Collagen Dressings

or:
The Great Coverup

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• Objectives:
  – Proteins vs Cells
  – Structure of the dermis
  – Structure of collagen
  – Mechanism of collagen dressings
  – Types of collagen dressings
    • Acellular
    • Biologic or Cellular
  – Research on collagen-containing dressing

• Disclaimer:
  – Not an exhaustive review of all collagen-containing dressings
  – Conclusions are mine alone, and alternate conclusions could be a good topic for your DNP project or PhD thesis
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• Reviews:
  – Just a lot of numbers!
  – I wanted to know what collagen dressing to use!
  – I didn’t like that the product names weren’t used!

Biochemistry Review!

• Biochemistry review!
• Amino acids consist of Carbon atom with amino group (NH2), Carboxyl group (COOH), a hydrogen atom, and a side chain, which can be variable
• Sometimes called residues
• Biochemistry review!
  – Peptides consist of short chain of amino acids (20 kinds of amino acids)
  – Polypeptides consist of a long peptide chain

• Biochemistry review!
  • Protein:
    – A building block of the cell (but NOT A CELL!)
    – A structural hierarchy of strings of amino acids which comprise a protein
    – The STRUCTURAL SHAPE of the protein helps determine it function

• Protein structures:
  – Primary: The linear sequence of amino acids
  – Secondary: The folding into a secondary structure
    • Alpha helix
    • Beta sheet
• Collagen is a protein with a helix structure:
  – A triple alpha helix
  – Which then assemble into fibrils
  – Which then assemble into fibers


• Collagen is:
  – A protein molecule (not a cell)
  – 2/3 of the dry weight of skin
  – 1/3 of the protein in humans
• What does the body do with collagen?
  – Tendon
  – Ligaments
  – In our case, is part of the composition of the ECM (extracellular matrix) which makes up the DERMIS

• ECM (extracellular matrix)
  – Secreted proteins that provide structural support of tissue, secreted by fibroblasts
    • Collagen
      – Types 1, 2, and 3 (Fibular collagens)
      – Type 4 (sheet type)
    • Laminin
    • Elastin

• Skin:
  – Epidermis
    • Cells are building blocks
    • Cells densely packed
  – Dermis
    • Cells are supported by ECM, lower density
In dermis, cell density (Fibroblasts) is sparse, supported by collagen in the ECM.

- Fibroblasts in the dermis synthesize and maintain:
  - Collagen
  - Elastin
  - Hyaluronic acid
  - MMPs
  - TIMPs


- Maintenance of the ECM
  - Regulation of the ECM
  - TIMPs
    - Tissue inhibitor of metalloprotease
  - MMPs
    - Matrix metalloproteases
  - Proteins, not cells

ECM maintenance is a delicate dance between MMPs and TIMPs.

- MMP functions in wound healing
  - Removal of damaged ECM
  - Help enable angiogenesis in wound by breaking down basement membrane around capillaries
  - Contraction of scar tissue
  - Remodeling of scar tissue

“Groot”

“Protein MMP1 PDB 1ayk” by Emw - Own work. Licensed under CC BY-SA 3.0 via Wikimedia Commons - http://commons.wikimedia.org/wiki/File:Protein_MMP1_PDB_1ayk.png#/media/File:Protein_MMP1_PDB_1ayk.png
• Collagen dressings:
  – Acellular: are usually less expensive.
    • Sometimes called “dermal template”
    • “Wound Matrix”
    • “Scaffold”
    • Collagen from animal sources
  – Cellular or Biologic
    • May contain fibroblasts, epithelial cells, growth factors, and cytokines
    • Collagen from human tissue

• Sources of collagen
  – Bovine
  – Ovine
  – Porcine
  – Human

• Acellular
  – Promogran, Prisma, and Fibracol
  – Oasis
  – Endoform

• Cellular or Biologic
  – Dermagraft
  – Apligraf
  – Theraskin
  – Epifix
• Acellular collagen dressings:
  – Processed to removes cells
    • Leaving only the collagen matrix
    • May degrade the structure of the collagen
    • Sterilized
  – More than just trying to replace missing human collagen
    • Does NOT replace human collagen permanently
    • Provides a TEMPORARY “scaffold” or matrix
    • A “sacrificial substrate” to bind MMPs, which then break down the dressing, and not the wound collagen

• Collagen processing
  • “Claim to fame”
    – Collagen/ORC denatured
    – Vs Minimally processed

• Mode of action of collagen dressing
  – Recruit fibroblasts (chemotaxis)
  – Promotes fibroblast attachment to the scaffold
  – Binds MMPs
  – Provides structure for wound healing
  – May stimulate angiogenesis
  – May provide growth factors

• So let’s examine some acellular collagen dressings first
  — And will review some of the evidence

• But first...
  — Mary’s pet peeve:
  — “I was taught”...

  "I'M DRAWING A LIST OF MY PET PEEVES."

• Research
  — Not big money in wounds
  — Many studies sponsored by manufacturer
    • Most are for DFUs or venous ulcers
  — Small n
  — Research designs less rigorous (least to most)
    • Case study or series
    • Retrospective
    • Prospective
    • Randomized, controlled
• Research
  – There's no money in wounds!

• Research
  – Most studies seem to compare dressing to “standard of care”
    • Debridement
    • Offloading
    • Wet to dry (ugh)
  – More recently:
    • Comparative effectiveness research
      – 2009 ACA
      – Compares two treatments for effectiveness in clinical arena
• Comparative Effectiveness Research
  – ACA established PCORI
  • Patient-centered Outcomes Research Institute
    – Funded by a tax on Medicare and private health insurance companies
  – Hoping to find most effective treatments through research
  – Some find this controversial
    • A slippery slope to health care rationing?

• Promoran: Collagen/ORC 45% ORC (Oxidized regenerated cellulose)
  – 55% collagen
• Prisma: Collagen/ORC/silver 44% ORC/55% collagen/1% silver
• Fibracol: Collagen/alginate
  – 90% collagen/10%
• Collagen source:
  – Bovine split hides from Australia

• These are “early” dressings
  – Approved by the FDA in the 90’s
  – Are less expensive
  – Evidence:
    • Difficult to compare
    • Small n
    • Some studies just tested the quantity of MMPs in the dressing, not wound healing
    • No big insurance hurdles
<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Results</th>
<th>More results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>Donaghue et al.</td>
<td>DFUs: 10 collagen/alginate 3 saline gauze</td>
<td>78% had 75% or greater size reduction vs 60%</td>
</tr>
<tr>
<td>2002</td>
<td>Veves, et. al</td>
<td>DFUs: 138 collagen/ORC 138 saline gauze</td>
<td>After 12 weeks: 37% healed vs 18.3% (not stat sig)</td>
</tr>
<tr>
<td>2013</td>
<td>Gottrop, et. al RCT</td>
<td>DFUs: 24 collagen/ORC/silver 14 foam</td>
<td>&gt;50% wound area reduction: 79% vs 43% (p&lt;0.035)</td>
</tr>
</tbody>
</table>


- Hey! What’s this p-value thing?
  - A statistic
  - Indication that the answer to the research question has a significant result
  - Usually p <= 0.05 is considered significant

- Oasis (acellular)
  - Approved by FDA in 2006
  - Described as both a “scaffold” and a “matrix”
  - Collagen source is small intestine submucosa of pigs (SIS)
  - Includes growth factors and other dermal proteins (not cells)
  - Comes in dry sheets
• Oasis Evidence
  – 2005: Randomized trial
  – Diabetic foot ulcers
  – Oasis vs Regranex gel (becaplermin)
  – N=73
  – 49% closure in 12 weeks with product O
  – 28% with becaplermin
  – p = 0.055 (almost statistically significant)

• Oasis Evidence
  – 2010: Randomized trial (UK)
  – Some funding from manufacturer (editorial assistance)
  – N=50, ABI >=0.6, no infection
  – Mixed venous/arterial LE ulcers
  – Compared to “standard of care” (petrolatum gauze)
  – 80% closure in 8 weeks with product O
  – 65% with “standard of care”


• Endoform (acellular)
  – Approved by FDA in 2010 (New Zealand)
  – Collagen source is sheep
    • Propria submucosa of ovine forestomach tissue
  – 90% intact collagen, 10% secondary ECM components
  – Inexpensive
  – Comes in dry sheets
• Endoform
  – “Dermal template” (acellular)
  – Approved by FDA 2010
  – Referred to as an “intact collagen ECM”
  – Different processing than other acellular collagens
  – 90% collagen, 10% other “ECM components”

• Endoform (acellular)
  – Now being distributed by large wound dressing company
  – Evidence:
    • Scant due to new dressing
    • 2 case series found

• Research #1:
  – Prospective case series
  – n=19 patients, 24 wounds
  – Venous, arterial, DFUs, and incisional wounds
  – Debridement and compression (for VLUs)
  – 50% of wounds closed at 12 weeks

• Research #2:
  – Retrospective case series
  – n=14 patients, 23 wounds
  – Venous ulcers
  – Debridement and compression
  – 97% of wounds closed at 12 weeks vs:
    • 71% pig SIS
    • 46% standard of care


• Issues?
  – No control groups
  – n is small
  – Study #1 had a wide assortment of wounds
  – Both studies acknowledge need for controlled studies with large n

• Biologic collagen dressings:
  – Have the properties of the acellular dressings AND MORE!
  – May contain:
    • Collagen
    • Fibroblasts
    • Growth factors
    • Cytokines
    • Keratinocytes
    • Epithelial tissue
• Biologic collagen dressings
  – Some have viable human cells
  – Come in a variety of media
    • Frozen
    • Dry sheets
    • In petri dish
  – More expensive
  – Less applications
  – More requirements from insurers

• Cytokines
  – Low molecular weight proteins
  – Act as signaling agents
    • Cellular communication
    • Bind to receptor on cell
    • Triggers “second messenger” within cell
    • Directs the cell to do something
      • Produce/secrete protein
      • Alter membrane
      • Proliferate
    – Sometimes also considered growth factors

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Function</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-alpha</td>
<td>Collagen synthesis</td>
<td>MMP regulation</td>
</tr>
<tr>
<td>IL-1</td>
<td>Signals presence of an injury</td>
<td>Attracts neutrophils to wound to clean up</td>
</tr>
<tr>
<td>IL-2, IL-6</td>
<td>Fibroblast infiltration</td>
<td></td>
</tr>
<tr>
<td>IL-4</td>
<td>Inhibits TNF</td>
<td></td>
</tr>
</tbody>
</table>

• **Growth factors**
  
  – **Proteins**
  
  – **Function**
    - Stimulate cell proliferation
    - Stimulate cell differentiation
  
  – **Mechanism**
    - Like cytokines, bind to receptor on cell membrane
<table>
<thead>
<tr>
<th>Growth factor</th>
<th>Full name</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGF</td>
<td>Epidermal growth factor</td>
<td>53 amino acid protein Normal cell growth, wound healing</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
<td>Attracts neutrophils to wound to clean up</td>
</tr>
<tr>
<td>PDGF</td>
<td>Platelet derived growth factor</td>
<td>Secreted by platelets and other cells</td>
</tr>
<tr>
<td>FGF</td>
<td>Fibroblast growth factor</td>
<td>Proliferation of fibroblasts, angiogenesis, endothelial cells, and others 100 + amino acids</td>
</tr>
</tbody>
</table>


- **Biologic Product Dermagraft**
  - Approved by FDA in 2001 for DFUs
  - Grown from neonatal foreskin tissue fibroblasts
  - Supplied frozen, must be thawed

- **Biologic Product Dermagraft**
  - Culture of neonatal dermal fibroblasts onto a bioabsorbable mesh scaffold.
  - Cryopreserved
  - Fibroblasts proliferate to fill the scaffold
    - Secrete collagen
    - Growth factors
    - Cytokines
    - Contains metabolically active living cells.
• Dermagraft Evidence
  – 2003 RCT by Marston, et al
    • 130 got Dermagraft, 115 got "conventional therapy".
    • At week 12, 30% of Dermagraft patients had full wound closure vs.
      18.3% of control
  – 2013 RCT by Harding, et al (from the UK) for venous
    • Product D + 4 layer compression for VLUs vs compression alone
    • 186 in Dermagraft group, 180 in control group
    • At 12 weeks:
      – 34% complete wound healing vs 31% control
      – If ulcers < 12 months duration, 52% vs 37%


• Apligraf
  – Venous ulcers and DFUs only
  – Approved by FDA:
    • 2000 for DFUs
    • 1998 for venous ulcers
  – From neonatal foreskins in a bovine type 1 collagen matrix
  – Neonatal dermis develops, with neonatal epidermis to cover

• Biologic Product Apligraf
  – 2 layers
    • Lower layer is bovine type 1 collagen and human fibroblasts
    • Top layer is human epidermal cells
      – From human keratinocytes
    • These are living cells
  – Supplied in petri dish
  – Not frozen, but has a shelf life
• **Apligraf Evidence for VLUs**
  - 1998 prospective, randomized, multicenter trial
  - Apligraf (n=146) with compression vs standard of care (compression only) (n=129)
  - 6 month follow up:
    - 63% Apligraf complete wound closure
    - 49% control group
    - p=.003


• **Apligraf Evidence for DFUs**
  - 2001 prospective, randomized, multicenter trial
  - P Apligraf (n=112) vs standard of care (saline gauze) (n=96)
  - For DFUs
  - 12 week follow up:
    - 56% product A complete wound closure
    - 38% control group


• **Comparative research**
  - Apligraf vs Oasis
  - 2014 study
  - Retrospective analysis, 2010-2012
    - Venous ulcers
    - Data from WoundExpert
    - 1451 wounds (1187 patients) got product A
    - 350 wounds (302 patients) got product O
    - Product A: Avg # treatments significantly lower than Product O (2.3 vs 3.3)
    - Estimated incidence of wound closure at week 12: Product A (31%) vs Oasis (26%)
    - At week 24: 50% vs 41%
• Comparative research
  – Apligraf vs Oasis
    • Good n, however...
    • No reliable measure whether compression was used or not
    • Funded by Apligraf
    • Subjects may have also been getting NPWT or HBOT, were not excluded from study
    • Apligraf may be marginally better at obtaining wound closure

• Amnion/Chorion containing Dressings
  – Amnion inner membrane
  – Chorion is outer membrane
  • Amnion contains:
    – Cytokines
    – Hyaluronan
    – Growth factors

• Biologic Epifix
  – Approved by FDA in 2013
  – Dehydrated human amnion/chorion allografts (dHACM)
  – Supplied in dry sheets
  – DFUs and in some areas and some insurance plans, VLUs
• **Biologic Epifix**
  
  – Contains human dermal collagen, growth factors, cytokines
  
  • PDGF, TGF, FGF, EGF, PLGF
  
  • IL-4, 6, 8, & 10
  
  • TIMP 1, 2, & 4
  
  • Native ECM
  
  • Both amnion and chorion layers
  
  • Non-living cells


• **Epifix Evidence**

  • N = 25 DFUs
  
  • 13 Product Ex, 12 Standard of care (silver gel or silver hydrofiber)
  
  • Funded by Mimedx (Epifix manufacturer)
  
  • At 6 weeks of treatment
    
    – 92% complete wound closure product EX
    
    – 8% (standard of care)
    
    – Subjects whose wounds failed to reduce by 50% after 6 weeks were exited


• **Epifix Evidence**

  • N = 84 VLUs
  
  • 53 Epifix + compression, 31 compression alone
  
  • Funded by MiMedx (Epifix)
  
  • At 4 weeks of treatment
    
    – 62% of Epifix group showed > 40% wound closure
    
    – 32% of compression group showed > 40% wound closure
    
    – 6 patients in Epifix group had complete wound closure
    
    – 4 patients in the compression group had complete wound closure

• Comparative research
  – Epifix vs Apligraf
    • N = 60 DFUs
    • Good design
    • 20 Epifix, 20 Apligraf, 20 collagen/ORC
    • Funded by MiMedx
    • At 6 weeks of treatment
      – 95% complete wound closure Epifix
      – 45% for Apligraf
      – 35% collagen/ORC
      – Subjects whose wounds failed to reduce by 50% after 6 weeks were exited


• Comparative research
  – Apligraf vs Epifix
    • N = 226 DFUs
    • 163 Apligraf, 63 Epifix
    • Funded by Organogenesis
    • Data culled from WoundExpert
    • Median time to closure
      – 13.3 weeks for Apligraf
      – 26 weeks for Epifix


• Biologic Theraskin
  – From donated human tissue (cadaver)
  – Contains:
    • Fibroblasts
    • Keratinocytes
    • ECM (collagen)
  – Can be used on any wound
    • Not just DFUs or VLUs
  – Shipped on dry ice
• Theraskin Evidence
  — 2011 retrospective study, both DFUs and VLUs
  — N=188 (134 VLUs, 54 DFUs)
  — By 12 weeks
    • DFUs 60.38% of wounds had closed
    • VLUs 60.77% of wounds had closed
  — By 20 weeks
    • DFUs 74.1% of wounds had closed
    • VLUs 74.6% of wounds had closed


• Comparative research
  — Theraskin vs Dermagraft
    • 2014 study
    • Dermagraft:
      — Human fibroblast derived dermal skin substitute
    • Theraskin:
      — Human skin allograft, from cadaver skin
    • Authors on advisory board of product Theraskin
    • Prospective, multicenter, randomized clinical trial
      — DFUs

• Comparative research
  — Theraskin vs Apligraf
  — 2011 study
    • N=29 patients with DFUs
    • 12 with Theraskin
    • 17 with Apligraf
    • At 12 weeks:
      – 41.3% of wounds closed with Apligraf
      – 66.7% of wounds closed with Theraskin


• Other biologics (not a complete list)
  — Biovance
    • Alliqua/Celgene
    • Dehydrated amnion
  — Amnioexcell/Amniomatrix
    • Derma Sciences
    • Dehydrated amnion
  — Grafix (frozen)
    • Osiris
    • Cryopreserved placental tissue

• Large reviews
  — NO Cochrane review on advanced wound dressings
  — VA 2012: 177 page review of advanced wound care therapies
  — AHRQ (2012) 64 page review
    • Agency for Healthcare Research and Quality


• Conclusions
  – Anything’s better than wet to dry
  – Many studies have small n
    • Few rigorous RCTs
    • No money in wound care!
  – Collagen/ORC/Silver/Alginate
    • Minimal significant results
  – Ovine dressing
    • Too soon to tell

• Conclusions
  – Biologics
    • Better results from studies
    • Obviously, more expensive
    • Must wrestle with insurance to use them
    • Sometimes, you just have to use your own clinical judgment!
    • Because we WOC nurses are awesome!

Thank you! Thank you very much!

mvercellino@sprynet.com if you want a copy of this presentation
• References
  - Molecular Cell Biology, 7th edition, Lodish, etc.
  - Advanced Wound Care Therapies for non-healing diabetic, venous and arterial ulcers: A systematic review. (2012). Department of Veterans’ Affairs, Quality Enhancement Research Initiative