THE PATHOPHYSIOLOGY OF CHRONIC WOUNDS AND RATIONALE FOR WOUND BED PREPARATION WITH NEGATIVE-PRESSURE THERAPY

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INTRODUCTION

Chronic wounds present a massive burden to health care facilities:

- Def: > 6 weeks
- Venous ulcers, diabetic feet and decubitus ulcers
- 1% European population suffered from chronic wounds in 2009 (8 million)
- 1% adult population suffer from venous ulceration
- 2-3% diabetics develop foot ulcers per year
- Most paraplegic patients develop a pressure ulcer at some stage
- Pathophysiology of chronic wounds
- Wound bed preparation
- Negative-pressure wound therapy NPWT

INDEX

- 1. Pathophysiology of chronic wounds
- 2. Wound bed preparation
- 3. Negative-pressure wound therapy NPWT

1.PATHOPHYSIOLOGY

- Hypotheses to chronic wound pathophysiology
- Persistant inflammatory phase
- Imbalance of MMP vs TIMPs
- Growth factors
- Extracellular Matrix (EM)
- Biofilm
- Epithelial-mesenchymal signalling
- Phenotype of chronic wound cells
- Stemcells

Matrix metalloproteinases MMPs

Tissue inhibitors of metalloproteinases TIMPs

HYPOTHESIS

Chronic wound pathogenesis is based on 3 fundamental factors:

- 1. The cellular and systemic changes of aging
- 2. Repeated ischaemia-reperfusion injury
- 3. Bacterial colonization

Mustoe T. Understanding Chronic wounds: a unifying hypothesis on their pathogenesis and implications for therapy. Am J Surg 2004;187:65S-70S.

OXYGEN IN WOUND HEALING

A BETTER HYPOTHESIS TO CHRONIC WOUND PATHOGENESIS! REQUIRED FOR EVERY STEP OF HEALING. OXYGENATION DELIVERY (DO2) TO WOUND TISSUE DETERMINED BY:

- Pulmonary gas exchange
- Blood haemoglobin
- Cardiac output
- Peripheral perfusion rate
- Capillary density

OXYGEN ROLE IN WOUND HEALING 1 OF 3

- Biological energy in form of ATP required by all cells
- Reactive oxygen species ROS require O₂ for bacterial killing (especially Neutrophils)
- Neutrophils loose their killing capacity below pO₂ 40_{mm}Hg
- Acute hypoxia stimulates angiogenesis via production of VEGF and HIF-lalpha from most wound healing cells which stimulate migration, proliferation of endothelial cells to form new capillaries
- New capillaries invading the provisional fibrin matrix provide the necessary O₂ and nutrition to macrophages to continue producing growth factors and to fibroblasts to produce collagen and extracellular matrix EM
- Chronic hypoxia obviously impairs this process

OXYGEN ROLE IN WOUND HEALING 2 OF 3

- Fibroblasts need a pO2 of at least 30mmHg for collagen production
- During collagen production a central oxygen-dependant step is the hydroxylation of proline and lysine residues and then collagen cross-linking which provides wound stability
- Again acute hypoxia stimulates fibroblast migration, proliferation and production of transforming growth factor beta TGFb but chronic hypoxia impairs the process.
- Fibroblasts and macrophages migrate into the wound matrix via cell surface recptors called integrins and is aided by plasmin which requires activation by a plasminogen activator
- These steps require biological energy which in turn requires Oxygen

OXYGEN ROLE IN WOUND HEALING 3 OF 3

- Different steps of epithelialization by keratinocytes
- Reduced expression of epidermal growth factor receptor EGFR on keratinocytes
- Wound remodelling : MMPs are release oxygen-dependently by macrophages,keratinocytes,fibroblasts and endothelial cells.

Babilas P et al.Oxygen in acute and chronic wound healing.Br J Dermatology 2010;163:257-268.

OTHER FACTORS PREDISPOSING TO CHRONIC WOUNDS

- Nutrition amino acids, carbohydrates, vit C, vit A, omega-3-fatty acids
- Immunosuppression ie.HIV/AIDS,cancer,steroids
- Chronic disease ie.cardiac failure, SLE and diabetes mellitus
- Infection
- Radiation

PERSISTENT INFLAMMATION 1 OF 2

- In acute /physiological wound healing the inflammatory phase lasts 7-10 days
- What causes the continued inflammation in chronic wounds?
- Inflammation is downregulated once a wound becomes epithelialized
- Deep wounds require healthy granulation tissue before keratinocytes will cover it
- Chronic wounds are hypoxic which precludes granulation tissue formation
- Episodes of reperfusion results in overproduction of ROS and continued infiltration of neutrophils into the wound
- Detoxification of ROS is also O₂ dependent

PERSISTENT INFLAMMATION 2 OF 2

- Chronic wounds have attenuated c-MET (mesenchymal epithelial transition factor) activation on keratinocytes and fibroblasts.
- c-MET is the receptor to hepatocyte growth factor HGF which is induced by IL1 and essential to the production of granulation tissue and epithelialization
- Chronic wounds have overexpression of cytokines ie. IL1 and IL6 but lack production of certain growth factors such as HGF
- TGFb receptor signalling via the Smad-signalling pathway is dysregulated in chronic venous ulcers

Schreml S et al. Cytokines, chemokines and growth factors in wound healing. JEADV 2012;26:812-820.

MATRIX DEGRADATION

Imbalance of MMPs and TIMPs:

- The oversupply of cytokines IL1 and IL6 stimulates keratinocytes and fibroblasts to continue producing MMPs which excessively breaks down the wound matrix
- In acute wound healing the MMP inhibitors alphal-antiproteinase, secretory leucocyte protease inhibitor, alpha2-macroglobulin and TIMPs are sufficiently present once the provisional wound matrix has been removed and then allows the production of granulation tissue.
- In chronic wounds all these inhibitors are downregulated

• Schreml S et al. Cytokines, chemokines and growth factors in wound healing. JEADV 2012;26:812-820.

EXTRACELLULAR MATRIX INTERACTIONS

Cells involved in wound healing require the matrix to migrate over and into the wound.Their binding is facilitated by integrins which in turn is a prerequisite for cells to respond to VEGF.Binding of macrophages to ECM is required for production of PDGF

Growth factors produced by cells have a bidirectional interaction with ECM:

- ECM bind directly to growth factors and then prevent their degradation and enhance their activity ie. Heparan sulphate binding FGF-2
- Growth factors ie. TGFb promotes the production of more ECM components

Schultz GS, Wysocki A. Interactions between extracellular matrix and growth factors in wound healing. Wound Rep Reg 2009;17:153-162.

EPITHELIAL-MESENCHYMAL INTERACTIONS

- Keratinocytes and fibroblasts produce growth factors that promote each other's proliferation and differentiation and the simultaneous growth of both are required for a wound to heal.
- Wound dressings/products should be tested to promote the growth of both cell types

Shrivastava R.Clinical evidence to demonstrate that simultaneous growth of epithelial and fibroblast cells is essential for deep wound healing.Diabetes Res Clin Practice 2011;92:92-99.

INTERACTION IN VITRO



FIBROBLAST MORPHOLOGY



STEM CELLS

- Stem cells from the hair follicle, sebaceous glands, the interfollicular epidermis as well as pericytes can differentiate into either epithelial cells or mesenchymal cells depending on the wound microenvironment
- This explains why superficial wounds heal rapidly because of the repopulation from the remaining stem cells but in deep wounds (where the stem cells are lost) the cells need to repopulate the wound from the edges
- Future therapies are focusing on methods of delivering stem cells to chronic wounds ie.adipose derived stem cells can be seeded onto biodegradable scaffolds/matrices and transferred to wounds

Longaker MT *et al.* The role of stem cells in cutaneous wound healing: What do we really know? Plast Rec Surg 2011;127:10s-20s.

BIOFILM

- Biofilm growth and persistence have been shown to impair wound healing and is an additional factor in chronic wound pathophysiology
- The biofilm state confers additional resistance to bacteria compared with their planktonic counterparts and rapid regrowth after antibiotic treatment occurs due to the presence of 'persister cells'.
- To completely eradicate biofilm persister cells the Minimum Biofilm Eradication Concentration (MBEC) should be determined for antibiotics as opposed to the MIC.

Percival SL *et al*.Antimicrobial tolerance and the significance of persister cells in recalcitrant chronic wound biofilms.Wound Rep Reg 2011;19:1-9.

WOUND BED PREPARATION

 Def: A changing paradigm in wound care that links treatment to the cause and focuses on 3 components of local wound care: debridement, moist interactive dressings and bacterial balance (Sibbald et al 2000)

 Redefined as the global management of a wound to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures (Schultz GS,Sibbald RG,Falanga V et al 2003)

 Global management reflects the fact that wound management must always start with an assessment of the overall health status of the patient to identify underlying conditions that limit wound healing

WOUND BED PREPARATION

- WBP is a cyclical process in which assessment is followed by intervention repeatedly
- Chronic wound cells have a dysregulated phenotype: fibroblasts do not proliferate or produce growth factors and keratinocytes at the wound edges hyperproliferate but do not migrate due to the absence of matrix and basement membrane proteins
- surgical debridement removes the diseased population of cells and allow the migration of a new set of stem cells

Schultz GS et al.Wound bed preparation and a brief history of TIME.Int Wound J 2004;1(1):19-31.

TIME

<u>T</u>issue (nonviable?)
<u>Infection / Inflammation</u>
<u>M</u>oisture balance
<u>Edge of wound (advancing?)</u>

DIM / DIME 1 OF 2

<u>Treat the underlying cause of chronic wound ie.control glucose, ARVs, venous</u> <u>hypertension</u>

- Define primary goal of wbp:
- Healable chronic wounds vs nonhealable/Maintenance wounds

Adress patient-centered concerns ie.pain, access to care and daily activities

Local wound care:

- <u>D</u>ebridement
- Infection/Inflammation
- <u>Moisture balance</u>

Sibbald RG *et al.* Special considerations in wound bed preparation 2011: An Update.Advances Skin&Wound Care 2011;24(9):415-436.

DIM/DIME 2 OF 2

Stresses that DIM must be controlled before the non-healing \underline{E} dge is addressed with advanced wound therapies and only if wound determined to be healable.

Advanced wound therapies:

- NPWT
- Dermal substitutes
- Growth factors
- Hyperbaric oxygen
- Stem cells

Sibbald RG et al.Special considerations in wound bed preparation 2011: An Update.Advances Skin&Wound Care 2011;24(9):415-436.

NPWT 1 OF 3

Multimodal action on wounds:

- Protects the wound (barrier)
- Reduces edema and so increases oxygen delivery
- Maintains moisture balance
- Contracts the wound (macrodeformation)
- Causes microdeformations to the wound bed which promotes granulation tissue
- Reduces patient total wound pain less dressing changes, comfort
- Protects the surrounding skin from maceration

Birke-Sorensen H *et al*.Evidence-based recommendations for negative pressure wound therapy: Treatment variables-Steps towards an international concencus.JPRAS 2011;64:s1-s16.

NPWT 2 OF 3

Patient indications (and goals) in CHRONIC WOUNDS :

- Must be used for wound bed preparation before definitive therapy of grade 3 and 4 pressure sores and diabetic foot ulcers without ischaemia AFTER surgical debridement to see if the wound will heal by secondary intention.
- NPWT as definitive therapy for grade 3 or 4 pressure sores smaller than 20cm₃
- **May** be used in venous ulcers after failed compression/elevation therapy and to prepare the wound for a skin graft or skin substitute.
- NPWT as palliative therapy for maintenance wounds or where patient inoperable

Vig S *et al*.Evidence-based recommendations for the use of negative pressure wound therapy in chronic wounds:Steps towards an international concensus.J Tissue Viability 2011;20:s1-s18.

NPWT 3 OF 3

Controversies:

- Bacterial load not necessarily reduced
- Protracted course of healing impedes quality of life especially in previously ambulatory patients
- Relatively contra-indicated when wound infected
- Wound filler:foam or gauze? Pain less with gauze
- Contact layer : only use when bolstering a skingraft with foam-type NPWT
- Pressure settings: -80 mm Hg and lower to -40 mm Hg if painful or ischaemia risk
- Birke-Sorensen H et al. Evidence-based recommendations for negative pressure wound therapy: Treatment variables-Steps towards an international concencus. JPRAS 2011;64:s1-s16.

FIG.1











CONCLUSION

Current knowledge of the pathophysiology of chronic wounds is essential to the successful treatment of these patients.

Approaching the patient holistically and determining the goal of wound bed preparation should be the first steps by the treating physician.

Expensive advanced therapies should only be used after successful wound bed preparation and only if wound is classified as healable.

NPWT should be used appropriately according to available evidence

THANK YOU