RENAL DISEASE, DIABETES & LOWER EXTREMITY COMPLICATIONS...WHAT WE KNOW & WHAT WE CAN DO TO BENEFIT OUR PATIENTS
OBJECTIVES

• Understand the significant connection between diabetes, renal disease & lower extremity complications, to include diabetic foot ulcers & amputation.

• Understand the significant morbidity & mortality that these patients experience compared to diabetic patients without renal disease.

• Understand the options that exist within a nephrology practice or dialysis facility in treating or referring patients with ulcers as well as the clinical outcomes.
WHAT WE KNOW!
Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

**Obesity (BMI ≥30 kg/m²)**

- **1994**
- **2000**
- **2013**

![Maps showing obesity prevalence from 1994 to 2013](image)

- No Data
- <14.0%
- 14.0%–17.9%
- 18.0%–21.9%
- 22.0%–25.9%
- ≥26.0%

**Diabetes**

- **1994**
- **2000**
- **2013**

![Maps showing diabetes prevalence from 1994 to 2013](image)

- No Data
- <4.5%
- 4.5%–5.9%
- 6.0%–7.4%
- 7.5%–8.9%
- ≥9.0%

2017 CDC Data Diabetic Foot Ulcers (DFUs) & Diabetic Foot Infections (DFIs) Rank #1 & #2

- 5.6 billion ambulatory care visits between 2007-2013
- 6.7 million DFUs or DFIs¹

**RESULTS**

- Chronic conditions & associated direct Emergency Department (ED)/inpatient (IP) admission hazard ratios
  - *DFIs – 6.7 times higher*
  - *DFUs – 3.4 times higher*
  - CHF-2.56
  - CVD-1.57
  - IHD-1.54
  - Cancer-1.36
  - Renal Failure-1.21
  - Diabetes-1.12
  - Obesity-1.01

¹Skrepnek, GH, Mills, JL, Lavery, LA, Armstrong, DG. Health Care Service and Outcomes Among an Estimated 6.7 Million Ambulatory Care Diabetic Foot Cases in the U.S. Diabetes Care May 11, 2017
The Cost is Prohibitive

- Mean one year cost from a health care public payer perspective was $44,200 for diabetic foot ulcer (DFU), $15,400 for pressure ulcer (PU) and $11,000 for leg ulcer (LU)\(^1\)
- 33% of the cost of diabetes directly linked to the care of lower extremity complications\(^2,3\)
- Inpatient admissions account for 74-77% of total costs attributed to lower-extremity complications in diabetes\(^4,5\)

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\(^1\)Chan; “Cost-of-illness studies in chronic ulcers: a systematic review.” Journal of Wound Care Vol 26. No.4, April 2017
\(^3\)Driver VR, Lavery LA. The costs of the diabetic foot: The economic case for the limb salvage team. J Vasc Surg
Prevalent Medicare fee-for-service patient counts and spending for beneficiaries aged 65 and older, by Diabetes Mellitus (DM), Congestive Heart Failure (CHF), and/or CKD, 2014

<table>
<thead>
<tr>
<th>Category</th>
<th>U.S. Medicare Population</th>
<th>Total Costs (millions, U.S. $)</th>
<th>PPPY Costs (U.S. $)</th>
<th>Population (%)</th>
<th>Costs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>24,496,020</td>
<td>$254,356</td>
<td>$10,803</td>
<td>100.00</td>
<td>100.00</td>
</tr>
<tr>
<td>With CHF or CKD or DM</td>
<td>8,140,540</td>
<td>$130,220</td>
<td>$17,013</td>
<td>33.23</td>
<td>51.20</td>
</tr>
<tr>
<td>CKD only (- DM &amp; CHF)</td>
<td>1,023,220</td>
<td>$15,109</td>
<td>$15,673</td>
<td>4.18</td>
<td>5.94</td>
</tr>
<tr>
<td>DM only (- CHF &amp; CKD)</td>
<td>4,093,320</td>
<td><strong>$47,846</strong></td>
<td>$12,116</td>
<td>16.71</td>
<td>18.81</td>
</tr>
<tr>
<td>CHF only (- DM &amp; CKD)</td>
<td>893,760</td>
<td>$16,955</td>
<td>$20,733</td>
<td>3.65</td>
<td>6.67</td>
</tr>
<tr>
<td>CKD and DM only (- CHF)</td>
<td>847,220</td>
<td>$14,856</td>
<td>$18,610</td>
<td>3.46</td>
<td>5.84</td>
</tr>
<tr>
<td>CKD and CHF only (- DM)</td>
<td>340,300</td>
<td>$8,829</td>
<td>$30,395</td>
<td>1.39</td>
<td>3.47</td>
</tr>
<tr>
<td>DM and CHF only (- CKD)</td>
<td>515,500</td>
<td>$12,599</td>
<td>$26,758</td>
<td>2.10</td>
<td>4.95</td>
</tr>
<tr>
<td>CKD and CHF and DM</td>
<td>427,220</td>
<td>$14,025</td>
<td>$38,561</td>
<td>1.74</td>
<td>5.51</td>
</tr>
<tr>
<td>No CKD or DM or CHF</td>
<td>16,355,480</td>
<td>$124,136</td>
<td>$7,812</td>
<td>66.77</td>
<td>48.80</td>
</tr>
<tr>
<td>All CKD (+/- DM &amp; CHF)</td>
<td>2,637,960</td>
<td>$52,819</td>
<td>$21,857</td>
<td>10.77</td>
<td>20.77</td>
</tr>
<tr>
<td>All DM (+/- CKD &amp; CHF)</td>
<td>5,883,260</td>
<td><strong>$89,327</strong></td>
<td>$16,003</td>
<td>24.02</td>
<td>35.12</td>
</tr>
<tr>
<td>All CHF (+/- DM &amp; CKD)</td>
<td>2,176,780</td>
<td>$52,409</td>
<td>$26,975</td>
<td>8.89</td>
<td>20.60</td>
</tr>
<tr>
<td>CKD and DM (+/- CHF)</td>
<td>1,274,440</td>
<td>$28,882</td>
<td>$24,854</td>
<td>5.20</td>
<td>11.36</td>
</tr>
<tr>
<td>CKD and CHF (+/- DM)</td>
<td>767,520</td>
<td>$22,854</td>
<td>$34,935</td>
<td>3.13</td>
<td>8.99</td>
</tr>
<tr>
<td>DM and CHF (+/- CKD)</td>
<td>942,720</td>
<td>$26,625</td>
<td>$31,902</td>
<td>3.85</td>
<td>10.47</td>
</tr>
</tbody>
</table>

2016 Annual Data Report, Vol 1, CKD, Ch 6
Association Between Renal Failure and Foot Ulcer or Lower-Extremity Amputation in Patients With Diabetes

- **OBJECTIVE**: Evaluate the association between foot ulcers (DFU) and lower-extremity amputation (LEA) and CKD in patients with diabetes.

- **RESEARCH DESIGN AND METHODS**: This was a retrospective cohort study of 90,617 individuals enrolled between 2002 and 2006 who were at least 35 years of age, had a history of diabetes, and were cared for in general practice.

- **RESULTS**:
  - 378 patients had an LEA and 2,619 had a DFU
  - Reference group (group 1 [eGFR 60 ml/min per 1.73 m2 ])
  - For Development of DFU, the hazard ratio (HR) for group 2 (eGFR 30 and 60 ml/min per 1.73 m2 ) was **1.85 times higher** (95% CI 1.71–2.01) and for group 3 (eGFR 30 ml/min per 1.73 m2 ) was **3.92 times higher** (3.23–4.75) (all P < 0.001).

- **SIGNIFICANCE**:
  - Prevalence of a DFU is likely to be 2-4 times higher than the standard diabetic population

General Population vs Dialysis: foot complications

**General population**
- Ulcer incidence 2-7%
- Amputation incidence 1% - 1 per 100
- Hospitalization 20%

**Dialysis population**
- Ulcer incidence 20%
- Amputation incidence 10% - 10 per 100
- Hospitalization 38%

Ndip: Diabetes Care 2010
Lavery, Diabetes Care 2004
Peters, Lavery, Diabetes Care, 2001
Uciolli, Diabetes Care 1995
Lavery LA: The impact of renal disease on survival after amputation. Diabetes Care 2010
## Dialysis: impact on amputation level

<table>
<thead>
<tr>
<th>Amputation Level</th>
<th>Dialysis N=128</th>
<th>Chronic Kidney Disease N=389</th>
<th>No Renal Disease N=526</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot</td>
<td>28.9%</td>
<td>40.4%</td>
<td>53.8%</td>
</tr>
<tr>
<td>BKA</td>
<td>43.8%</td>
<td>35.7%</td>
<td>23.9%</td>
</tr>
<tr>
<td>AKA</td>
<td>27.3%</td>
<td>27.0%</td>
<td>19.2%</td>
</tr>
</tbody>
</table>

Lavery LA: The impact of renal disease on survival after amputation. Diabetes Care 2010
## Dialysis: death after amputation 2010

<table>
<thead>
<tr>
<th>Survival</th>
<th>Dialysis</th>
<th>Chronic Kidney Disease</th>
<th>No Renal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year</td>
<td>49.2%</td>
<td>23.4%</td>
<td>14.4%</td>
</tr>
<tr>
<td>2 Year</td>
<td>57.8%</td>
<td>32.9%</td>
<td>23.0%</td>
</tr>
<tr>
<td>3 Year</td>
<td>71.1%</td>
<td>43.7%</td>
<td>26.8%</td>
</tr>
<tr>
<td>5 Year</td>
<td>82.8%</td>
<td>59.1%</td>
<td>39.7%</td>
</tr>
</tbody>
</table>

Lavery LA: The impact of renal disease on survival after amputation. Diabetes Care 2010
The impact of renal disease on survival after amputation: Risk factors

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.031</td>
<td>1.023 – 1.039</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKDα</td>
<td>1.465</td>
<td>1.213 – 1.771</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hemodialysisα</td>
<td>3.912</td>
<td>3.071 – 4.982</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Below-knee amputationβ</td>
<td>1.669</td>
<td>1.355 – 2.055</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Above-knee amputationβ</td>
<td>2.672</td>
<td>2.137 – 3.341</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

α: reference group for comparison is ‘no renal disease’, β: reference group for comparison is ‘foot amputation’. Hazards ratios are estimated using \( \text{Exp}(B) \).

Lavery LA: The impact of renal disease on survival after amputation. Diabetes Care 2010
Relevant ESCO Quality Measures (QM’s)

Chronic Disease Management

• **Diabetes Care: Foot Exam**
• **Diabetes Care: Eye Exam**
• **Rate of Lower Extremity Amputation Among Patients with Diabetes**
• **Diabetic Retinopathy: Communication with the Physician Managing Ongoing Diabetes Care**

“Why don’t you do foot exams?”

- “Afraid of what I might find”
- “If I find something, I may need to do something”

Are those the right answers?
Diabetic Foot Care Management Model is Effective

- MCO in South Texas over 28 months
  - 47% reduction in amputations
  - 38% reduction in hospitalizations
  - 22% reduction in length of stay
  - 70% reduction in SNF admissions

WHAT CAN WE DO!
Traditional Prevention Strategies

• Risk Assessment
• Education - “do’s-don'ts” - Self-care practices
• Protective shoes – insoles
• Regular foot assessment
Patient Selection Criteria for Advanced Therapies

Sheehan et al. “Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial.” Diabetes Care. 2003;26:1879-1882.
EpiFix®

- Dehydrated human amnion/chorion (dHACM) allograft
- Processed using proprietary PURION Process
- Applications in acute & chronic wounds
- Available in multiple sizes
- Reimbursement coverage in all MACs and select payers
Unique Characteristics of EpiFix

• Easy Logistics
  • Standard shipping
  • Ambient condition storage for 5 years
• Ease of Use
  • Handling characteristics
  • Embossed
• Testing/ Sterilization
  • Living donor testing
  • Terminal sterilization
PURION Processed dHACM
Bilayer Laminate Composed of Amnion and Chorion

- Cells preserved
  - Not ‘acellular’
  - Structurally intact
  - Bioactive

- Extracellular matrix intact
  - Collagens I, III, IV, V, VII
  - Laminin, fibronectin, proteoglycans

- Biological activity preserved
  - Growth factors, cytokines, chemokines

H&E – cell nuclei stained dark blue
Biological Activity of PURION Processed dHACM

1-8

Fibroblasts
Endothelial Cells
Hematopoietic Stem Cells
Bone Marrow Mesenchymal Stem cells
Adipose Tissue-Derived Stem Cells
Healthy & Diabetic Type I, II

Proliferation
Migration
Biosynthesis

Publications on the bioactivity in PURION Processed dHACM

Organizing New Tissue Building Blocks

- dHACM is a Stem Cell Magnet™
  - *In vivo* mouse study: significantly more mesenchymal stem cell migration compared to Sham at day 7
  - *In vivo* parabiosis study: Recruited Hematopoietic Stem Cells – Results show increased progenitor cell engraftment intragraft (c) and compared to control (d)

Diabetic Foot Ulcer Randomized Clinical Trial (RCT) Outcomes

- EpiFix with Standard of Care vs. Standard of Care alone
- 92% healed in 6 weeks compared to 8% for control
- Average of 2.5 grafts to closure

<table>
<thead>
<tr>
<th>Ulcers healed</th>
<th>SOC (n=12)</th>
<th>EpiFix (n=13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Weeks</td>
<td>0 (0%)</td>
<td>10 (77%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 Weeks</td>
<td>1 (8%)</td>
<td>12 (92%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

DFU Retrospective Crossover Study

EpiFix mean time to complete healing = 4.2 ± 3.1 weeks

(p = 0.003 Treatment vs. Control at Week 2)

Application of EpiFix

Size EpiFix using sterile instruments and dry gloves.

Trim EpiFix to cover entire wound. It is acceptable to overlap margins by 1mm. Fenestrate if needed.

EpiFix will self-adhere to wound site. Reposition if necessary. Hydrate with sterile saline solution if necessary. Use suture material or tissue adhesive to fixate EpiFix if desired.

Cover with a non-adherent contact layer. If possible, do not disturb.

Use Steri-Strips™ if necessary.

Use appropriate moisture management dressings.

EpiFix is compatible with offloading, compression, & negative pressure therapies.
Patients cannot participate in their own foot care?
MiMedx can provide valuable information to assist with wound care treatment options!

1. Wound care treatment support information:
   a) **Treatment**
      • We provide the support & information if you decide to set-up wound care treatment as part of your practice.
   b) **Referral**
      • We can provide information on existing advanced wound care treatment facilities to improve outcomes in patients with chronic lower extremity wounds.
Summary

- Patient population
- Severe disease... High risk
- High level of amputation
- High mortality
- Opportunity to treat pre-dialysis patients in the nephrology office
- Potential to treat ESRD patients in the dialysis center
- Referral to advanced wound care network in local geography
Questions???
THANK YOU
FOR MORE INFORMATION
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SMCCORMACK@MIMEDX.COM