Adjunctive Biofilm Management Thru The Mitigation of Microvascular Hyperpermeability; A Theory

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ABSTRACT

Biofilms are present in the vast majority (80 plus %) of chronic wounds and are implicated in delayed wound healing.[1] Biofilm recognition within chronic wounds is typically underappreciated, though new technologies are aiding the identification and management of biofilms in an attempt to improve outcomes.[2] A biofilm wound blot technology that selectively detects and localizes biofilm communities in wound beds had high predictive validity for clinical wound healing outcomes with 83% of wounds with biofilm staining remaining non-healed and 70% of wounds without biofilm staining healed at a 1-month follow-up visit (83.3% sensitivity and 70% specificity.).[3] Debridement is one of the most important treatment strategies against biofilms, but typically does not remove all biofilm which can rapidly reform.[1] Repeated debridement alone is unlikely to prevent biofilm regrowth, though adjunctive, effective topical antiseptic application within a time-dependent window may adequately suppress biofilm reformation.[1] Antimicrobials must reach the bacteria in an active form and not be neutralized by the biofilm Extracellular Polymeric Substances (EPS) and be of adequate bactericidal concentration.[1] Therefore, multifaceted strategies combining serially (weekly) debridement and effective non-tissue toxic cleansers (hypochlorous acid, biofilm disrupting gels, surfactants) have become the standard of care for biofilm attempted eradication and management. Based on the Global Consensus Panel publication of 2017, the major emerging concept was “the need for strong initial combination treatment to rapidly and effectively reduce biofilm levels within wounds, and subsequently reduce inflammation, reactive oxygen species, and protease activities.”[1] This strategy is now known generally as the “step-down/step-up” strategy to Biofilm Based Wound Care (BBWC). The proposed result of consistent application of this strategy is enhanced healing of wounds, overall cost reduction, decreased tissue loss/amputation risk in critical limb ischemia with progressive tissue loss, and the potential to improve patient quality of life.[1]

Wolcott et al. published a 2008 paper discussing the impact of biofilms upon surgical site infection, wound dehiscence and delayed healing.[4] An unreferenced statement on p. 109 describes another potential critical component to biofilm management thru the mitigation of microvascular hyperpermeability associated with many wounds and the subsequent deprivation of a potential biofilm nutrient source; *“The up-regulation of proinflammatory cytokine production characteristically found in chronic wounds may be explained by the presence of biofilm infection leading to the production of exudate from surrounding capillaries. This highly nutritious exudate will percolate through the biofilm and provide nutrients to the resident microbiota of the biofilm. The supply of ‘food’ helps to maintain biofilm security and the sustainability, stability and fitness of the biofilm. Consequently, from an evolutionary perspective a highly virulent biofilm will have a selective advantage based on its microbial composition and net pathogenic effect and therefore enhanced survival rates when compared with a less virulent biofilm.”*[4]

The noted chronic pro-inflammatory state associated with chronic wounds occurs in the three-dimensional aspects of the wound within the soft tissue region, including the less recognized and untreated posterior aspect of the wound and soft tissues. Associated with chronic inflammation is microvascular dysfunction, *endothelial glycocalyx dysfunction and “glycocalyx shedding”* (loss into the surrounding tissues or breakdown of the complex sugar glycocalyx components such as glycoproteins, proteoglycans, albumin, hyaluronic acid, syndecans, integrins, etc)[5,6,7]. Glycocalyx shedding results in endothelial cell dysfunction (loss of mechanotransduction properties) and *microvascular hyperpermeability* (arteriole[5,6], venule[8] and dermal lymphatics[9]). *Microvascular hyperpermeability is a direct result of both the loss of cytokine and endothelial nitric oxide production, decreased quenching of inflammatory markers and increased endothelial gap junctions.*[5,6] The dermal lymphatic stasis in the totality of the peri-wound margins (often recognized as epibole) contributes to this enhanced periwound inflammation.[8] *Increased shedding of the endothelial glycocalyx and microvascular hyperpermeability potentially could contribute to the highly nutritious exudate from surrounding capillaries that Wolcott et al alluded to.*[4]

Dysfunction of endothelial cells and shedding of the endothelial glycocalyx is now well recognized to contribute to many pathological conditions including pathologies of diabetes, venous ulcers, atherosclerosis, sepsis, and trauma [8,10,11,12] Could strategies to enhance glycocalyx preservation and/or restoration that improves endothelial cell function with decreased microvascular hyperpermeability enhance biofilm management by removing the potential nutritional source to the posterior aspect of wound beds? Decreasing peri-wound edema would also ideally improve microarterial prefusion deficits by correcting states of rarefaction, enhancing nutrient and oxygen delivery to peri-wound tissues, potentially also improving therapeutic bactericidal levels of antibiotic tissue delivery. The lowering of inflammatory markers, cytokines and associated edema reduction has been demonstrated to enhance healing of venous ulcerations with a variety of venotonics, including Micronized Purified Flavonoid Fraction (MPFF, composed of diosmin and hesperidin fraction), rutosides, berberine, and sulodexide (not available in the US).[13,14] L-Arginine, commonly used in arterial wounds, has been noted to reduce edema in a rabbit reperfusion model.[15]

Lower extremity wounds are often associated with edema in critical limb ischemia and reperfusion states after revascularization. Wolcott et al demonstrated a significant improved healing frequency with a BBWC strategy in patients with critical limb ischemia, with 77% demonstrating complete healing in a typically “hard to heal” patient population with an elevated risk of limb loss.[16] Clearly strategies that enhance external BBWC when applied in a routine systematic fashion are successful, though this is not the general outcome in the vast majority of wound centers or hospitals.

In the management of certain acute or chronic wounds, Hyperbaric Oxygen Therapy (HBOT) can be beneficial in selected patients with demonstrated outcomes that decrease edema in the periwound region. When breathing 100% oxygen under pressures of at least 2.0 atmospheres absolute, tissue oxygen levels of more than threefold that of normal ambient air breathing can be achieved.[17] At this level, tissue edema reduction is thought to be achieved at the microcirculation level by way of Starling forces with vasoconstriction of the inflow arterioles at the site of tissue injury that results in decreased hydrostatic pressures in the downstream capillaries which would allow for interstitial fluid reabsorption into the outflow vessels.[18] However, other suggested mechanisms of edema reduction with HBOT include the mitigation of ischemia-reperfusion injury, decreased plasma volume loss, and possibly decreased capillary fluid extravasation by down regulation of tight junction protein apoptosis gene expression in animal model studies.[19,20,21] The evidence of pericyte regulation of endothelial function at the capillary level may also be a significant component of edema reduction.[22]

RESULTS

FIGURE 1

Theory of endothelial microvascular dysfunction and glycocalyx shedding contributing to biofilm persistence.

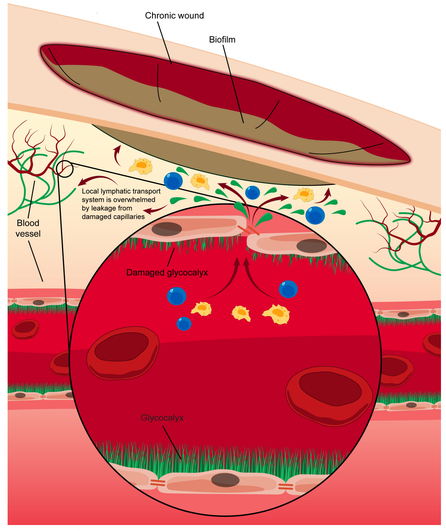

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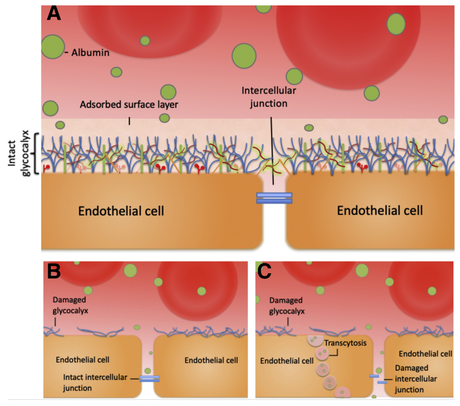
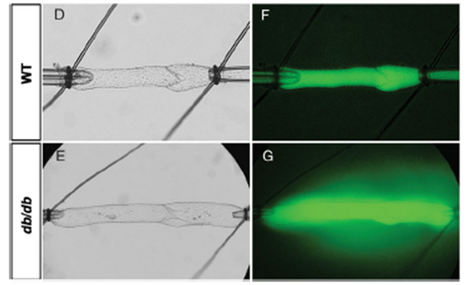
FIGURE 2



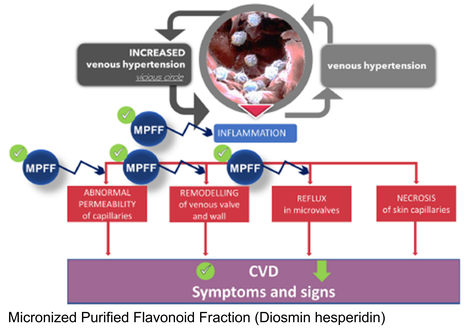
Damage to the endothelial glycocalyx results in microvascular hyperpermeability. Ref 7.

FIGURE 3



Lymphatic vascular integrity is disrupted in hyperglycemia. Comparison of wild type lymphatic mouse model (D,F) to obese diabetic hyperglycemia lymphatic mouse model (E,G) demonstrating fluorescent albumin leakage. Ref. 5

FIGURE 4



Micronized Purified Flavonoid Fraction (Diosmin hesperidin) as a venotonics, lymphotonic and pleiotropic effects to reduce inflammation Ref 6.

FIGURE 5

Hyperbaric oxygen contributes to decreasing edema and oxygen delivery. Photos from Mayo Facility HBO (provided by HBO Department)

CONCLUSIONS

The opportunity to improve wound outcomes may require a strategy that emphasizes an external BBWC approach and an “internal” approach that decreases microvascular hyperpermeability and edema, manages the associated inflammation, improves endothelial function, prevents glycocalyx shedding, supports regenerative glycocalyx restoration, resulting in enhanced microvascular arterial perfusion, oxygen delivery, and dermal lymphatic function, while decreasing the “nutrient” source to the posterior aspect of wounds; an “outside/inside” approach to biofilm management that compliments the consensus guideline “step-down/step-up” biofilm therapeutic strategy. While the “outside/inside” approach remains a proposal and hypothesis, associations cannot be validated as conclusions and further benchtop to animal to clinical evaluation is necessary.

REFERENCES