embase, Web of Science. The main search was for articles with the word magnet or magnetic in the title and diabet* anywhere in the article text. The asterix (*) served as a wildcard. To provide a focused search, any paper that contained the following terms within their text were excluded from the search: “resonance”, “transcranial”, nano*, particle*, capsule*, magnetize* and magnetite. This yielded 102 articles satisfying the search criteria. The titles and abstracts were reviewed for relevance to EMFT-related healing that reduced this number to 39 relevant articles that were reviewed in depth. The bibliographies of these articles were reviewed and an additional 14 articles were identified. Finally, articles relevant to the potential role of EMFT-related impacts on blood flow were included yielding a total of 71 articles in the present review.

Presentation of results

Effects of EMFT, either SMF or PEMF, are presented for each of the following five major impact categories: Wound Healing, Diabetic Neuropathy, Blood Glucose, Blood Flow, and Inflammation and Oxidative Stress.

Wound Healing

Streptozotocin (STZ) injections are often used to induce diabetes in mice and rats for research purposes [14]. Using this model, the effect of a SMF on diabetic wound healing in rats was evaluated [15]. In this study, rats were assigned to one of three groups: diabetic wound + sham treatment (n=16), diabetic wound + SMF treatment (n=16) and 16 non-diabetic control rats. A 1.5 cm diameter circular wound was created on the dorsum of all rats. Wounds were then treated with a wound dressing alone (control), a wound dressing plus a magnet (180 mT) or a wound dressing plus a sham magnet. Wound areas were measured on days 5, 12 and 19 after wounding to measure healing rate and healing time. At each measurement, control non-diabetic animals had a statistically significant ($P < 0.05$) greater healing rate vs. either diabetic group. However, the SMF treated group had a greater healing rate vs. the sham-treated group ($p<0.05$). The time for complete wound closure was less in the SMF-treated group (20 days) vs. the sham-treated group (27 days, $p<0.05$).

A similar study investigated the impact of a 230 mT SMF magnet vs. sham-magnet treatment on wound healing rate and time-to-heal in 20 STZ-induced diabetic rats [10]. Ten rats wore magnets over the wound and 10 wore sham magnets continuously for 21 days after the creation of a two cm diameter back wound. An additional non-diabetic control group that wore neither the magnet or sham was included. Wound area was measured on days 7, 14 and 21 days, but rats were continuously followed until complete wound closure. It was reported that at each measurement day, control non-diabetic rats healed faster than either diabetic group but that the SMF-treated healing rate was faster than for sham treated animals ($p<0.05$). Full wound closure occurred after 22.3 ± 2.5 days in the non-diabetic controls, 29.5 ± 3.8 days in SMF-treated and 36.5 ± 4.4 days in sham-treated showing significant differences ($p<0.05$). SMF treatment effects were also evaluated in the STZ-induced diabetic mouse model after causing 8-mm punch biopsy wounds on the animal’s back [6]. The mice were placed in a cage with magnetic or nonmagnetic plates. The magnetic plates had 24 embedded magnets each with a surface field of 0.6T with adjacent magnets having alternate poles facing the plate surface. Percentage wound area closure was assessed at days 3, 7, and 14 post-wounding in 8 SMF-treated and 8 non-treated diabetic mice. Wound closure, measured at each of the measurement days was reported to be significantly greater for the SMF-treated mice ($p<0.05$).

Other measurements made in parallel suggest that the improved healing rate may be related to upregulation of inflammatory gene expression modifying macrophage function during the healing process.

PEMF effects on wound healing have also been evaluated in STZ-induced diabetic and non-diabetic mice [16]. Skin flaps were created on the backs of 24 mice, 12 were STZ-induced diabetic mice and 12 were non-diabetic controls. Six of each group were treated with PEMF that consisted of 4.5 ms pulses of 1.2mT peak at 15 Hz using a commercial bone-healing device (EBI, Parsippany, New Jersey, United States). The other half of each group was not treated with PEMF. The treated mice were exposed to PEMF while in their cages for eight hours a day for 14 days. Wounds were examined and measured until full wound closure. PEMF-treated mice, whether diabetic or control wild-type mice, healed at a faster rate and achieved full wound closure sooner than the corresponding non-PEMF treated mice. For the PEMF-treated, average full closure time for the wild type was at 11 ± 2 days and for the diabetes mice it was 16 ± 4 days. Contrastingly, for untreated mice, it was 15 ± 3 and 24 ± 5 days respectively. Based on additional measurements including wound bed blood perfusion, vascularity and fibroblast growth factor (FGF-2) the authors suggested a linkage between pulsed electromagnetic field therapy (PEMFT) and upregulation of FGF-2 promoting angiogenesis and increased cellular motility. In a separate study, wounds were created by making a 35mm dermal incision on the right side of the paravertebral region of STZ-induced diabetic and non-diabetic rats [17]. PEMF was created by a function generator connected to copper coils that resulted in a 4 ms pulse train at 20 Hz producing an 8 mT PEMF signal. Rats were divided into four groups: non-treated control, PEMF-treated control, non-treated diabetic, and PEMF-treated diabetic. Treated rats were exposed to PEMF for one hour daily for 16 days, while non-treated groups were not exposed to PEMF. Percent wound closure was assessed on days 0, 4, 8, 12, and 16 after wound-induction. Results showed a statistically significant improvement in healing rate in PEMF-treated rats and a reduced time to wound closure in non-diabetic rats ($p<0.01$) and in diabetic rats ($p<0.001$).

Other findings have less support for the use of PEMF to accelerate wound healing based on the STZ-induced diabetic rat model [18]. Seven days after STZ injection, 2 cm x 2 cm full-thickness square wounds were made on the rat's back and then randomly divided into a PEMF-treatment group (n=28) or a control group (n=28). PEMF-treatment was done using a commercial device (Model XKC-600W Magnetopulse International, Griffin, Australia). This device produces sinusoidal pulse trains at 25Hz with a pulse width of 40 ms and a peak intensity of 5 mT. Treatment was one hour per day with measurements made at day 0 (wound induction), 7, 10, 14, and 21 post wounding. Examination of their data indicates some minor improvements in in early healing rate with PEMF-treatment but essentially no difference in endpoint (21-day) wound area closures, being on average about 99% closed for each group. Subsequently the same rat model was used to evaluate the effect of PEMFT on collagen during wound healing in 20 PEMF-treated vs. 20 non-PEMF-treated control rats using the same PEMF treatment parameters [19]. Rats received treatment for one hour daily with measurements made on days 7, 10, and 14 post-wounding. At the 7-day evaluation, the PEMFT group had a higher amount of type I collagen deposition ($p = 0.013$) that continued to increase through day 14, but due to wide standard errors in values, differences between groups beyond 7-days did not prove to be statistically different. There were also no significant between-group differences for collagen fibril alignment and collagen fiber orientation. A recent study provided strong evidence supporting the role of SMF as a modality that accelerates wound healing in a diabetic mouse model that had experimentally induced 5 mm punch biopsy back wounds [20]. They pre-treated genetically obese leptin receptor-deficient db/db diabetic mice with 7-weeks of continuous SMF exposure of about 15mT at the wound site and continued treatment for 3-weeks post-wounding. Wound closure percentages were determined at 4-, 9- and 22-days post-wounding. Similar procedures were done to db/db mice exposed to sham magnets and also to normal non-diabetic mice as controls. At the 22-day assessment wound closure for the sham treated group was about 65% whereas for the SMF treated groups it was about 90% ($p<0.001$).

Another study used PEMF to treat a small number of patients with diabetic foot ulcers [21]. In this study 13 patients with diabetes-related foot ulcers were treated with a commercial PEMF device (Model XKC-600W Magnetopulse International, Griffin, Australia). This device produces sinusoidal pulse trains at 12Hz with a pulse width of 40 ms and a peak intensity of 1.2 mT. Patients received 14 PEMF treatments (n=7) or 14 sham treatments (n=6) each lasting 1-hour over an interval of 3-weeks. The results of this small pilot study indicated that PEMFT did

hour over an interval of 3 weeks. The results of this small pilot study indicated that PEMF did not significantly decrease wound area but may have decreased wound depth in the PEMF treated group. Diabetic foot ulcers have also been treated with a novel PEMF device dubbed Therapeutic Magnetic Resonance (TMR) [22]. This device, reported to generate a complex pulse train with varying frequencies and polarities and average generated field intensity of 40-60mT, was used to treat 20 patients with sham treatments of 20 others. The reported outcome of active treatment was an increase in granulation tissue components that included collagens and integrins along with a reduction in proinflammatory interleukins and increased growth factor expression.

Diabetic Neuropathy

Detailed aspects of diabetic neuropathy have recently been extensively reviewed [23] and its impacts on patient's daily lives described [24]. Various methods for its pain-related mitigation have also been reviewed [25] and PEMF as a possible treatment has been suggested [26]. In this section the potential role of EMFT on pain related aspects are considered. In experimental work to assess treatment-related changes, two commonly used assessment parameters are allodynia and hyperalgesia because of their presence in persons with diabetic neuropathy [27]. In this context allodynia describes pain caused by a stimulus that would not ordinarily cause pain and hyperalgesia describes heightened pain to a stimulus that would ordinarily cause lesser pain.

Using a STZ-rat model, effects of PEMFT on allodynia and hyperalgesia were evaluated using PEMF spiked pulse-trains of different frequencies with peak field intensities of 1.5 mT [28]. The treatment pattern used repeating 4-minute bursts of impulses alternating between either 1-Hz and 5-Hz or between 30-Hz and 40-Hz for an overall treatment interval of 60-minutes. Animals were treated for 5-weeks with weekly evaluations. Allodynia and hyperalgesia were evaluated with a thermal plantar test that measures paw withdrawal time and a device that uses a touch-stimulator to measure the force at which paw withdrawal occurs [29, 30]. Allodynia was assessed based on the paw-withdrawal threshold to a light touch of the hind paw. Severity of hyperalgesia was assessed by paw withdrawal latency to thermal stimulation. Induction of STZ-diabetes was associated with an increase in both allodynia and hyperalgesia but the 1-Hz and 5-Hz treatment significantly blunted both of these changes ($p<0.05$). There were minimal effects of the 30-Hz and 40-Hz treatment. Subsequent work using this rat model used a similar treatment pulse-train pattern now consisting of one repeated sequence of 1, 3, 5 and 7 Hz also delivered over 4-minutes with rats treated daily for one hour/day for 4-weeks [8]. After 2-weeks of PEMFT, allodynia and hyperalgesia measures statistically improved by 11% and 15% and by 4-weeks both were restored to near non-diabetic levels. A parallel sham-treated group showed no significant improvement. A slightly different PEMF pattern, consisting of pulse trains of 1.5 mT peak delivered at 10-Hz or 30-Hz, was used to assess neuropathy pain mitigation and biomarkers of PEMFT changes [31]. Both patterns improved allodynia and hyperalgesia measures with the 10-Hz pattern being more effective and sham-treatment producing no improvement. In addition to pain parameters, certain genes were determined using Polymerase Chain Reaction (PCR) before and after STZ induction and during PEMF treatment. It was reported that the gene (SCN11A that codes for the voltage-gated sodium channel NaV1.9 was reduced after neuropathy induction but that PEMF 10-Hz treatment brought it back to near normal levels. The authors concluded that PEMF 10-Hz therapy may reduce pain by modulating voltage gated sodium channels at the level of transcription and that 10 Hz can more effectively manage pain than 30-Hz PEMF treatment.

Several studies have used various forms of PEMFT to try to mitigate diabetic neuropathic pain in patients. In one, use was made of a bed shaped device (Viofor JPS device, Med & Life, Komorow, Poland)[32]. Patients could lie on the device and be exposed to a complex PEMF signal consisting of frequencies between 180-195 Hz with a reported field intensity up to 100 mT. PEMF treatment was given to 32 patients with a starting average visual analog pain score (VAS) of 73 mm and sham treatments were given to 29 patients who had an average starting VAS of 69 mm. After 5-weeks of PEMF or sham treatment both groups reported significant decreases in VAS to 22 mm and 44 mm respectively with no statistical difference in reductions between groups. Another study used VAS scores to evaluate impacts of PEMF treatment in 24 patients with refractory foot neuropathic pain. The treatment consisted of a patented priority unspecified pulse sequence of frequencies near 30-Hz and a peak field intensity of 2 mT delivered to the soles of the feet during nine 1-hour treatments over a two week interval [33]. The outcome was reported as a significant decrease in average pain score from a pretreatment value of 6.26 cm to 3.96 cm assessed 4-weeks after end of treatment ($p<0.01$). It should be noted that this study did not focus explicitly on patients who were diabetic and

there was no sham control used. However, the author suggested that the pain reduction might be related to the PEMFT causing either repolarization or hyperpolarization of sodium channels associated with unmyelinated c-fibers or small A-delta nociceptors located within epidermis and dermis of the treated foot.

Blood Glucose

Effects of 200, 400 and 600 mT SMF on blood glucose in Type 1 and Type 2 diabetic mice were evaluated via continuous 60-day treatment [34]. Type 1 diabetes was induced using alloxan and a high fat diet, whereas Type 2 diabetes was STZ-induced. Treatment was delivered via multiple neodymium magnets or sham magnets placed in the bottom of the cage in which mice were housed. Blood glucose changes were measured on days 30 and 60 of treatment in response to an intra-gastric dose of starch. Blood glucose levels were measured at standardized times after starch administration. On day 30, mice with type 1 diabetes who were treated with 400 mT showed a statistically significant reduction ($p < 0.05$) in blood glucose compared to sham treated mice. On day 60, all treatment groups showed statistically significant reductions ($p < 0.05$). For mice with type 2 diabetes, glucose was significantly reduced ($p < 0.01$) only for mice treated with 600 mT. A similar reduction trend for resting blood glucose of STZ-induced diabetic mice was reported for mice housed in cages and exposed to nonhomogeneous fields for 30 minutes/day for 6-weeks [35]. The SMF-treated diabetic mice were exposed to about 477 mT at their feet and about 2.8 mT at the top of their heads. A corresponding group was sham treated. At 6-weeks, both groups had elevated blood glucose levels compared to non-STZ treated mice, but compared to sham treated diabetic mice, the magnet treated had a significantly reduced blood glucose level ($p<0.001$).

The potential effect of the direction of the magnetic field on blood glucose was also investigated when treating STZ-induced diabetic mice [36]. Four groups were considered, a sham group, an average upward field (≈ 100 mT), an average downward field (≈ 100 mT), and an alternating upward and downward pattern producing between 40 and 50 mT. Six mice per group were treated for 2-hour/day for 12-weeks. Downward SMF treatment reduced fasting blood glucose levels vs. sham treated ($p < 0.05$) and also improved intra-peritoneal glucose tolerance test results vs. sham treated ($p<0.05$). In contrast, upward SMF treatment decreased glucose clearance vs. control ($p < 0.01$) thereby indicating a negative treatment effect on hyperglycemia.

A novel approach was undertaken to study effects on fasting glucose and glucose tolerance when mice were exposed to a SMF aligned mainly along the long axis of mice combined with an electric field aligned perpendicular to their long axis when housed in non-magnetic cages [37]. A major finding reported was improvements in both glycemia and glucose tolerance only when both magnetic and electric field exposure was present. No effects or even negative effects were present when either alone was used. In a series of related experiments these researchers suggested that the various beneficial effects of the combined fields on insulin resistance were likely at least in part attributable to reaction product modifications in line with the concept of field induced radical pair mechanisms [38-41]. Subsequently an alternate explanation was put forward in which it was hypothesized that the combined magnetic and electric fields affected the vestibular system via modifications of inner ear endolymph currents [42]. It was suggested that this triggered a stress response with an associated increases in catecholamines and AMP-activated protein kinase, both of which can decrease insulin resistance and decrease hyperglycemia. This view was considered unlikely since the magnitude of the fields used in the original study were not large enough (3 mT and 7 kV/m) to explain the insulin-sensitizing effects originally reported [43]. The effects of PEMFT on blood glucose has also been investigated in the STZ diabetic rat model [44]. The primary focus was on diabetic neuropathy symptoms of hyperalgesia and allodynia, but also reported ameliorating effects of PEMF on blood glucose. After 4-weeks of PEMF exposure, blood glucose levels decreased by a mean 15% ($P < 0.05$) but sham-treated rats experienced no significant change.

Blood Flow

There is substantial evidence of involvement of microcirculatory deficits in diabetes [45-50]. It is thus useful to consider reported effects of static and time varying magnetic fields on blood flow that may indirectly provide insight into potential linkages to diabetic therapy targeting microvascular deficits. Measurements of human skin blood flow (SBF) when hands or fingers

were exposed to a perpendicular SMF have yielded varying results with SBF reported to decrease [51], not change [52-54] or show increased vasomotion-related changes [55]. Other work using SMF on experimental animals has also reported varying results with SMF exposure causing blood flow to decrease [56, 57], not change [58], increase vascular diameter [11], increase or decrease vascular diameter depending on their basal state [59] and cause alterations in microvascular vasomotion patterns [60, 61]. Other aspects of SMF-related impacts on microcirculation in relation to diabetes and wound healing have been presented [62-64]. The effects of time-varying or pulsed electromagnetic fields on blood flow have also been documented as having varying effects on skin blood flow. Exposure of hand and finger skin to field intensities between 32-48 mT at 3.8 KHz caused a transient decrease in blood flow lasting about 10 seconds but no sustained change in blood flow [65]. Contrastingly there have been reports suggesting a positive angiogenic role of PEMFT and an increase in blood flow in an experimental ischemic skin model [66, 67]. Other reports suggest no blood flow effect attributable to specific forms of PEMFT [68]. It is likely that further research is needed to pin down the role of EMFT as an effective blood flow modulator and to define the conditions to which it is applicable.

However, there are some aspects of its role in the treatment diabetes conditions of relevance. In a small study (n = 7 treated and 6 sham) diabetic plantar ulcers were treated with 12 Hz pulsed fields stated to achieve an intensity of 1.2mT. Compared to the sham-treated outcomes, these workers reported improved wound healing along with an increase in capillary red cell velocity measured on the great toe dorsum associated with the PEMF treatment [21]. However, the small number of patients in this study and the absence of experimental details as to the placement of the treatment device, suggests these findings should be interpreted cautiously. A more clearly defined study used a similar 12-Hz signal with an intensity of 0.5 mT to evaluate PEMF treatment effects on small superficial veins of the foot and great toe skin blood flow in 22 persons with diabetes and 21 persons free of diabetes as controls [69]. They report increases in blood velocity in small veins in both diabetic and healthy persons but no such increase with sham treatment. Based on their data, an average velocity increase of 26% and 27% was calculated for the diabetes group and controls respectively. Further research will be needed to more clearly characterize the potential of EMFT in blood flow modification.

Inflammation and Oxidative Stress

Inflammation is often a component or complication of diabetes so it is of value to examine studies that have investigated EMFT effects on inflammatory markers. One such study, already discussed from its wound healing outcomes, also reported a role of SMF treatment in resolving inflammation associated with wound healing [6]. Results of Immunofluorescent staining indicated that SMF treatment accelerated wound healing by shifting macrophage polarization towards M2 phenotype in comparison to M1. This was thought to occur by upregulating anti-inflammatory gene expression STAT6 while suppressing proinflammatory STAT1 in macrophages.

Results from studies using PEMF have also yielded relevant information regarding impacts of EMFT on inflammatory processes. Using a 50-Hz, 7 mT peak intensity sinusoidal signal as 7-day treatment for Wistar rats revealed that plasma levels of various pro-inflammatory cytokines depended on whether treatment was delivered 1-hour/day or continuously for 24-hours [70]. Continuous exposure but not 1-hour repetitive treatment significantly increased interleukins IL-1B, IL-2 and IL-6 ($p < 0.001$) in comparison to controls. PEMF-related changes in the inflammatory-mediators defensin and C-reactive protein (CRP) were investigated in 32 patients with diabetic painful neuropathy using the same commercial bed-shaped device previously described (Viofor JPS, Komorow Poland) [71]. As noted, this device generates a 100mT intensity field using a complex pulse train varying between180 and 195 Hz. Treatment was given for 20 min/day for 15 days over 3-weeks with no significant effects on either CRP or defensin in the diabetic patients. Others have suggested that SMF may have a role in mitigating oxidative stress [72]

Summary Discussion

The summated result of the present investigation indicates both successful and unsuccessful applications of EMFT as applied to the diabetic condition. There is some evidence for potentially useful outcomes for diabetic wounds, neuropathic pain, inflammation, blood glucose levels, and possibly blood flow. Lower frequency EMFTs appeared to have a greater effect in treating symptoms of neuropathy in animal models. For future human trials, it will be important to see if this finding is similar. With increasing prevalence of diabetic complications, EMFT may potentially be considered as an innovative and cost-effective alternative to the

standard management of diabetic complications [26]. Pharmaceutical approaches are commonly used to suppress immune system responses and inflammation to treat diabetic complications but may be costly and may hinder wound healing. Contrastingly it has been reported that SMF-treatment may positively influence wound healing and tissue regeneration by balancing the signaling of the pro-inflammatory gene STAT1 with the anti-inflammatory gene STAT6; thereby reducing inflammation [6].

The benefit of SMF is also potentially useful seen in the treatment of other diabetic complications as reported for improvements in blood glucose levels, neuropathy scores, and tissue perfusion via vascular vasodilation. SMF treatment has also been reported to improve healing rates, reduce healing time, and increase tensile strength in diabetic wounds [10, 15]. SMF treatment also may reduce burning, numbness, tingling, and foot pain in cases of diabetic neuropathy. When treated with combined SMF and electric fields an important effect on insulin sensitivity was reported that was not present for either treatment modality alone [37]. While the mechanism behind this improvement is unclear it would appear that this avenue of research is worthy of pursuit. PEMF treatment in some studies had directionally similar effects as SMF in diabetic wounds and was reported to decrease wound-healing time and improve the quality of granulation tissue [12, 22]. PEMF treatment also increased type 1 collagen deposition, which promoted wound healing [19] and upregulated FGF-2, which may be an important factor in facilitating wound healing. In animal models of diabetic neuropathy, PEMF had anti-allodynic effects [8]. Additionally, SMF and PEMF beneficial effects were also reported in human trials [9, 33]. However, further studies are needed to confirm. There have also been studies that suggest EMFT therapy is not as effective. In a double-blind study, subjects with polyneuropathy were given PEMF over the course of three weeks [71]. The results showed that there was no reduction in CRP or defensin levels two weeks following treatment. Another study looked at effects of EMFT on VAS scores and found no difference between sham and PEMF-treatment subjects [32]. These negative studies further support the need for more research to investigate EMFT therapy as a viable treatment option for diabetes conditions.

Conclusions

Reports from both animal and human studies provide support for the adjunctive use of EMFT, including both SMF and PEMF, to address complications of diabetes including wounds, chronic pain, and neuropathy. These noninvasive modalities show promise with no known reports of untoward effects. Currently, there are insufficient high-quality systematic studies on humans to provide high levels of confidence in such treatments and as such, it would appear prudent that utilization of EMFT for diabetic-related complications should be used in conjunction with standard of care.

If such care is not easily available, however, EMFT may serve as an interim single therapy. Further research with specific targets of this modality could provide additional understanding and confidence in this potential treatment modality. Finally, it should be emphasized that while many studies showcase positive attributes of EMFT, the biological pathways behind these reported outcomes have yet to be discovered. Going forward, the mechanisms behind the use of EMFT to treat diabetic and potentially other conditions appear to be a worthwhile goal to help mitigate the worsening diabetic complications seen as a result of the COVID-19 pandemic.

A key limitation of EMFT is that the mechanism of action is not understood. Multiple studies have shown positive results; however, more research should be done to discover how EMFT is able to improve diabetic complications and what its limitations are. Most studies conducted have also occurred in laboratory settings or using animal models, illustrating the need for further clinical studies before implementing EMFT in humans.

References

1. Hurlow JJ, Humphreys GJ, Bowling FL, McBain AJ: Diabetic foot infection: A critical complication (https://dx.doi.org/10.1111/iwj.12932). Int Wound J. 2018, 15:814-821. 10.1111/iwj.12932 (https://dx.doi.org/10.1111/iwj.12932)
2. Migdalis IN, Czupryniak L, Lalic N, Papanas N, Valensi P: Chronic Diabetic Complications: Current Challenges and Opportunities (https://dx.doi.org/10.3390/jcm11030673). J Clin Med. 2022, 11:10.3390/jcm11030673 (https://dx.doi.org/10.3390/jcm11030673)
3. Nellaiappan K, Preeti K, Khatri DK, Singh SB: Diabetic Complications: An Update on Pathobiology and Therapeutic Strategies

(https://dx.doi.org/10.2174/1573399817666210309104203). Curr Diabetes Rev. 2022, 18:030821192146. 10.2174/1573399817666210309104203 (https://dx.doi.org/10.2174/1573399817666210309104203)

4. Rossboth S, Rossboth B, Schoenherr H, Ciardi C, Lechleitner M, Oberaigner W: Diabetic foot complications-lessons learned from real-world data derived from a specialized Austrian hospital (https://dx.doi.org/10.1007/s00508-021-01864-5). Wien Klin Wochenschr. 2022, 134:7-17. 10.1007/s00508-021-01864-5 (https://dx.doi.org/10.1007/s00508-021-01864-5)
5. Tao F, Tang X, Tao H, et al.: Surgical treatment of diabetic foot ulcers during the COVID-19 pandemic in China (https://dx.doi.org/10.1016/j.jdiacomp.2020.107622). J Diabetes Complications. 2020, 34:107622. 10.1016/j.jdiacomp.2020.107622 (https://dx.doi.org/10.1016/j.jdiacomp.2020.107622)
6. Shang W, Chen G, Li Y, et al.: Static Magnetic Field Accelerates Diabetic Wound Healing by Facilitating Resolution of Inflammation (https://dx.doi.org/10.1155/2019/5641271). J Diabetes Res. 2019, 2019:5641271. 10.1155/2019/5641271 (https://dx.doi.org/10.1155/2019/5641271)
7. Lv H, Liu J, Zhen C, Wang Y, Wei Y, Ren W, Shang P: Magnetic fields as a potential therapy for diabetic wounds based on animal experiments and clinical trials (https://dx.doi.org/10.1111/cpr.12982). Cell Prolif. 2021, 54:12982. 10.1111/cpr.12982 (https://dx.doi.org/10.1111/cpr.12982)
8. Mert T, Sahin E, Yaman S, Sahin M: Pulsed magnetic field treatment ameliorates the progression of peripheral neuropathy by modulating the neuronal oxidative stress, apoptosis and angiogenesis in a rat model of experimental diabetes (https://dx.doi.org/10.1080/13813455.2020.1788098). Arch Physiol Biochem. 2020, 1-8. 10.1080/13813455.2020.1788098 (https://dx.doi.org/10.1080/13813455.2020.1788098)
9. Weintraub MI, Wolfe GI, Barohn RA, et al.: Static magnetic field therapy for symptomatic diabetic neuropathy: A randomized, double-blind, placebo-controlled trial (https://dx.doi.org/10.1016/s0003-9993(03)00106-0). Arch Phys Med Rehabil. 2003, 84:736-746. 10.1016/s0003-9993(03)00106-0 (https://dx.doi.org/10.1016/s0003-9993(03)00106-0)
10. Zhao J, Li YG, Deng KQ, Yun P, Gong T: Therapeutic Effects of Static Magnetic Field on Wound Healing in Diabetic Rats (https://dx.doi.org/10.1155/2017/6305370). J Diabetes Res. 2017, 2017:6305370. 10.1155/2017/6305370 (https://dx.doi.org/10.1155/2017/6305370)
11. Gmitrov J: Static Magnetic Field Versus Systemic Calcium Channel Blockade Effect on Microcirculation: Possible Mechanisms and Clinical Implementation (https://dx.doi.org/10.1002/bem.22272). Bioelectromagnetics. 2020, 41:447-457. 10.1002/bem.22272 (https://dx.doi.org/10.1002/bem.22272)
12. Abbruzzese L, Iacopi E, Coppelli A, Bonino G, Goretti C, Piaggesi A: Safety and effectiveness of therapeutic magnetic resonance in the management of postsurgical lesion of the diabetic foot (https://dx.doi.org/10.1177/1534734614568374). Int J Low Extrem Wounds. 2015, 14:4-10. 10.1177/1534734614568374 (https://dx.doi.org/10.1177/1534734614568374)
13. Harry M C Choi AKKC, Gabriel Y F Ng, Gladys L Y Cheing: Effects of pulsed electromagnetic field (PEMF) on the tensile biomechanical properties of diabetic wounds at different phases of healing (https://dx.doi.org/10.1371/journal.pone.0191074). 2018. 10.1371/journal.pone.0191074 (https://dx.doi.org/10.1371/journal.pone.0191074)
14. Furman BL: Streptozotocin-Induced Diabetic Models in Mice and Rats: Current Protocols, A Wiley Brand (https://dx.doi.org/10.1002/cpz1.78). 2021, 1:10.1002/cpz1.78 (https://dx.doi.org/10.1002/cpz1.78)
15. Jing D, Shen G, Cai J, et al.: Effects of 180 mT static magnetic fields on diabetic wound healing in rats (https://dx.doi.org/10.1002/bem.20592). Bioelectromagnetics. 2010, 31:640-648. 10.1002/bem.20592 (https://dx.doi.org/10.1002/bem.20592)
16. Callaghan MJ, Chang EI, Seiser N, et al.: Pulsed electromagnetic fields accelerate normal and diabetic wound healing by increasing endogenous FGF-2 release (https://dx.doi.org/10.1097/01.prs.0000293761.27219.84). Plast Reconstr Surg. 2008, 121:130-141. 10.1097/01.prs.0000293761.27219.84 (https://dx.doi.org/10.1097/01.prs.0000293761.27219.84)
17. Goudarzi I, Hajizadeh S, Salmani ME, Abrari K: Pulsed electromagnetic fields accelerate wound healing in the skin of diabetic rats (https://dx.doi.org/10.1002/bem.20567). Bioelectromagnetics. 2010, 31:318-323. 10.1002/bem.20567 (https://dx.doi.org/10.1002/bem.20567)
18. Cheing GL, Li X, Huang L, Kwan RL, Cheung KK: Pulsed electromagnetic fields (PEMF:

promote early wound healing and myofibroblast proliferation in diabetic rats (https://dx.doi.org/10.1002/bem.21832). Bioelectromagnetics. 2014, 35:161-169. 10.1002/bem.21832 (https://dx.doi.org/10.1002/bem.21832)

19. Choi MC, Cheung KK, Li X, Cheing GL: Pulsed electromagnetic field (PEMF) promotes collagen fibre deposition associated with increased myofibroblast population in the early healing phase of diabetic wound (https://dx.doi.org/10.1007/s00403-015-1604-9). Arch Dermatol Res. 2016, 308:21-29. 10.1007/s00403-015-1604-9 (https://dx.doi.org/10.1007/s00403-015-1604-9)
20. Feng CL, Yu B, Song C, et al.: Static Magnetic Fields Reduce Oxidative Stress to Improve Wound Healing and Alleviate Diabetic Complications. Cells (https://dx.doi.org/10.3390/cells11030443). 2022, 11:17. 10.3390/cells11030443 (https://dx.doi.org/10.3390/cells11030443)
21. Kwan RL, Wong WC, Yip SL, Chan KL, Zheng YP, Cheing GL: Pulsed electromagnetic field therapy promotes healing and microcirculation of chronic diabetic foot ulcers: a pilot study (https://dx.doi.org/10.1097/01.ASW.0000462012.58911.53). Adv Skin Wound Care. 2015, 28:212-219. 10.1097/01.ASW.0000462012.58911.53 (https://dx.doi.org/10.1097/01.ASW.0000462012.58911.53)
22. Ferroni L, Gardin C, De Pieri A, et al.: Treatment of diabetic foot ulcers with Therapeutic Magnetic Resonance (TMR(R)) improves the quality of granulation tissue (https://dx.doi.org/10.4081/ejh.2017.2800). Eur J Histochem. 2017, 61:2800. 10.4081/ejh.2017.2800 (https://dx.doi.org/10.4081/ejh.2017.2800)
23. Franceschi R, Mozzillo E, Di Candia F, et al.: A systematic review of the prevalence, risk factors and screening tools for autonomic and diabetic peripheral neuropathy in children, adolescents and young adults with type 1 diabetes (https://dx.doi.org/10.1007/s00592-022-01850-x). Acta Diabetol. 2022, 59:293-308. 10.1007/s00592-022-01850-x (https://dx.doi.org/10.1007/s00592-022-01850-x)
24. Khan KS, Andersen H: The Impact of Diabetic Neuropathy on Activities of Daily Living, Postural Balance and Risk of Falls - A Systematic Review (https://dx.doi.org/10.1177/1932296821997921). J Diabetes Sci Technol. 2022, 16:289-294. 10.1177/1932296821997921 (https://dx.doi.org/10.1177/1932296821997921)
25. Xu L, Sun Z, Casserly E, Nasr C, Cheng J, Xu J: Advances in Interventional Therapies for Painful Diabetic Neuropathy: A Systematic Review (https://dx.doi.org/10.1213/ANE.0000000000005860). Anesth Analg. 2022, 10.1213/ANE.0000000000005860 (https://dx.doi.org/10.1213/ANE.0000000000005860)
26. Mert T: Pulsed magnetic field treatment as antineuropathic pain therapy (https://dx.doi.org/10.1515/revneuro-2017-0003). Rev Neurosci. 2017, 28:751-758. 10.1515/revneuro-2017-0003 (https://dx.doi.org/10.1515/revneuro-2017-0003)
27. Jensen TS, Finnerup NB: Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms (https://dx.doi.org/10.1016/S1474-4422(14)70102-4). Lancet Neurol. 2014, 13:924-935. 10.1016/S1474-4422(14)70102-4 (https://dx.doi.org/10.1016/S1474-4422(14)70102-4)
28. Mert T, Gisi G, Celik A, Baran F, Uremis MM, Gunay I: Frequency-dependent effects of sequenced pulsed magnetic field on experimental diabetic neuropathy (https://dx.doi.org/10.3109/09553002.2015.1068460). Int J Radiat Biol. 2015, 91:833-842. 10.3109/09553002.2015.1068460 (https://dx.doi.org/10.3109/09553002.2015.1068460)
29. Cheah M, Fawcett JW, Andrews MR: Assessment of Thermal Pain Sensation in Rats and Mice (https://dx.doi.org/10.21769/BioProtoc.2506). Using the Hargreaves Test. Bio Protoc. 2017, 7:10.21769/BioProtoc.2506 (https://dx.doi.org/10.21769/BioProtoc.2506)
30. Deuis JR, Dvorakova LS, Vetter I: Methods Used to Evaluate Pain Behaviors in Rodents (https://dx.doi.org/10.3389/fnmol.2017.00284). Front Mol Neurosci. 2017, 10:284. 10.3389/fnmol.2017.00284 (https://dx.doi.org/10.3389/fnmol.2017.00284)
31. Coskun C, Ocal I, Gunay I: A Low-Frequency Pulsed Magnetic Field Reduces (https://dx.doi.org/10.1002/bem.22343). Neuropathic Pain by Regulating NaV1.8 and NaV1.9 Sodium Channels at the Transcriptional Level in Diabetic Rats. Bioelectromagnetics. 2021, 42:357-370. 10.1002/bem.22343 (https://dx.doi.org/10.1002/bem.22343)
32. Wrobel MP, Szymborska-Kajanek A, Wystrychowski G, et al.: Impact of low frequency pulsed magnetic fields on pain intensity, quality of life and sleep disturbances in patients with painful diabetic polyneuropathy (https://dx.doi.org/10.1016/j.diabet.2008.02.003). Diabetes Metab. 2008, 34:349-354. 10.1016/j.diabet.2008.02.003 (https://dx.doi.org/10.1016/j.diabet.2008.02.003)

33. Weintraub MI, Cole SP: Pulsed magnetic field therapy in refractory neuropathic pain secondary to peripheral neuropathy: electrodiagnostic parameters—pilot study. (https://dx.doi.org/10.1177/0888439003261024). Neurorehabil Neural Repair. 2004, 18:42-46. 10.1177/0888439003261024 (https://dx.doi.org/10.1177/0888439003261024)
34. Li Q, Fang Y, Wu N, et al.: Protective Effects of Moderate Intensity Static Magnetic Fields on Diabetic Mice (https://dx.doi.org/10.1002/bem.22305). Bioelectromagnetics. 2020, 41:598-610. 10.1002/bem.22305 (https://dx.doi.org/10.1002/bem.22305)
35. Laszlo JF, Szilvasi J, Fenyi A, Szalai A, Gyires K, Porszasz R: Daily exposure to inhomogeneous static magnetic field significantly reduces blood glucose level in diabetic mice (https://dx.doi.org/10.3109/09553002.2010.518200). Int J Radiat Biol. 2011, 87:36-45. 10.3109/09553002.2010.518200 (https://dx.doi.org/10.3109/09553002.2010.518200)
36. Yu B, Liu J, Cheng J, et al.: A Static Magnetic Field Improves Iron Metabolism and Prevents High-Fat-Diet/Streptozocin-Induced Diabetes (https://dx.doi.org/10.1016/j.xinn.2021.100077). Innovation (N Y. 2021, 2:100077. 10.1016/j.xinn.2021.100077 (https://dx.doi.org/10.1016/j.xinn.2021.100077)
37. Carter CS, Huang SC, Searby CC, et al.: Exposure to Static Magnetic and Electric Fields Treats Type 2 Diabetes (https://dx.doi.org/10.1016/j.cmet.2020.11.001). Cell Metab. 2020, 32:1076. 10.1016/j.cmet.2020.11.001 (https://dx.doi.org/10.1016/j.cmet.2020.11.001)
38. Okano H: Effects of static magnetic fields in biology: role of free radicals (https://dx.doi.org/10.2741/3141). Front Biosci. 2008, 13:6106-6125. 10.2741/3141 (https://dx.doi.org/10.2741/3141)
39. Jones AR, Scrutton NS, Woodward JR: Magnetic field effects and radical pair mechanisms in enzymes: a reappraisal of the horseradish peroxidase system (https://dx.doi.org/10.1021/ja060463q). J Am Chem Soc. 2006, 128:8408-8409. 10.1021/ja060463q (https://dx.doi.org/10.1021/ja060463q)
40. Scaiano JC, Cozens FL, Mohtat N: Influence of combined AC-DC magnetic fields on free radicals in organized and biological systems. Development of a model and application of the radical pair mechanism to radicals in micelles (https://dx.doi.org/10.1111/j.1751-1097.1995.tb09142.x). Photochem Photobiol. 1995, 62:818-829. 10.1111/j.1751-1097.1995.tb09142.x (https://dx.doi.org/10.1111/j.1751-1097.1995.tb09142.x)
41. Harkins TT, Grissom CB: Magnetic field effects on B12 ethanolamine ammonia lyase: evidence for a radical mechanism (https://dx.doi.org/10.1126/science.8310292). Science. 1994, 263:958-960. 10.1126/science.8310292 (https://dx.doi.org/10.1126/science.8310292)
42. Peterson KF, Rothman DL, Shulman GI: Point: An alternative hypothesis for why exposure to static magnetic and electric fields treats type 2 diabetes (https://dx.doi.org/10.1152/ajpendo.00657.2020). American Journal of Physiology-Endocrinology and Metabolism. 2021, 320:999-1000. 10.1152/ajpendo.00657.2020 (https://dx.doi.org/10.1152/ajpendo.00657.2020)
43. Carter CS, Huang SC, Searby CC, et al.: Counterpoint: An alternative hypothesis for why exposure to static magnetic and electric fields treats type 2 diabetes (https://dx.doi.org/10.1152/ajpendo.00110.2021). Am J Physiol Endocrinol Metab. 2021, 320:1001-1002. 10.1152/ajpendo.00110.2021 (https://dx.doi.org/10.1152/ajpendo.00110.2021)
44. Mert T, Gunay I, Ocal I: Neurobiological effects of pulsed magnetic field on diabetes-induced neuropathy (https://dx.doi.org/10.1002/bem.20524). Bioelectromagnetics. 2010, 31:39-47. 10.1002/bem.20524 (https://dx.doi.org/10.1002/bem.20524)
45. Kozlov I, Zherebtsov E, Masalygina G, Podmasteryev K, Dunaev A: Laser Doppler Spectrum Analysis Based on Calculation of Cumulative Sums Detects Changes in Skin Capillary Blood Flow in Type 2 Diabetes Melitus (https://dx.doi.org/10.3390/diagnostics11020267). Diagnostics (Basel. 2021, 11:10.3390/diagnostics11020267 (https://dx.doi.org/10.3390/diagnostics11020267)
46. Jan YK, Liao F, Cheing GLY, Pu F, Ren W, Choi HMC: Differences in skin blood flow oscillations between the plantar and dorsal foot in people with diabetes mellitus and peripheral neuropathy (https://dx.doi.org/10.1016/j.mvr.2018.11.002). Microvasc Res. 2019, 122:45-51. 10.1016/j.mvr.2018.11.002 (https://dx.doi.org/10.1016/j.mvr.2018.11.002)
47. Mizeva I, Zharkikh E, Dremin V, Zherebtsov E, Makovik I, Potapova E, Dunaev A: Spectral analysis of the blood flow in the foot microvascular bed during thermal testing in patients with diabetes mellitus (https://dx.doi.org/10.1016/j.mvr.2018.05.005). Microvasc Res. 2018, 120:13-20. 10.1016/j.mvr.2018.05.005 (https://dx.doi.org/10.1016/j.mvr.2018.05.005)
48. Clough GF, Kuliga KZ, Chipperfield AJ: Flow motion dynamics of microvascular blood

flow and oxygenation: Evidence of adaptive changes in obesity and type 2 diabetes mellitus/insulin resistance (https://dx.doi.org/10.1111/micc.12331). Microcirculation. 2017, 24:10.1111/micc.12331 (https://dx.doi.org/10.1111/micc.12331)

49. Mayrovitz HN, Sims N: Effects of support surface relief pressures on heel skin blood flow in persons with and without diabetes mellitus (https://dx.doi.org/10.1097/00129334-200405000-00019). Adv Skin Wound Care. 2004, 17:197-201. 10.1097/00129334-200405000-00019 (https://dx.doi.org/10.1097/00129334-200405000-00019)
50. Mayrovitz HN, Larsen PB: Functional microcirculatory impairment: a possible source of reduced skin oxygen tension in human diabetes mellitus (https://dx.doi.org/10.1006/mvre.1996.0048). Microvasc Res. 1996, 52:115-126. 10.1006/mvre.1996.0048 (https://dx.doi.org/10.1006/mvre.1996.0048)
51. Mayrovitz HN, Groseclose EE: Effects of a static magnetic field of either polarity on skin microcirculation (https://dx.doi.org/10.1016/j.mvr.2004.11.002). Microvasc Res. 2005, 69:24-27. 10.1016/j.mvr.2004.11.002 (https://dx.doi.org/10.1016/j.mvr.2004.11.002)
52. Mayrovitz HN, Astudillo A, Shams E: Finger skin blood perfusion during exposure of ulnar and median nerves to the static magnetic field of a rare-earth magnet: A randomized pilot study (https://dx.doi.org/10.1080/15368378.2020.1856682). Electromagn Biol Med. 2021, 40:1-10. 10.1080/15368378.2020.1856682 (https://dx.doi.org/10.1080/15368378.2020.1856682)
53. Mayrovitz HN, Groseclose EE, King D: No effect of 85 mT permanent magnets on laser-Doppler measured blood flow response to inspiratory gasps (https://dx.doi.org/10.1002/bem.20096). Bioelectromagnetics. 2005, 26:331-335. 10.1002/bem.20096 (https://dx.doi.org/10.1002/bem.20096)
54. 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 (https://dx.doi.org/10.1002/bem.78 [pii). Bioelectromagnetics. 2001, 22:494-502. 10.1002/bem.78 [pii (https://dx.doi.org/10.1002/bem.78 [pii)
55. Yan Y, Shen G, Xie K, et al.: Wavelet analysis of acute effects of static magnetic field on resting skin blood flow at the nail wall in young men (https://dx.doi.org/10.1016/j.mvr.2011.03.008). Microvasc Res. 2011, 82:277-283. 10.1016/j.mvr.2011.03.008 (https://dx.doi.org/10.1016/j.mvr.2011.03.008)
56. Brix G, Strieth S, Strelczyk D, et al.: Static magnetic fields affect capillary flow of red blood cells in striated skin muscle (https://dx.doi.org/10.1080/10739680701410850). Microcirculation. 2008, 15:15-26. 10.1080/10739680701410850 (https://dx.doi.org/10.1080/10739680701410850)
57. Ichioka S, Iwasaka M, Shibata M, Harii K, Kamiya A, Ueno S: Biological effects of static magnetic fields on the microcirculatory blood flow in vivo: a preliminary report (https://dx.doi.org/10.1007/BF02522863). Med Biol Eng Comput. 1998, 36:91-95. 10.1007/BF02522863 (https://dx.doi.org/10.1007/BF02522863)
58. Steyn PF, Ramey DW, Kirschvink J, Uhrig J: Effect of a static magnetic field on blood flow to the metacarpus in horses (https://dx.doi.org/10.2460/javma.2000.217.874). J Am Vet Med Assoc. 2000, 217:874-877. 10.2460/javma.2000.217.874 (https://dx.doi.org/10.2460/javma.2000.217.874)
59. Morris C, Skalak T: Static magnetic fields alter arteriolar tone in vivo (https://dx.doi.org/10.1002/bem.20047). Bioelectromagnetics. 2005, 26:1-9. 10.1002/bem.20047 (https://dx.doi.org/10.1002/bem.20047)
60. Gmitrov J, Ohkubo C, Okano H: Effect of 0.25 T static magnetic field on microcirculation in rabbits (https://dx.doi.org/10.1002/bem.10007). Bioelectromagnetics. 2002, 23:224-229. 10.1002/bem.10007 (https://dx.doi.org/10.1002/bem.10007)
61. Okano H, Gmitrov J, Ohkubo C: Biphasic effects of static magnetic fields on cutaneous microcirculation in rabbits (https://dx.doi.org/10.1002/(SICI)1521-186X(1999)20:3<161::AID-BEM2>3.0.CO;2-O). Bioelectromagnetics. 1999, 20:3-161. 10.1002/(SICI)1521-186X(1999)20:3<161::AID-BEM2>3.0.CO;2-O (https://dx.doi.org/10.1002/(SICI)1521-186X(1999)20:3<161::AID-BEM2>3.0.CO;2-O)
62. Mayrovitz HN: Electromagentic Linkages in Soft Tissue Wound Healing (https://www.taylorfrancis.com/chapters/edit/10.3109/9780203021651-37/electromagnetic-linkages-soft-tissue-wound-healing-harvey-mayrovitz). Bioelectric Medicine. Rosch, P.J. and Markov, M. (ed): Marcel Dekker, New York; 2004. 461-483.
63. Mayrovitz HN: Electromagnetic Fields for Soft Tissue Wound Healing. Electromagnetic Fields in Biology and Medicine. Markov MS (ed: CRC Press, Boca Raton, Florida; 2015:231-251.
64. Mayrovitz HN: Blood and Vascular Targets for Magnetic Dosing. Dosimetry in

Bioelectromagnetics. Markov MS (ed) (https://www.taylorfrancis.com/chapters/edit/10.1201/9781315370248-14/vascular-targets-magnetic-field-dosing-harvey-mayrovitz). CRC Press, Boca Raton, Florida; 2017:285-313.
65. Ueno S, Lovsund P, Oberg PA: Effects of alternating magnetic fields and low-frequency electric currents on human skin blood flow (https://dx.doi.org/10.1007/BF02441606). Med Biol Eng Comput. 1986, 24:57-61. 10.1007/BF02441606 (https://dx.doi.org/10.1007/BF02441606)
66. Peng L, Fu C, Wang L, Zhang Q, Liang Z, He C, Wei Q: The Effect of Pulsed Electromagnetic Fields on Angiogenesis: Bioelectromagnetics (https://dx.doi.org/10.1002/bem.22330). 2021, 42:250-258. 10.1002/bem.22330 (https://dx.doi.org/10.1002/bem.22330)
67. Lee JW, Kim JY, Lee NR, Lee YH: Effect of pulsed electromagnetic fields stimulation on ischemic skin model (https://dx.doi.org/10.1080/15368378.2021.1963763). Electromagn Biol Med. 2022, 41:15-24. 10.1080/15368378.2021.1963763 (https://dx.doi.org/10.1080/15368378.2021.1963763)
68. Biermann N, Sommerauer L, Diesch S, et al.: The influence of pulsed electromagnetic field therapy (PEMFT) on cutaneous blood flow in healthy volunteers1 (https://dx.doi.org/10.3233/CH-209224). Clin Hemorheol Microcirc. 2020, 76:495-501. 10.3233/CH-209224 (https://dx.doi.org/10.3233/CH-209224)
69. Sun J, Kwan RL, Zheng Y, Cheing GL: Effects of pulsed electromagnetic fields on peripheral blood circulation in people with diabetes: A randomized controlled trial (https://dx.doi.org/10.1002/bem.21983). Bioelectromagnetics. 2016, 37:290-297. 10.1002/bem.21983 (https://dx.doi.org/10.1002/bem.21983)
70. Wyszkowska J, Jedrzejewski T, Piotrowski J, Wojciechowska A, Stankiewicz M, Kozak W: Evaluation of the influence of in vivo exposure to extremely low-frequency magnetic fields on the plasma levels of pro-inflammatory cytokines in rats (https://dx.doi.org/10.1080/09553002.2018.1503428). Int J Radiat Biol. 2018, 94:909-917. 10.1080/09553002.2018.1503428 (https://dx.doi.org/10.1080/09553002.2018.1503428)
71. Szymborska-Kajanek A, Strzelczyk JK, Karasek D, et al.: Impact of low-frequency pulsed magnetic fields on defensin and CRP concentrations in patients with painful diabetic polyneuropathy and in healthy subjects (https://dx.doi.org/10.3109/15368371003635376). Electromagn Biol Med. 2010, 29:19-25. 10.3109/15368371003635376 (https://dx.doi.org/10.3109/15368371003635376)
72. Coballase-Urrutia E, Navarro L, Ortiz JL, Verdugo-Diaz L, Gallardo JM, Hernandez ME, Estrada-Rojo F: Static Magnetic Fields Modulate the Response of Different Oxidative Stress Markers in a Restraint Stress Model Animal: Biomed Res Int (https://dx.doi.org/10.1155/2018/3960408). 2018, 2018:3960408. 10.1155/2018/3960408 (https://dx.doi.org/10.1155/2018/3960408)