ADIPOCYTES
Plastic and Reconstructive Surgery Advance Online Article

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Autologous adipose stromal cells seeded on a human collagen matrix for dermal regeneration in chronic wounds: clinical proof of concept

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Therapy with autologous adipose-derived regenerative cells for the care of chronic ulcer of lower limbs in patients with peripheral arterial disease

Gerardo Marino, MD, Marco Moraci, MD, Emilia Armenia, MD, Consiglia Orabona, MD, Renato Sergio, MD, Gabriele De Sena, MD, Vincenza Capuozzo, MD, Manlio Barbarisi, MD, Francesco Rosso, MD, Giovanni Giordano, MD, Francesco Iovino, MD, and Alfonso Barbarisi,

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POSITION STATEMENT

Stromal cells from the adipose tissue-derived stromal vascular fraction and culture expanded adipose tissue-derived stromal/stem cells: a joint statement of the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society for Cellular Therapy (ISCT)

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MIXED CELLS
Review Article

P.R.L. Platelet Rich Lipotransfert: Our Experience and Current State of Art in the Combined Use of Fat and PRP

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The authors report their experience about the use of P.R.L. PLATELET RICH LIPOTRANSFERT method (platelet rich plasma mixed fat grafting) in 223 patients affected by soft tissue defects (ulcers, Romberg syndrome, Hemifacial atrophy, loss of substance, and signs of aging). This paper introduces the reader to PRP therapy and reviews the current literature on this emerging treatment modality, showing at the current clinical use of PRP in plastic and reconstructive surgery, with description of innovative methods and future prospects. This technique provides a promising alternative to surgery by promoting safe and natural healing. Here recent studies concerning the use of PRP in the treatment of chronic ulcers and soft tissue defect are reviewed.
Figure 4: P.R.L. PLATELET RICH LIPOTRANSFERT procedure. (a) Platelet rich plasma preparation according to Cascade centrifuge; (b) fat graft preparation according to Coleman Centrifuge; (c) purified fat graft after centrifugation; (d) addition of PRP to purified fat graft; (e) mix of 0.4 mL of PRP with 1 mL of fat graft in a 10 mL luer-look syringes (P.R.L. PLATELET RICH LIPOTRANSFERT); (f) injection of P.R.L. PLATELET RICH LIPOTRANSFERT according to lipostructure technique.
ADVANCED THERAPIES IN WOUND HEALING

• Materials
• Cellular therapies
  • Engineered tissues
• Physical therapies
• Smart technologies
<table>
<thead>
<tr>
<th>No.</th>
<th>Therapy</th>
<th>Indication for use</th>
<th>Level of evidence (for each indication)</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Mesenchymal stem cells</td>
<td>Acute wounds (such as burns)</td>
<td>1A</td>
<td>High-quality studies and good evidence of effectiveness and safety</td>
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<tr>
<td>2</td>
<td>Mesenchymal stem cells</td>
<td>Chronic wounds/ulcers</td>
<td>1A</td>
<td>High-quality studies and good evidence of effectiveness and safety</td>
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<td>3</td>
<td>Platelet rich plasma</td>
<td>Acute wounds (such as burns)</td>
<td>1C</td>
<td>Few studies but good evidence of effectiveness and safety</td>
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<td>4</td>
<td>Platelet rich plasma</td>
<td>Chronic wounds/ulcers</td>
<td>1C</td>
<td>Few studies but good evidence of effectiveness and safety</td>
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<tr>
<td>5</td>
<td>Platelet rich plasma</td>
<td>Aesthetic procedures</td>
<td>1C</td>
<td>Few studies but good evidence of effectiveness and safety</td>
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<tr>
<td>6</td>
<td>Monocytes</td>
<td><em>In vitro</em> application</td>
<td>2C</td>
<td>Very few studies and low-quality evidence of effectiveness. Further research is requested</td>
</tr>
<tr>
<td>7</td>
<td>Epidermal skin substitutes</td>
<td>Acute wounds (such as burns)</td>
<td>1A</td>
<td>High-quality studies and good evidence of effectiveness and safety</td>
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<td>8</td>
<td>Epidermal skin substitutes</td>
<td>Chronic wounds/ulcers</td>
<td>1A</td>
<td>High-quality studies and good evidence of effectiveness and safety</td>
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<tr>
<td>9</td>
<td>Dermal skin substitutes</td>
<td>Acute wounds (such as burns)</td>
<td>1A</td>
<td>High-quality studies and good evidence of effectiveness and safety</td>
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<tr>
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<td>Dermal skin substitutes</td>
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<td>11</td>
<td>Dermo-epidermal skin substitutes</td>
<td>Acute wounds (such as burns)</td>
<td>1A</td>
<td>High-quality studies and good evidence of effectiveness and safety</td>
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<td>12</td>
<td>Dermo-epidermal skin substitutes</td>
<td>Chronic wounds/ulcers</td>
<td>1A</td>
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<tr>
<td>13</td>
<td>Acellular dermal matrix</td>
<td>Acute wounds (such as burns)</td>
<td>2C</td>
<td>Few studies with weak evidence</td>
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<tr>
<td>14</td>
<td>Acellular dermal matrix</td>
<td>Chronic wounds/ulcers</td>
<td>2C</td>
<td>Few studies with weak evidence</td>
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<tr>
<td>15</td>
<td>Placental-based allografts</td>
<td>Acute wounds (such as burns)</td>
<td>1C</td>
<td>Few studies but good evidence of effectiveness and safety</td>
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<tr>
<td>16</td>
<td>Placental-based allografts</td>
<td>DFU</td>
<td>1B</td>
<td>High-quality studies with good evidence of effectiveness and safety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VLUs</td>
<td>1C</td>
<td>Few high-quality studies but good evidence of effectiveness and safety</td>
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<tr>
<td>17</td>
<td>Food-grade lactic acid bacteria</td>
<td>Chronic wounds/ulcers</td>
<td>1C</td>
<td>Few studies but good evidence of effectiveness and safety</td>
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<tr>
<td>18</td>
<td>Dressings based on autologous platelet-rich fibrin and leucocyte</td>
<td>Chronic wounds/ulcers</td>
<td>1C</td>
<td>Few studies but good evidence of effectiveness and safety</td>
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ADVANCED THERAPIES IN WOUND HEALING

• Materials
• Cellular therapies
• Engineered tissues
• Physical therapies
• Smart technologies
Trends in Wound Repair: Cellular and Molecular Basis of Regenerative Therapy Using Electromagnetic Fields

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3Human Medical Genetics Program, University of Colorado at Denver and Health Sciences Center, Aurora, Colorado, USA

Abstract: Chronic ulceration of the leg represents a major, underestimated problem of modern health care, involving physical and cosmetic impairment and social stigma along with high community costs for patients' treatment. The increasing prevalence of chronic ulcers, currently reported to be as much as 0.3% in the general population, should stimulate identification of more efficacious therapeutic approaches to achieve complete healing. The strategies of regenerative medicine based on small molecules, biomimetic scaffolds, gene or cell therapy, and electromagnetic field manipulation represent some of the modern therapeutic alternatives for wound healing. Here we review an integrated, interdisciplinary approach the modern cellular and molecular mechanistic concepts regarding the involvement of extremely low frequency electromagnetic fields (ELF-EMF) in the complex process of tissue repair, with particular focus on chronic wounds. The data analysis supports three main effects of electromagnetic fields on the wound healing pathways: 1) an anti-inflammatory effect, by modulation of cytokine profile that induces the transition of the healing process from a chronic pro-inflammatory to an anti-inflammatory state; 2) a neo-angiogenic effect, by increased endothelial cells proliferation and tubulization and production of fibroblast growth factor (FGF)-2; and 3) a re-epithelialization effect, by stimulation of collagen formation. We believe that utilization of ELF-EMF in larger clinical trials designed to optimize these functional parameters would facilitate a better understanding of ELF-EMF-induced healing mechanisms and lead to improved therapeutic outcomes for this disabling condition which is often totally resistant to treatment.

Keywords: Cellular and molecular mechanisms, chronic ulcers, electromagnetic fields, wound healing.
Underneath the skin tissue a negative polarity of 25–40 mW exists physiologically.

[Piaggesi et al. IWJ 2018]
The wound eliminates the difference in electric polarity across the skin. An electric current is generated between the healthy tissue and the wound.

[Piaggesi et al. IWJ 2018]
When applying an electric field to the wound, the margins open or close depending on the polarity.
AN APPLIED ELECTRIC FIELD ACTIVATES INTRACELLULAR SIGNALING PATHWAYS

Zhao et al. [Nature. 2006;442(7101):457–60].
Zhao et al. (Nature. 2006;442(7101):457–60).
Safety and Effectiveness of Therapeutic Magnetic Resonance in the Management of Postsurgical Lesion of the Diabetic Foot

Lorenza Abbruzzese, DPM, Elisabetta Iacopi, MD, Alberto Coppelli, MD, Giovanni Bonino, DPM, Chiara Goretti, MD, and Alberto Piaggesi, MD

Abstract
To evaluate the safety and effectiveness of therapeutic magnetic resonance (TMR) in the management of the diabetic foot (DF), we treated a group of consecutive type 2 diabetic inpatients with wide postsurgical lesions (Group A: N = 10; age 67.7 ± 18.9 years, duration of diabetes 22.3 ± 6.6 years, 8.1 ± 1.1%, body mass index 29.4 ± 2.1 kg/m²), for 2 consecutive weeks, while admitted, with a low-intensity magnetic resonance equipment, in addition to standard treatment. Patients, compared with a matched control group with the same clinical characteristics (Group B), were then followed monthly for 6 months to evaluate healing rate (HR), healing time (HT), rate of granulation tissue (GT) at 3 months, and adverse events. HR was of 90% in Group A and 30% in Group B (P < .05); GT was 73.7 ± 13.2% in Group A versus 51.84 ± 18.77% in Group B (P < .05). HT in Group A was 84.46 ± 54.38 days versus 148.54 ± 78.96 days in Group B (P < .01). No difference in adverse events (5 in Group A and 6 in Group B) was observed throughout the study period. In this pilot study, the use of TMR at this dose and duration was safe. The results also permit the observation that TMR plus standard care offered a faster healing rate compared with standard care alone.

Keywords
magnetic fields, therapy, diabetic foot, ulcers
Figure 2. Healing rate at 6 months of the lesions of patients treated with the TMR (Group A), or controls (Group B).

Figure 3. Area of the lesions of patients treated with the TMR (Group A), or controls (Group B).

Figure 4. Pain score evaluated with visual analog scale (VAS) in patients treated with the TMR (Group A), or in controls (Group B).
Start of treatment

Red color = granulation tissue

After 15 days of treatment

keratinized epidermis
dermal papillae

Patient code: NS120140 GROUP B - ACTIVE

[Courtesy Dr. Barbara Zavan]
After 15 days of treatment

Keratinocytes
3 layers

keratinized epidermis

blood vessels

dermal papillae

Patient code: NS120140  GROUP B - ACTIVE

[Courtesy Dr. Barbara Zavan]
IMMUNOFLUORESCENCE CONFIRMS CHANGE IN TISSUE STRUCTURE

*Immunofluorescence: Collagen type I + Pan Cytokeratin*

Before

Blu: Nucleus
Green: Pan Cytokeratin
Red: Collagen type I

After

Blu: Nucleus
Green: Pan Cytokeratin
Red: Collagen type I

After the treatment the keratinocytes are organized in a pluri-stratified and well-differentiated epidermis anchored by an organized dermal-epidermal junction.
EUREKA study – the evaluation of real-life use of a biophotonic system in chronic wound management: an interim analysis

Objective: Interest has grown regarding photobiomodulation (PBM) with low-level light therapy, which has been shown to positively affect the stages of the wound healing process. In a real-life context clinical setting, the objective of the EUREKA study was to investigate efficacy, safety, and quality of life associated with the use of a BioPhotonic gel (LumiHeal™) in the treatment of chronic wounds such as venous leg ulcers (VLUs), diabetic foot ulcers (DFUs), and pressure ulcers (PUs). This BioPhotonic gel represents a new, first-in-class emission spectrum of light, including fluorescence, to induce PBM and modulate healing.

Design: The multicenter, prospective, interventionnal, uncontrolled, open-label study enrolled 100 patients in 12 wound centers in Italy. We performed an early interim analysis based on the first 33 subjects (17 VLUs, 17 DFUs, 3 PUs) in seven centers who completed the study.

Main results: Seventeen patients (52%) achieved total wound closure (full re-epithelialization) for 2 weeks during the study period. Two patients (6%) were considered “almost closed” (a decrease of more than 90% in wound area at study end) and three others (9%) were considered “ready for skin grafting”. No related serious adverse events were observed, and the compliance was excellent. After the treatment, the average time to “pain-free” was 11.9 days in the VLUs group. Quality of life was improved with overall increase of 26.4% of the total score (Cardiff Wound Impact Schedule, p=<0.001).

Conclusion: The study revealed a positive efficacy profile of the BioPhotonic gel in promoting wound healing and reactivating the healing process in different types of chronic, hard-to-heal wounds. The treatment was shown to be safe and well tolerated by the patients, and a reduction of pain perception was also detected during the treatment period. The improvement of the quality of life was accompanied by a high level of clinician satisfaction.

Keywords: photobiomodulation, fluorescence biomodulation, biophotronics, phototherapy, light, venous leg ulcers, VLUs, pressure ulcers, PUs, diabetic foot ulcers, DFUs, hard-to-heal wounds

Introduction
Chronic wounds such as pressure ulcers (PUs), venous leg ulcers (VLUs), and diabetic foot ulcers (DFUs) remain a challenging clinical problem and efficient wound management is crucial to effectively assist the healing process. The socioeconomic burden of chronic wounds represents an enormous annual cost for health care systems. The impact of chronic wounds and their high rate of occurrence is also worsened by the aging global population. For example, it has been estimated that chronic wounds have an incidence rate of 120 per 100,000 people aged between 45 and 65 years and it rises to 800 per 100,000 people >75 years of age. In addition, it is important to highlight that underlying pathologies, particularly diabetes, may explain the failure of
Healing Rate at Follow-up (9.0 ± 1.0 weeks)

- **Not healed**
- **Healed**

Number of lesions
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indication</th>
<th>Level of evidence (for each indication)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESWT</td>
<td>DFU, PU, VLU</td>
<td>1C</td>
<td>Few studies, very good risk/benefit ratio, can be considered an adjuvant therapy in a wide range of clinical conditions</td>
</tr>
<tr>
<td>EF</td>
<td>DFU, PU, VLU</td>
<td>1C</td>
<td>Good evidence of effectiveness in experimental models, but few studies with poor-quality in clinical fields, useful in stimulating wound edges' progression</td>
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<tr>
<td>MF</td>
<td>DFU, PU, VLU</td>
<td>1C</td>
<td>Relatively recent evidence, still few studies, few good-quality clinical trials, solid evidence in bone fracture repair; some indication of anti-inflammatory effects, evidence in stimulating collagen synthesis and granulation tissue formation</td>
</tr>
<tr>
<td>PBM</td>
<td>DFU, PU, VLU</td>
<td>2B</td>
<td>Still controversial mechanisms of action, not clear the full range of effects on wound repair; few studies of low- or very low-quality, some evidence of antibacterial activity and pain reduction</td>
</tr>
<tr>
<td>NT</td>
<td>DFU, MU, VLU</td>
<td>1C</td>
<td>Promising results, but a sufficient evidence base is not yet available, good results in prevention of DFU and antibacterial activity, few RCTs</td>
</tr>
</tbody>
</table>

ESWT—extracorporeal shock wave therapy; EF—electric fields; MF—magnetic fields; PBM—photobiomodulation; NT—nanotechnologies; DFU—diabetic foot ulcer; MU—mixed ulcer; PU—pressure ulcer; VLU—venous leg ulcer
ADVANCED THERAPIES IN WOUND HEALING

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<th>Hemostasis</th>
<th>Inflammation</th>
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<tr>
<td>Polymatic Nanoparticles (Drugs)</td>
<td>Nanoceria</td>
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<tr>
<td>Zinc Oxide Nanoparticles</td>
<td>Liposomes (Drugs and growth factors)</td>
</tr>
<tr>
<td>Nanoceria</td>
<td>Polymeric Nonoparticles (Drugs, nitric, oxide, curcumin)</td>
</tr>
<tr>
<td><strong>Proliferation</strong></td>
<td>Gold Nonoparticles (Drugs)</td>
</tr>
<tr>
<td>Polymeric Nonoparticles (Drugs, nitric, oxide, curcumin)</td>
<td>Copper Nonoparticles</td>
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<tr>
<td>Gold Nanoparticles (Drugs and siRNA)</td>
<td>Silver Nonoparticles (Drugs and oligo nucleotide)</td>
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<tr>
<td>Fullerene, Graphene Oxide, Carbon Nanotubes</td>
<td>Ceramic Nanoparticles (Nitric oxide, curcumin)</td>
</tr>
<tr>
<td>Zinc Oxide Nanoflowers</td>
<td><strong>Remodeling</strong></td>
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<tr>
<td>Polymeric Nonofibers (Plasmid DNA)</td>
<td>Fullerene, Graphene Oxide, Carbon Nanotubes</td>
</tr>
<tr>
<td>Polymeric Nonoscaffolds (Plasmid DNA)</td>
<td>Polymeric Nonoparticles (siRNA)</td>
</tr>
<tr>
<td>Bioactive Glass Particles</td>
<td>Nanoceria</td>
</tr>
<tr>
<td>Dendrimers (Plasmid DNA)</td>
<td>Iron oxide nanoparticles (Nitric Oxide)</td>
</tr>
<tr>
<td>Liposomes (Growth factors and drugs)</td>
<td>Polymeric Nanoscaffolds</td>
</tr>
</tbody>
</table>

Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial

Michael Edmunds, José Luis Lazaro-Martinez, Jesus Mariano Alfayate-Garcia, Jacques Martini, Jean-Michel Petit, Gerry Regan, Ralf Lehmann, Luigi Uccioli, Anne Sauvaget, Serge Robbet, Jean-Charles Luthur, Alberto Frangialli

Summary

Background Diabetic foot ulcers are serious and challenging wounds associated with high risk of infection and lower-limb amputation. Ulcers are deemed neuroischaemic if peripheral neuropathy and peripheral artery disease are both present. No satisfactory treatment for neuroischaemic ulcers currently exists, and no evidence supports one particular dressing. We aimed to assess the effect of a sucrrose octasulfate dressing versus a control dressing on wound closure in patients with neuroischaemic diabetic foot ulcers.

Methods We did a randomised, double-blind clinical trial (Explorer) in 43 hospitals with specialised diabetic foot clinics in France, Spain, Italy, Germany, and the UK. Eligible participants were inpatients or outpatients aged 18 years or older with diabetes and a non-infected neuroischaemic diabetic foot ulcer greater than 1 cm² and of grade IC or IH (as defined by the University of Texas Diabetic Wound Classification system). We excluded patients with a severe illness that might lead to them discontinuing the trial and those who had surgical revascularisation in the month before study entry. We randomly assigned participants (1:1) via a computer-generated randomisation procedure (concealed block size two; stratified by study centre and wound area [1–5 cm² and 5–30 cm²]), to treatment with either a sucrrose octasulfate wound dressing or a control dressing (the same dressing without sucrrose octasulfate) for 20 weeks. Both groups otherwise received the same standard of care for a 2-week screening period before randomisation and throughout the 20-week trial. Dressings were applied by nursing staff or by instructed relatives (for some outpatients). Frequencies of dressing changes were decided by the investigator on the basis of the clinical condition of the wound. Patients were assessed 2 weeks after randomisation, then monthly until week 20 or occurrence of wound closure. The primary outcome, assessed by intention-to-treat, was proportion of patients with wound closure at week 20. This trial is registered with ClinicalTrials.gov, number NCT01717183.

Findings Between March 21, 2013, and March 31, 2016, we randomly assigned 240 individuals to treatment: 126 to the sucrrose octasulfate dressing and 114 to the control dressing. After 20 weeks, wound closure occurred in 60 patients (48%) in the sucrrose octasulfate dressing group and 34 patients (30%) in the control dressing group (18 percentage points difference, 95% CI 13–30; adjusted odds ratio 2.60, 95% CI 1.43–4.73; p=0.002). In both groups, the most frequent adverse events were infections of the target wound: 13 wound infections in 25 (20%) patients of 126 in the sucrrose octasulfate dressing group and 36 in 32 (28%) patients of 114 in the control dressing group. Minor amputations not affecting the wound site were also reported in one (1%) patient in the sucrrose octasulfate dressing group and two (2%) patients in the control dressing group. Three (2%) patients assigned to the sucrrose octasulfate dressing and four (4%) assigned to the control dressing died, but none of the deaths were related to treatment, procedure, wound progression, or subsequent to amputation.

Interpretation A sucrrose octasulfate dressing significantly improved wound closure of neuroischaemic diabetic foot ulcers without affecting safety after 20 weeks of treatment along with standard care. These findings support the use of sucrrose octasulfate dressing as a local treatment for neuroischaemic diabetic foot ulcers.

Funding Laboratoires Urigo Medical.

Introduction

Diabetic foot ulceration is a serious and common complication of type 1 and type 2 diabetes, affecting 9–126.1 million people annually worldwide and approximately 19–34% of people with diabetes at least once in their life. Because the global prevalence of diabetes continues to increase substantially, with a prediction of 642 million people worldwide in 2040, the complex and costly management of these disabling and recurrent wounds remains a therapeutic challenge. The prognosis of patients with diabetic foot ulcers is deeply affected by the high prevalence of infection and amputation associated with these wounds. The risk of death at 5 years for a person with a diabetic foot ulcer is 2.5 times higher than for a...
LCT – Lipido-Colloidal Technology

Idro-colloidal particles

Lipidic particles

Sucralfate particles
HEALING RATE AT 20 WEEKS

$\Delta$ 18%; OR 2.6 (95% CI 1.43 – 4.73; $p = 0.002$)
<table>
<thead>
<tr>
<th>Time to Closure Difference (Control-Treatment)</th>
<th>Log rank (Mantel-Cox)</th>
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</thead>
<tbody>
<tr>
<td>ITT analysis</td>
<td>60.8 days</td>
</tr>
<tr>
<td>Control group (n=114)</td>
<td>TLC-NOSF group (n=126)</td>
</tr>
<tr>
<td>180.5 ± 8.7 (163.4-197.7)</td>
<td>119.7 ± 4.7 (110.5-128.9)</td>
</tr>
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</table>
Temperature- and pH-sensitive wearable materials for monitoring foot ulcers

This article was published in the following Dove Press journal:
International Journal of Nanomedicine
28 November 2016
Number of times this article has been viewed

Abstract: Foot ulcers account for 15% of comorbidities associated with diabetes. Presently, no device allows the status of foot ulcers to be continuously monitored when patients are not hospitalized. In this study, we describe a temperature and a pH sensor capable of monitoring diabetic foot and venous leg ulcers developed in the frame of the seventh framework program European Union project SWAN-iCare (smart wearable and autonomous negative pressure device for wound monitoring and therapy). Temperature is measured by exploiting the variations in the electrical resistance of a nanocomposite consisting of multiwalled carbon nanotubes and poly(styrene-b-(ethylene-co-butylene)-b-styrene). The pH sensor used a graphene oxide (GO) layer that changes its electrical potential when pH changes. The temperature sensor has a sensitivity of ~85 Ω/°C in the range 25°C–50°C and a high repeatability (maximum standard deviation of 0.1% over seven repeated measurements). For a GO concentration of 4 mg/mL, the pH sensor has a sensitivity of ~42 mV/pH and high linearity (R²=0.99).

Keywords: diabetic foot ulcer, wearable sensors, wound temperature, wound pH
Figure 1. The temperature sensor.

Notes: Left: drawing of the Kapton substrate for the temperature sensor. Right: substrate with an electrode pair coated by a film of MWCNTs–SEBS. Abbreviations: MWCNTs, multiwalled carbon nanotubes; SEBS, poly(styrene-b-(ethylene-co-butylene)-b-styrene).
New and Future Directions in Integrative Medicine Research Methods with a Focus on Aging Populations: A Review

Lindsey M. Knowles\textsuperscript{a}  Perry Skeath\textsuperscript{a}  Min Jia\textsuperscript{a}  Bijan Najafi\textsuperscript{b}  Julian Thayer\textsuperscript{c}  Esther M. Sternberg\textsuperscript{a}

\textsuperscript{a}Arizona Center for Integrative Medicine, Institute on Place and Wellbeing, Department of Psychology, and \textsuperscript{b}Interdisciplinary Consortium on Advanced Motion Performance (iCAMP), Southern Arizona Limb Salvage Alliance (SALSA), University of Arizona, College of Medicine, Tucson, Ariz., and \textsuperscript{c}The Ohio State University, Columbus, Ohio, USA
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<th>No.</th>
<th>Therapy</th>
<th>Indication for use</th>
<th>Level of evidence (for each indication)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 1   | Electrical stimulation                  | Wound healing 
    DFU 
    PU 
    VLU 
    Mixed ulcers                          | 1B                                                   | There is a clear effectiveness evidence, including a systematic review of 21 RCT studies that confirmed benefit and safety of TENS to accelerate wound healing irrespective of the type of ulcers. The major hurdles seem to be poor adherence to regular therapy and difficulty of stimulation parameters adjustment by non-tech savvy patients. Thus, successful implementation at large remains unclear. |
| 2   | Electrical stimulation                  | Improving postural control and gait             | 2A                                                   | Recent RCT studies confirmed acceptability, safety, and efficacy of TENS for use to improve balance, gait, and skin perfusion. It seems delivering electrical stimulation via plantar region could improve acceptability and adherence particularly among people with a loss of plantar sensation, who may not feel uncomfortable tingling caused by the electrical stimulation |
| 3   | Nanotechnology-based therapy            | Wound healing 
    —chronic DFU, deep wounds, ischaemic wounds | 1A                                                   | Several level one evidence studies, including few systematic reviews, are supportive of the benefit of dermal substitutes and its low risks. However, there are very few comparative studies to demonstrate which dermal substitute product is superior to the others. While in low complicated wounds, there is no noticeable difference between products, it seems the difference is more pronounced for complicated wounds, such as ischemic wounds. However, most studies excluded those with ischemic wounds, which makes a fair comparative comparison difficult. |
| 4   | Ultrasonic assisted treatment           | Chronic VLU                                    | 2A                                                   | There is level two evidence (case-control) indicating the effectiveness and the low risk in its ability to accelerate wound healing.                                                                                                                            |
| 5   | Pulsed radio frequency energy           | VLU                                            | 1C                                                   | There few studies including a recent level one study (RCT trial) supporting the safety and effectiveness of this therapy to speed up wound healing.                                                                                                                     |
| 6   | Active dressing with continuous diffusion of oxygen | Chronic and non-chronic DFU                     | 1C                                                   | A recent RCT study and multicentre study is supportive for benefit of active dressing with continuous diffusion oxygen to speed up wound healing. However, more independent studies are needed to confirm the effectiveness of such therapy. |
| 7   | Physical activity dosage management    | DFU                                            | 2B                                                   | There is a recent RCT study supporting the importance of managing the dosage of physical activity including the total number of daily steps and standing bouts to hasten wound healing. However, more studies are required to confirm the ease of implementation for this guideline to hasten wound healing |
| 8   | Stress management                      | DFU                                            | 2C                                                   | Few recent studies suggest that stress management could speed up wound healing. However, there is no level one study to confirm the effectiveness of implementing stress management strategies to speed up wound healing. |

Table 23. Evaluation of evidence levels: smart technologies
COMING SOON
[Courtesy L. Teòt]
VIOLET EXCITATION LIGHT

SKIN
Collagen from skin and wound produce green fluorescence.

BACTERIA
Potentially harmful bacteria produce red fluorescence.
Human Type 1 Collagen from Tobacco
[Rupp J. Human collagen from tobacco? vol 6, issue 36, Nov 16, 2016]
PIVOT CLINICAL TRIAL – POST SURGICAL LESION IN DF

24 PATIENTS RANDOMIZED INTO TWO GROUPS – VERGENIX vs SOC

[Piaggesi et al. JWC submitted]
Group A 83.3% vs Group B 58.3%, \( \chi^2 13.6, p<0.001 \)
CAD – CAM ORTHESIS FOR DF
Novel Wearable Technology for Assessing Spontaneous Daily Physical Activity and Risk of Falling in Older Adults with Diabetes

Bijan Najafi, Ph.D., M.Sc.,1,2,3 David G. Armstrong, M.D., D.P.M., Ph.D.,1,2
and Jane Mohler, N.P-c., M.P.H., Ph.D.1,3
Monitoring Location-Specific Physical Activity via Integration of Accelerometry and Geotechnology Within Patients With or At Risk of Diabetic Foot Ulcers: A Technological Report

Ryan T. Crews, MS¹, Sai V. Yalla, PhD¹, Navdeep Dhatt, BS¹, Drew Burdi, BS¹, and Sungsoon Hwang, PhD²
Standing 11.10%
Walking 8.65%
Lying 15.28%
Lying 70.18%
Sitting 22.14%
Standing 5.27%
Walking 2.41%
Lying 0.00%
Sitting 78.31%

Other 64.96%
Work 13.71%
Walking 7.98%

[Crews RT et al. Journal of Diabetes, Science and Technology 2016]
“I came here with some confused ideas in my mind about this topic. Coming out I am still confused, but at an higher level....”

[Enrico Fermi, 1901 – 1954]