Il piede diabetico: innovazioni tecnologiche e telemedicina

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Gestione infezione

Perdita tessuti

Rivascolarizzazione

Osso infetto

Guarigione

Prevenzione recidive
Gestione dell’infezione

DOI 10.1007/s00125-006-0491-1

High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study

L. Prompers · M. Huijberts · J. Aapelqvist · E. Jude · A. Piaggi · K. Bakker · M. Edmonds · P. Holstein · A. Jirkovská · D. Mauricio · G. Ragnarson-Tennvall · H. Reike · M. Spraul · L. Uccioli · V. Urbancic · K. Van Acker · J. van Baal · F. van Merode · N. Schaper

Table 1  Classification of foot disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Number of patients</th>
<th>Percentage of study population</th>
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<tbody>
<tr>
<td>A</td>
<td>PAD −, infection −</td>
<td>270</td>
<td>24</td>
</tr>
<tr>
<td>B</td>
<td>PAD −, infection +</td>
<td>305</td>
<td>27</td>
</tr>
<tr>
<td>C</td>
<td>PAD +, infection −</td>
<td>205</td>
<td>18</td>
</tr>
<tr>
<td>D</td>
<td>PAD +, infection +</td>
<td>347</td>
<td>31</td>
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</table>
Treatment of infection

Superficial ulcer with limited soft tissue (mild) infection:
- Cleanse, debride all necrotic tissue and surrounding callus

Deep or extensive (potentially limb-threatening) infection (moderate or severe infection):
- Urgently evaluate for need for surgical intervention to remove necrotic tissue, including infected bone, release compartment pressure or drain abscesses
Criticità gestione dell’infezione

Estensione infezione

Dimensioni lesioni

Germi resistenti

Supporto vascolare
Fotobiomodulazione
Fotobiomodulazione

RLP068/Cl, fotosensibilizzante di natura ftalocianinica, tetratosstituito con gruppi di ammonio quaternario

Il device è progettato per la terapia fotodinamica e per essere quindi utilizzato in combinazione con la sorgente di luce rossa (sorgente LED a 630 nm).

Con specifica lunghezza d’onda e intensità il fascio di luce trasferisce energia all’ossigeno presente nei tessuti con formazione di ossigeno di singoletto e altre specie reattive dell’ossigeno (ROS), responsabili del danno ossidativo irreversibile a componenti cellulari essenziali dei microrganismi, favorendo così il processo di guarigione, senza danneggiare le cellule del tessuto ospite.
Gestione dell’infezione: fotobiomodulazione

- Eradication MRSA and *Pseudomonas aeruginosa* infections with short-interval (<1 hour) applications by irradiating chronically infected ulcers with UVC (254nm, 15.54mW/cm²).

- The antimicrobial effect of photobiomodulation has been confirmed for use on biofilm-producing bacteria, which include the majority of the cases of chronic wounds colonisation, and which are particularly resistant to systemic antibiotic therapy.

Cellular stimulation

Cellular inhibition

Fluorescence biomodulation systems yielded significant biological effects that impacted inflammation, stimulated markers of proliferation and angiogenesis, and improved markers of tissue remodeling.

Both in vitro and in vivo results demonstrated:
- improved inflammatory profiles, with down-regulation of pro-inflammatory cytokines like IL-6 and TNF-α and up-regulation of anti-inflammatory cytokines like IL-10 and TGF-β3.
- protein microarrays suggest that dermal human fibroblasts cells were less likely to produce IL-4, a cytokine that appears to be linked to the pathogenesis of chronic wounds
- Growth factors such as TGF-β, FGF, PDGF, and VEGF were also elevated

Scapagnini et al. Photonic Diagnosis and Treatment of Infections and Inflammatory Diseases II, 108630W (7 March 2019)
Edmonds et al. raised the question if ischemic foot disease could be explained by one disease (atherosclerosis), or by the occurrence of 2 diseases (diabetic macroangiopathy [SAD] and classical atherosclerosis [BAD]). They concluded that “the detailed nature of PAD in diabetes has not been fully defined. Of course, in a diabetic patient, particularly a patient who develops arterial disease in later life, both diseases may co-exist”.


**Diabetic Peripheral Arteriopathy: A Tale of Two Diseases**

Michael E. Edmonds\(^a\) · C. Shanahan\(^b\) · Nina L. Petrova\(^a\)
<table>
<thead>
<tr>
<th>Aggregated segments</th>
<th>Prevalence of disease (%)</th>
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<tr>
<td>ATG</td>
<td>9.8</td>
</tr>
<tr>
<td>SFA</td>
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<td>P-TPT</td>
<td>46.3</td>
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<table>
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<td>37.7</td>
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<tr>
<td>3 arteries</td>
<td>23.7</td>
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<td>13.2</td>
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<tr>
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<tr>
<td>2 arteries</td>
<td>44.9</td>
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<tr>
<td>3 arteries</td>
<td>16.4</td>
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<th>BTA vessel s</th>
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<td>27.9</td>
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<tr>
<td>1 artery</td>
<td>20.2</td>
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<tr>
<td>2 arteries</td>
<td>31.5</td>
</tr>
<tr>
<td>3 arteries</td>
<td>20.4</td>
</tr>
</tbody>
</table>

| Arch                | 25.1          |

> 50% 2-3 foot BAD

25% arch disease = SAD
Arterializzazione vene
Effect of Repetitive Intra-Arterial Infusion of Bone Marrow Mononuclear Cells in Patients With No-Option Limb Ischemia

The Randomized, Double-Blind, Placebo-Controlled Rejuvenating Endothelial Progenitor Cells via Transcutaneous Intra-arterial

Rischio di amputazione e morte
Stem-cell and ischaemia

At 4 weeks in legs injected with bone marrow-mononuclear cells compared with those injected with peripheral blood-mononuclear cells:
- ABI increased (difference 0.09 [95% CI 0.06-0.11]; p<0.0001)
- transcutaneous oxygen pressure (13 [9-17]; p<0.0001)
- rest pain (-0.85 [-1.6 to -0.12]; p=0.025)
- pain-free walking time (1.2 [0.7-1.7]; p=0.0001)

These improvements were sustained at 24 weeks.

**Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial.** Tateishi et al.
Gestione infezione

Rivascolarizzazione

Osso infetto

Perdita tessuti

Guarigione

Prevenzione recidive
Infezione ossea
Innesti ossei

Autologo-eterologo-di sintesi

Evoluzione tecnologica materiali (porosità, migrazione cellulari, interconnessione, meccanica)

Possibilità di associazione con antibiotico
Trattamento
Outcome clinico
Outcome radiologico
Gestione infezione

Perdita tessuti

Rivascolarizzazione

Osso infetto

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Prevenzione recidive
Perdita tessuti

Medicina Rigenerativa

Processo di creazione tessuti funzionali per riparare o sostituire tessuti o organi funzionali persi per età, malattia, danno o difetti congeniti
Guidelines for the IWGDF state:

We suggest not using the following agents reported to improve wound healing by altering the wound biology: growth factors, autologous platelet gels, bioengineered skin products, ozone, topical carbon dioxide and nitric oxide, in preference to best standard of care. (Weak; Low)
Sostituti dermici ed epidermici

Materiale bioingegnerizzato che sostituisce il derma/epidermide

Substrati con componente cellulare
Prevedono una parte di colonizzazione in vitro

Substrati con componente acellulare
Rapida colonizzazione da parte delle cellule dell’ospite
Growth factors for treating diabetic foot ulcers

Arturo J Martí-Carvajal¹, Christian Gluud², Susana Nicola³, Daniel Simancas-Racines³, Ludovic Reveiz⁴, Patricio Oliva⁵, Jorge Cedeño-Taborda⁶

¹Iberoamerican Cochrane Network, Valencia, Venezuela. ²The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Department 7812, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. ³Facultad de Ciencias de la Salud Eugenio Espejo, Universidad Tecnológica Equinoccial, Quito, Ecuador. ⁴Free time independent Cochrane reviewer, Potomac, MD, USA. ⁵Faculty of Dentistry, Universidad del Desarrollo, Concepción, Chile. ⁶Coordinador de la Sección de Endocrinología, Centro de Investigación UNILIME / Universidad de Carabobo, Valencia, Venezuela

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Editorial group: Cochrane Wounds Group.
Review content assessed as up-to-date: 3 March 2015.


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Any growth factor compared with placebo or no growth factor increased the number of participants with complete wound healing (345/657 (52.51%) versus 167/482 (34.64%); RR 1.51, 95% CI 1.31 to 1.73; I^2 = 51%, 12 trials; low quality evidence). The result is mainly based on platelet-derived wound healing formula (36/56 (64.28%) versus 7/27 (25.92%); RR 2.45, 95% 1.27 to 4.74; I^2 = 0%, two trials), and recombinant human platelet-derived growth factor (becaplermin) (205/428 (47.89%) versus 109/335 (32.53%); RR 1.47, 95% CI 1.23 to 1.76, I^2 = 74%, five trials).
Biological skin equivalents

Growth factors/small molecules

Stem cells

Healed wound
Review

The role of stem cells in the treatment of diabetic foot ulcers

Sheila N. Blumberg, Alexandra Berger, Lisa Hwang, Irena Pastar, Stephen M. Warren, Weilam Chen

A New York University School of Medicine, Department of Surgery, Division of Wound Healing & Regenerative Medicine, New York, NY 10016, United States
b New York University School of Medicine, Department of Plastic Surgery, New York, NY 10016, United States

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ABSTRACT

Diabetic foot ulcers (DFUs) are a significant and rapidly growing complication of diabetes and its effects on wound healing. Over half of diabetic patients who develop a single ulcer will subsequently develop another ulcer of which the majority will become chronic non-healing ulcers. One-third will progress to lower extremity amputation. Over the past decade, the outcomes for patients with DFUs ulcers have not improved, despite advances in wound care. Successful treatment of diabetic foot ulcers is hindered by the lack of targeted therapy that hones in on the healing processes dysregulated by diabetes. Stem cells are a promising treatment for DFUs as they are capable of targeting, as well as bypassing, the underlying abnormal healing mechanisms and deranged cell signaling in diabetic wounds and promote healing. This review will focus on existing stem cell technologies and their application in the treatment of DFUs.

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Autologous Bone Marrow–Derived Cultured Mesenchymal Stem Cells Delivered in a Fibrin Spray Accelerate Healing in Murine and Human Cutaneous Wounds*

DELIVERY OF STEM CELLS TO HUMAN AND MURINE WOUNDS

FIG. 4. Application of bone marrow–derived cultured MSC to acute human wounds. (A) The cells were applied directly to the wound using a fibrin polymer spray delivered from a double-barreled syringe. The arrows point to the individual barrels filled with either thrombin or the cell-containing fibrinogen solution.
Adipose tissue derived mesenchymal stem cell (AD-MSC) promotes skin wound healing in diabetic rats

Mohsen Khosravi Maharlooei\textsuperscript{a}, Mansooreh Bagheri\textsuperscript{a,\textdagger}, Zhabiz Solhjou\textsuperscript{a}, \ldots
Gestione infezione

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Prevenzione recidive
Rethinking regenerative medicine: a macrophage-centered approach

Bryan N. Brown\textsuperscript{1,2}\textsuperscript{,} \textcopyright{}, Brian M. Sicari\textsuperscript{1,3}\textsuperscript{,} \textcopyright{} and Stephen F. Badylak\textsuperscript{1,3} \textcopyright{}

\textbf{THE M1/M2 PARADIGM IN TISSUE ENGINEERING AND REGENERATIVE MEDICINE}

I Macrofagi M2 rappresentano una componente fondamentale nella riparazione tessutale

Strategie di medicina rigenerativa devono mirare alla promozione del fenotipo M2

TERAPIE CELLULARI

SCAFFOLD BIOLOGI

A MACROPHAGE CENTRIC APPROACH
Nelle patologie vascolari, nel diabete, in alcune patologie infiammatorie, invecchiamento, la polarizzazione in M2, necessaria alla guarigione della lesione, NON AVVIENE.

L’infiammazione acuta si cronicizza, i macrofagi rimangono attivati in M1.
Ruolo fondamentale dei macrofagi nel wound healing

E’ stato dimostrato che la **deplezione sperimentale** dei macrofagi in modello animale blocca tutti i fenomeni riparativi. (1,2,3)

Inoltre la deplezione dei macrofagi è associata a angiogenesi difettosa, insufficiente differenziazione dei miofibroblasti, ridotta deposizione di collagene e mancata guarigione dell’ulcera (3)

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Peripheral Blood - MNC: Monociti/macrofagi e linfociti

- EMAZIE
- GLOBULI ROSSI
- MEGACARIOCITI PIASTRINE
- LEUCOCITI GLOBULI BIANCHI
- GRANULOCITI
  - NEUTROFILI 70%
  - BASOFILI 0.5-1%
  - EOSINOFILI 2-4%
  - MONOCITI 3-8%
  - LINFOCITI 20-40%
- AGRANULOCITI MONONUCLEATE

PB-MNC
Iniezioni intramuscolari di macrofagi nel trattamento delle ulceré difficili

<table>
<thead>
<tr>
<th>Autore</th>
<th>Titolo</th>
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<td>Zuloff-Shani, A. et al</td>
<td>Hard to heal pressure ulcers (stage III–IV): Efficacy of injected activated macrophage suspension (AMS) as compared with standard of care (SOC) treatment controlled trial</td>
<td>Arch Gerontol Geriatr Nov-Dec;51(3):268-72 (2010)</td>
</tr>
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</table>
Schock wave therapy

the application of stress to the cytoskeleton of the cells in the lesion (mechano-biological interaction) is able to produce a number of effects:

- the repression/depression of genes and changes in protein synthesis of a number of cells, including keratinocytes, fibroblasts, endothelial cells, and bone marrow stromal cells

- increase vascular endothelial growth factor (VEGF) and nitric oxide (NO) concentrations, which promote angiogenesis.

- reduction in the production of pro-inflammatory cytokines and to the increase of the proliferation of fibroblast induced by ESWT

Safety: a high safety standard for the technology.

These promising observations are unfortunately not paralleled by an adequate level of evidence generated via clinical trial. Two recent reviews on the subject are concordant in stating that according to the Cochrane standards, ESWT is not adequately supported by evidence.
Exposure to normobaric argon gas promotes multiple steps of the wound healing process.
- accelerated angiogenesis, associated with upregulation of pro-angiogenic Angiopoietin-1 and vascular endothelial growth factor (VEGF) signalling in vitro and in vivo.
- Treatment with argon enhanced expression of transforming growth factor (TGF)-β, early recruitment of macrophages and keratinocyte proliferation.
- pro-survival effect, inducing expression of cytoprotective mediators B-cell lymphoma 2 and heme oxygenase 1.

Argon was able to accelerate wound closure in a diabetic mouse model.
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Prevenzione recidive
Recidive ulcerative

Follow up di 3 anni post guarigione: 57% re-ulcerazione

Elevato rischio di re-ulcerazione nei pazienti con ulcera plantare, osteomielite, crp

Fattori rischio per re-ulcerazione

- Vibration perception threshold >25 V
- Presence of a preulcerative lesion
- Presence of peripheral artery disease
- Presence of a preulcerative lesion
- Presence of ulcer on the plantar foot
- Presence of previous ulcer at plantar hallux
- Presence of osteomyelitis
- Geriatric Depression Scale score ≥10
- C-reactive protein >15 mg/liter
- Glycated hemoglobin >7.5
- Loss of protective sensation
- No in-shoe peak pressure <200 kPa and footwear adherence >80%
- Barefoot dynamic peak plantar pressure (per 100 kPa)
- Day-to-day variation in step activity (per 100 strides)
- Day-to-day variation in step activity (per 100 strides)
- Cumulative duration of previous foot ulcers (per mo)

Odds Ratio

Diabetic Foot Ulcers and Their Recurrence
DG. Armstrong et al. NEJM 2017
Study protocol for a randomized controlled trial to test for preventive effects of diabetic foot ulceration by telemedicine that includes sensor-equipped insoles combined with photo documentation

Antao Ming, Isabell Walter, Ahmad Alhajjar, Martin Leuckert and Peter R. Mertens*
Warning signal: temperature differences $>1.5\, ^\circ C$ between left and right corresponding sensor sites

- **Level 0**: no warning signal
- **Level 1**: first warning signal
- **Level 2**: second warning signal after at least 4 hours
- **Level 3**: third warning signal after at least 20 hours
- **Level 4**: fourth warning signal after at least 32 hours

**Intervention Period**
- Foot relaxing and activities reduction for 5 days
- Photo documentation at the last day

**Patient’s interactive feedback**

**Reset alarm level**

**Legends:**
- Foot Inspection
- Photo Documentation
- Foot Relaxing & Activities Reduction
- Medical interpretation
Progetto Renewing Health
193 individuals were randomized to telemedical monitoring and 181 to standard care.

A cause-specific Cox proportional hazards model showed no difference in individuals monitored through telemedicine regarding wound healing (hazard ratio 1.11 [95% CI 0.87, 1.42], P = 0.42) or amputation (0.87 [0.54, 1.42], P = 0.59)

Higher mortality incidence in the telemedical monitoring group (8.68 [6.93, 10.88], P = 0.0001).
Subjects in telemedicine, as well as control groups had statistically similar:
healing time (43 vs 45 days; P = .83),
healing time ratio adjusted for age (1 vs 1.4; P = .1),
unhealed ulcers
loss to follow-up (3 of 20 vs 7 of 120; P = .13)
amputations (12 of 193 vs 14 of 182; P = .59)
ulcer healing (odds ratio = 0.86; 95% CI = 0.57-1.33; P = .53).

Subjects in the telemedicine group experienced a significantly higher mortality rate (8 of 193 vs 1 of 181; P = .0001) due to unexplained factors. No adverse events were attributed to using the telemedicine technology.
Con la loro bassa validità e affidabilità, le immagini dei telefoni cellulari non devono essere utilizzate come strumento diagnostico autonomo per la valutazione remota delle ulcere del piede diabetico. I medici che utilizzano le immagini del telefono cellulare nella pratica clinica quotidiana dovrebbero ottenere quante più informazioni aggiuntive possibili quando prendono decisioni terapeutiche basate su queste immagini ed essere cauti della bassa precisione diagnostica. Ulteriori metodi possono migliorare l'accuratezza diagnostica, ma questi devono essere ulteriormente sviluppati prima di poter essere utilizzati nella pratica clinica quotidiana.

Scientific reports 2017
The validity and reliability of remote diabetic foot ulcer assessment using mobile phone images. Van Netten et al.
Il nostro studio mostra che un efficace percorso di cura delle ferite per i pazienti con ulcere del piede diabetico dipendeva dalla competenza e dalle capacità professionali dei professionisti nella gestione delle ferite e dalla continuità delle cure.

Telemedicina può essere un supplemento.

An integrated wound-care pathway, supported by telemedicine, and competent wound management—Essential in follow-up care of adults with diabetic foot ulcers

Hilde Smith-Strøma,b, Int J Medical informatics 2016
Grazie per l'attenzione