Evidence-Based Solutions for the Treatment of Diabetic Foot Ulcers

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Evidence-Based Solutions for the Treatment of Chronic Wounds

Dr. Michael R. Zenn, MD, Professor and Vice President of Plastic Surgery at Duke University introducing Dr. Shawn Cazzell, DPM
Illuminating Evidence-Based Wound Care Management

Michael R. Zenn, MD, MBA Professor of Plastic Surgery Duke University Medical Center Durham, North Carolina

Chief Medical Officer, NOVADAQ
Introducing the NOVADAQ Wound Care Focus

- Assisting clinicians in improving patient outcomes by providing real-time, clinically relevant information
- Focusing on supporting and improving physician and patient education in chronic wound care diagnostics and therapies
- Partnering with specialists and their teams to improve the management of patients with acute and chronic wounds
Objective Assessment

Cost-Effective Solutions

DermACELL®
Advanced Decellularized Dermis
Introducing DermACELL AWM® for Chronic Wounds
A Partnership for People

Saving Lives.
Restoring Health.
Giving Hope.

Over 7,500 Lives Saved
Millions of Lives Restored
Over 500,000 implants distributed per year
More Than 50 Utility or Design U.S. Patents
TITLE: Healing Rates in a Multicenter Assessment of a Sterile, Room Temperature, Acellular Dermal Matrix Versus Conventional Care Wound Management and an Active Comparator in the Treatment of Full-Thickness Diabetic Foot Ulcers

AUTHORS: J Walters, S Cazzell, H Pham, D Vayser, A Reyzelman

JOURNAL: ePlasty

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- The Largest Multicenter, Randomized Control Trial to date for Human Acellular Dermal Matrices in Chronic Wounds
- A high-quality, rigorous study with increased emphasis on percent reduction vs. closure rate
- Statistically significant healing rates vs. conventional care
Shawn Cazzell, D.P.M., specializes in Podiatry and Foot and Ankle Surgery. Dr. Cazzell has advanced training in wound care and limb salvage techniques. Dr. Cazzell completed his residency training through St. Mary’s Medical Center, San Francisco. He attended California School of Podiatric Medicine at Samuel Merritt University, Oakland, CA. His undergraduate education was completed at UC San Diego.

Dr. Cazzell’s main areas of interest are in: advanced wound care, limb preservation and traumatic lower extremity reconstruction.

He is a Fellow of the American Professional Wound Care Association, Member of the Academy of Physicians in Wound Healing, and the Founder of the Limb Preservation Platform.
DermACELL AWM Webinar Objectives:

I. Introducing Dermacell AWM for the treatment of chronic wounds

II. Results and Rigor of the Largest, Multicenter, Randomized, Controlled Trial to date for Human ADM in Chronic Wounds

III. A Changing Paradigm: Dermacell AWM, A One-Application, Cost-Effective Solution

IV. Q&A
I. Introducing DermACELL AWM for Chronic Wounds
DermACELL AWM Clinical Applications

- **Dermacell AWM** is a technologically advanced *Acellular Dermal Matrix (ADM)* that is used to treat diabetic foot ulcers and other chronic non-healing wounds. Dermacell AWM is processed using Matracell® technology, which is a validated and patented process which renders the Dermacell AWM graft acellular, without compromising the biomechanical or desired biochemical properties of the graft. This process is gentle, yet robust enough to ensure the native scaffold, vascular channels, growth factors and proteins are preserved to assist in the healing of the wound.

- **Chronic wounds** often have an *excess of MMPs* (Matrix Metalloproteinases) and reduced growth factor activity. Together, these result in the degradation of the native ECM (*extracellular matrix*). For wound healing to occur, the balance between protease and growth factor activity has to be adjusted. Pre-clinical information available about the mode of action of an acellular matrix (such as Dermacell AWM) shows that it may assist in the following ways:
  - Acts as a scaffold to support cell in-growth and angiogenesis
  - Has receptors that permit fibroblasts to attach to the scaffold
  - Tissue granulation
  - Contains certain growth factors

3/17/2016
DermACELL AWM Indications for Use

WAGNER ULCER GRADING SYSTEM

Grade 0
- No Ulcer on High Risk Foot

Grade 1
- Superficial ulcer involving the full thickness but not underlying tissues

Grade 2
- Deep ulcer penetrating down to ligament and muscle, but no bone involvement or abscess formation

Grade 3
- Deep ulcer with cellulitis or abscess formation, often with osteomyelitis

Grade 4
- Localized gangrene

Grade 5
- Extensive gangrene involving the whole foot
DermACELL AWM Processing

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells and &gt; 97% DNA Removed</td>
<td>* Biocompatible*</td>
</tr>
<tr>
<td>Intact Acellular Framework</td>
<td>• Retains native growth factors, collagen and elastin**</td>
</tr>
<tr>
<td>Room Temperature Storage***</td>
<td>• Excellent handling. Minimal Prep Time</td>
</tr>
<tr>
<td>Strength</td>
<td>• Pull-out strength and load to failure are comparable to existing allograft products**</td>
</tr>
<tr>
<td>Sterile (10⁻⁶ Sterility Assurance Level)</td>
<td>• Maximized safety for patients</td>
</tr>
</tbody>
</table>

* ISO 10993-5 (Testing Results on File)
** Data on file at LifeNet Health, Virginia Beach, VA.
*** 15° – 30° C
Debridement
• Remove the obvious necrotic tissue, excessive bacterial burden and cellular burden of dead and senescent cells

Application
• Apply Dermacell AWM over the wound bed using sterile technique, with the reticular (dermal) side facing against the wound.

Fixation
• Dermacell AWM should be secured to the wound bed.
• Secure Dermacell AWM using Staples, Steri-strips® or Sutures
II. Results & Rigor of the Largest, Multicenter, Randomized, Controlled Trial to date for Human Acellular Dermal Matrices in Chronic Wounds
A Clinical Trial of DermACELL AWM for Diabetic Foot Ulcers

- **Title:**
  
  Healing Rates in a Multicenter Assessment of a Sterile, Room Temperature, Acellular Dermal Matrix Versus Conventional Care Wound Management and an Active Comparator in the Treatment of Full-Thickness Diabetic Foot Ulcers

- **Published:** February 2016 in ePlasty

- **Authors:**
  
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  Shawn Cazzell, DPM - Limb Preservation Platform, Valley Vascular Surgical Assoc.
  Hau Pham, DPM – Boston Univ. School of Medicine, Boston Medical Center
  Dean Vayser, DPM, FACFAS – ILD Research Center, San Diego CA
  Alexander Reyzelman, DPM, FACFAS – UCSF Center for Limb Preservation
Primary Endpoint:
- Assessment of complete re-epithelialization with no drainage or dressing requirements up to 16 weeks.
- In further stringency, an assessment of wound closure required confirmation at 2 consecutive study visits performed 2 weeks apart.
- The healing rate of wounds at 16 weeks and the percentage of reduction in wound size from baseline up to 16 weeks were also analyzed.

Rigor of Study: It is important to note that the study reported here uses a more rigorous healed ulcer criteria than other reports and as outlined in the FDA guidance on skin substitutes and the 2011 report from the AHRQ on the design of products to assist with wound healing. This study required that an ulcer must demonstrate complete healing on 2 consecutive visits to be considered healed rather than being considered healed at the first instance of wound closure.
Objective: The purpose of this 16-week, multicenter, randomized, controlled trial was to assess the healed ulcer rate of a human acellular dermal matrix, Dermacell AWM, compared with conventional care and a second acellular dermal matrix, GraftJacket, in the treatment of full-thickness diabetic foot ulcers.

Three treatment arms:
Study Methods:

Methods: One hundred sixty-eight patients were randomized into Dermacell AWM, conventional care, and GraftJacket treatment arms in a 2:2:1 ratio. Patients in the acellular dermal matrix groups received either 1 or 2 applications of the graft at the discretion of the investigator. A second application was allowed to be administered no fewer than 3 weeks but no longer that 12 weeks (weeks 3-12) after the first application. Weekly follow-up visits were conducted until the ulcer healed or the endpoint was reached.

- 2:2:1 Ratio
- 1 or 2 applications
- Weekly follow-up
Inclusion Criteria

- Inclusion criteria included:
  - The patient having a single, full-thickness target DFU with a **Wagner ulcer classification grade of 1 or 2**
  - A wound area of **1 cm² or greater and less than 25 cm²**
  - A wound depth of 9 mm or less
  - Adequate circulation to the affected area, defined as having at least one of the following criteria within the past 60 days:
    - **Transcutaneous oxygen** measurement at the dorsum of the foot **30 mm Hg or more**
    - **Ankle-brachial index** ranging from **0.8 to 1.2**
    - Or at least biphasic Doppler arterial waveforms at the dorsalispedis and posterior tibial arteries
Exclusion Criteria

- Exclusion criteria included:
  - Circulating **hemoglobin A1c exceeding 12%** within 90 days of the screening visit
  - Serum creatinine concentrations of 3.0 mg/dL or greater within 30 days before screening
  - Having had wound treatments involving **biomedical or topical growth factors** within 30 days before screening
  - Having undergone a **revascularization procedure** aimed at increasing blood flow in the target limb
  - Or receiving a **living skin equivalent** within 4 weeks before screening
# Patient Population

## Table 1. Comparison of demographic variables between treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Conv Care (N = 56)</th>
<th>D-ADM (N = 53)</th>
<th>GJ-ADM (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>57.1</td>
<td>58.0</td>
<td>58.7</td>
</tr>
<tr>
<td>Median</td>
<td>56.0</td>
<td>57.0</td>
<td>61.0</td>
</tr>
<tr>
<td>SD</td>
<td>10.9</td>
<td>13.1</td>
<td>10.4</td>
</tr>
<tr>
<td>Range</td>
<td>33–85</td>
<td>24–85</td>
<td>34–80</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>32.9</td>
<td>31.2</td>
<td>31.7</td>
</tr>
<tr>
<td>Median</td>
<td>31.5</td>
<td>31.4</td>
<td>32.2</td>
</tr>
<tr>
<td>SD</td>
<td>6.8</td>
<td>5.7</td>
<td>5.3</td>
</tr>
<tr>
<td>Range</td>
<td>18.6–50.2</td>
<td>19.9–44.6</td>
<td>23.4–44.2</td>
</tr>
<tr>
<td>Diabetes type*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>1 (1.8%)</td>
<td>1 (1.9%)</td>
<td>2 (8.7%)</td>
</tr>
<tr>
<td>Type 2</td>
<td>55 (98.2%)</td>
<td>51 (96.2%)</td>
<td>21 (91.3%)</td>
</tr>
</tbody>
</table>

*One patient in the D-ADM arm was considered prediabetic. Conv Care indicates conventional care; BMI, body mass index.
Table 2. *Approved dressings for patient care*

<table>
<thead>
<tr>
<th>Oil emulsion</th>
<th>Hydrogels</th>
<th>Foams</th>
<th>Gauze</th>
<th>Alginates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrity</td>
<td>Derma-Gel</td>
<td>Dermafoam</td>
<td>Kendall 4 x 4</td>
<td>Gentell</td>
</tr>
<tr>
<td>Invacare</td>
<td>Elasto-Gel</td>
<td>Optifoam</td>
<td>Curity Fluffs</td>
<td>Silvercel</td>
</tr>
<tr>
<td>Curad</td>
<td>Flexigel</td>
<td>Covidien</td>
<td>J &amp; J Gauze</td>
<td>Tagaderm High Gelling</td>
</tr>
<tr>
<td>Kendall Curity</td>
<td>Restore</td>
<td>Deroyal Polyderm</td>
<td>Kerlix Bandage Rolls</td>
<td>Tagaderm High Integrity</td>
</tr>
<tr>
<td>Shur-Conform</td>
<td>Carrasyn</td>
<td>Allevyn Foam</td>
<td>Kerlix Lite Bandage Rolls</td>
<td>Maxorb Extra</td>
</tr>
<tr>
<td>Adaptic</td>
<td>Vigilon</td>
<td>Aquacel</td>
<td>J &amp; J Kling Bandage Rolls</td>
<td></td>
</tr>
<tr>
<td>Systagenix</td>
<td>Kendall Amorphous</td>
<td>Aquacel AG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepitel</td>
<td>Sliverseal</td>
<td>Aquacel AQ Extra</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restore</td>
<td>Prisma</td>
<td>Optilock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bridal Veil</td>
<td>Promogran Matrix</td>
<td>Repara Hydrocellular Foam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kendall Telfa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Combined Study Results: Summary

Results:

- At 16 weeks, the Dermacell AWM arm had:
  - A significantly higher proportion of completely healed ulcers than the conventional care arm
    - 67.9% vs 48.1%; $P = .0385$
  - A non-significantly higher proportion than the GraftJacket arm
    - 67.9% vs 47.8%; $P = .1149$

- The Dermacell AWM arm also exhibited a greater average percent reduction in wound area than:
  - The conventional care arm
    - 91.4% vs 80.3%; $P = .0791$
  - The GraftJacket arm
    - 91.4% vs 73.5%; $P = .0762$

- The proportion of severe adverse events and the proportion of overall early withdrawals were similar among the 3 groups based on relative population size ($P \geq .05$).
Combined Results: Complete Healing at 16 weeks

At 16 Weeks, the Dermacell AWM arm had:

- A statistically significant higher proportion of completely healed ulcers than the conventional care arm (67.9% vs 48.1%; $P = .0385$)

- A non-significantly higher proportion than the GraftJacket arm (67.9% vs 47.8%; $P = .1149$)
At 16 weeks, the Dermacell AWM arm exhibited a greater average percent (%) reduction in wound area than:

- The conventional care arm (91.4% vs 80.3%; $P = .0791$)

- And the GraftJacket arm (91.4% vs 73.5%; $P = .0762$).
Significance of % Wound Reduction

D-ADM–treated ulcers demonstrated a greater reduction in wound size than both the conventional care and GJ-ADM arms at 12 weeks and 16 weeks

- Early prediction of wound healing
- Reversal of ulcer gradation using the Wagner scale
- Improvement in performance on foot pressure tests.\(^7\)\(^-\)\(^9\)
- Higher healed ulcer rates are critical to reducing the escalating cost of treating DFUs faced by both patients and the health care system.\(^1\)\(^1\) Amputation and hospitalization expenses averaged $18,084 for a minor procedure and $13,258 per stay,\(^1\)\(^2\) respectively, making early and effective treatment important to avoid spiraling costs.
## One-Application Data

<table>
<thead>
<tr>
<th># of patients</th>
<th>12 Week Wound Closure</th>
<th>16 Week Wound Closure</th>
<th>Healing Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-application</td>
<td><strong>Statistically significant</strong> higher rates of closure than conventional care and higher closure rate than 1-app GJ-ADM</td>
<td><strong>Statistically significant</strong> higher rates of closure than conventional care and strong but nonsignificant over GJ-ADM</td>
<td>The difference in % average wound area reduction was <strong>significant at weeks 3 and 6-15 vs. conv care</strong></td>
</tr>
</tbody>
</table>
One Application Data – 12 Weeks
One & Done
A Cost-Effective, One Application Solution

- Complete Healing at 12 Weeks
  - Dermacell AWM (40 Patients): 65%
  - Conventional Care (56 Patients): 41.1%
  - GraftJacket (16 Patients): 56.3%

- Percent (%) Wound Reduction
  - Dermacell AWM (40 Patients): 94.6%
  - Conventional Care (56 Patients): 71.6%
  - GraftJacket (16 Patients): 88%

A single application of Dermacell AWM demonstrated **Statistical Significance** over the Conventional Care arm in both Complete Healing \( (P=0.0203) \) and % Wound Reduction \( (P=0.0004) \) at 12 Weeks
Integra IDRT – Founder Study*

- It should also be noted that of the 53 D-ADM patients, 40 patients received 1 application and 13 patients received 2 applications of D-ADM.

- In contrast, Integra IDRT patients received as many as 15 applications.

This study required that an ulcer must demonstrate **complete healing on 2 consecutive visits** to be considered healed rather than being considered healed at the first instance of wound closure.

While this analysis likewise relied on the disposition by the respective principal investigators of whether a wound was healed, we also sought the opinion of a **blinded third-party adjudicator**. At the 12-week primary endpoint, more than 87% agreement in assessment of complete healing was obtained between the blinded adjudicator and the principal investigator.

The more stringent healed ulcer criteria should be taken into account when comparing the healing rates of this study with others that have been published, especially those before 2011. **Several ulcers in this study had 100% wound size reduction** at a given week but were not considered healed because of these criteria.
Preoperative diabetic foot ulcer at baseline with an area of 6.4 cm² after debridement.

Wound was completely closed at 12 weeks following treatment with a single application of D-ADM.
III. A Changing Paradigm: DermACELL AWM as a One-Application, Cost-Effective Solution
As a leader in the Wound Care field, your ultimate goal is to provide evidence based, high-quality and fiscally responsible treatments to your patients.

Dermacell AWM provides a cost-effective, one-application treatment solution for patients with chronic lower extremity ulcerations. In the largest and most rigorous randomized, controlled trial (RCT) to date for human ADM products in chronic wounds, Dermacell AWM demonstrated superior rates of healing and wound closure in Diabetic Foot Ulcers than conventional care and an active comparator. Unlike many other human tissue products, Dermacell AWM can be stored for up to 4 years in ambient temperature, does not require special handling and is fast and easy to apply.

• One Application
• Cost-Effective
• Rigorous Level I Clinical Data
Putting It All Together

The Future of Wound Care Management

Dermacell AWM

The Mission of NOVADAQ Wound Care

LUNA Case Manager

The Future of Wound Care Management
References

1. LNH Sterile Decellularized Dermis IFU 63-0050-01
2. Acellular Matrices For The Treatment Of Wounds; International Consensus; Wounds International Enterprise House; 2011
3. DermACELL Application Instructions 68-40-148.00
4. DermACELL Application Guide 68-50-237 .01
Questions?

- Please send your questions to: Clinical.Education@WoundCareJobs.com

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