INTRODUCTION

Chronic wounds are wounds that are unresponsive to initial therapy or persistent in the face of appropriate care (1). The growing incidence of chronic wounds is becoming a public health crisis in the US and accounts for over $25 billion in annual expenditure on related treatments (2). Individuals with chronic wounds often present with other medical comorbidities such as diabetes mellitus, peripheral neuropathy, chronic renal disease, and impaired mobility secondary to disease complications (3). Approximately 7.8% of the US population has diabetes mellitus and the diabetic foot ulcer and associated lower extremity ulcers remain a critical clinical challenge to clinicians from all disciplines (1). Untreated diabetic foot ulcers can eventually lead to amputations and it is estimated that diabetic patients account for a staggering 67% of all lower extremity amputations (4).

The research on wound healing, especially for chronic wounds such as pressure ulcerations, venous stasis ulcerations, and diabetic neuropathic ulcerations has been extensive. Current treatment plans include occlusive wound dressing, surgery, hyperbaric oxygen therapy, and biologic products (1,5). Wound care is a growing industry with new wound care products becoming available in the market each year. Nonetheless, quality prospective randomized studies are still lacking and currently there is no consensus among providers on the optimal product or its treatment protocol. Furthermore, these products often pose a significant financial burden to both the patients and the healthcare system (2,6).

As a result, developing a cost-effective treatment method for these chronic wounds is crucial in managing this public health crisis.

The biologic dermal substitutes have been gaining popularity in its applications over the past two decades in the treatment of chronic wounds (5,7). Derivatives of hyaluronic acid (HA) have been extensively studied and several forms (cream, gel, scaffold, HA-embedded membrane) are now available (8). The HA wound products have gained popularity in the treatment of burn wounds since its introduction, but it is also indicated for partial- or full-thickness wounds (9). In particular, the benzyl ester form of HA (HYAFF) has been extensively studied and its safety and efficacy in the treatment of chronic lower extremity ulcerations were demonstrated in previous studies (10-12). The tissue regeneration mechanisms of HYAFF include enhancement of angiogenesis, regulation of collagen deposition and organization, promotion of cell migration, and scavenging free radicals (5,7,10,13). Therefore, the promising results of HYAFF encouraged us to further assess its efficacy in treating chronic lower extremity ulcerations in complex patients with multiple medical comorbidities. Here we present two cases demonstrating the tissue regeneration effect of an HA 3D-scaffold membrane (Hyalomatrix PA) in patients with diabetic foot ulcerations and surgical wound dehiscence with exposed tendon and bone.

CASE REPORT 1

A 56-year-old man with non-insulin dependent (type II) diabetes mellitus complicated by peripheral neuropathy presented to the hospital with wet gangrene of the right foot after a right transmetatarsal amputation. The patient subsequently developed surgical wound dehiscence that resulted in an extensive dorsal soft tissue defect measuring 45 cm² with exposed tendon and bone (Figure 1). Hyalomatrix PA was then applied to the soft tissue defect after the wound base was sharply debrided and prepared. The wound was then closely followed on an outpatient basis with weekly renewal of the secondary dressing. The Hyalomatrix PA was changed every 3 weeks.

![Figure 1. Appearance of surgical dehiscence prior to application of Hyalomatrix PA.](image-url)
At week 3, significant clinical progression was noted with granulation tissue filling in the previous deep soft tissue defect and re-epithelization of the wound margins (Figure 2). The patient achieved complete wound healing at 24 weeks. In this case, the hyaluronic acid membrane allowed the promotion and stabilization of granulation tissue with tissue regeneration effects for a deep soft tissue defect with exposed tendon and bone. The successful outcome of Hyalomatrix PA in this case saved the patient from a more proximal level amputation.

CASE REPORT 2

The second case featured a 67 year-old man with type II diabetes mellitus complicated with peripheral neuropathy who initially presented with left hallux osteomyelitis after a partial left first ray resection. Surgical dehiscence with an exposed first metatarsal shaft was noted at the follow-up clinic visit (Figure 4). The wound base was carefully debrided and prepared and Hyalomatrix PA was then applied to the wound with weekly renewal of secondary dressings. The Hyalomatrix PA was changed every 3 weeks.
After the removal of the silicone top layer at week 3, it appeared that the Hyalomatrix PA membrane had turned into seemly fibrotic tissue (Figure 5). This however, is a normal manifestation during the intake of the Hyalomatrix PA membrane and the tissue should not be debrided. In this case, only the wound edges were sharply debrided and curetted with application of new Hyalomatrix PA membrane at these peripheral sites to facilitate closure from the wound margins. The clinical appearance of the wound continued to progress and the exposed first metatarsal bone was completely covered with skin at week 9 (Figure 6).

**DISCUSSION**

With the abundance of wound care products that are available on the market, clinicians are often perplexed with the optimum product or treatment protocol for these chronic wounds. In patients with diabetes mellitus, prompt and efficacious healing of lower extremity ulcerations is crucial to preserve the quality of life, and even the survival of these patient because exposed wounds are more prone to develop deep infections that may result in sepsis or lost limbs (14). Nonetheless, the relative tissue ischemia, presence of both macrovascular and small vessel disease, ambulation in a neuropathic limb, and impaired immune system all pose significant challenges to the complete healing of lower extremity ulcerations (14,15).

The choice for wound coverage is determined by many factors including the size, the exposure of deeper structures such as tendon or bone, the presence of infection, the location of the wound, and the local vascular supply (11). Although advanced surgical reconstruction techniques such as the use of free predicable or muscle flaps do exist, the financial burden and risks of surgery and anesthesia should also be considered. The use of advanced biologic dressings, therefore, provide an alternative treatment option as they are able to achieve wound coverage as well as provide a local environment that may be favorable for tissue regeneration. Among the available biologic wound products, HA is the most studied and is currently available in multiple forms and combinations (10). It is also important to mention the fact that HA has a relatively low cost compared to the other advanced wound care products currently on the market (Table 1).

<table>
<thead>
<tr>
<th>Product</th>
<th>Cost</th>
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<tbody>
<tr>
<td>Bovine Collagen Bilayer</td>
<td>$3.88/cm²</td>
</tr>
<tr>
<td>Hyaluronic Acid Scaffold</td>
<td>$16.32/cm²</td>
</tr>
<tr>
<td>Neonatal Foreskin</td>
<td>$33.11/cm²</td>
</tr>
<tr>
<td>Human Allograft</td>
<td>$140.70/cm²</td>
</tr>
<tr>
<td>Dehydrated Human</td>
<td>$229.71/cm²</td>
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<tr>
<td>Amnion/Chorion Membrane</td>
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Hyaluronic acid is one of the extracellular matrix (ECM) components and has multiple roles in maintaining the structural, mechanical, and trophic functions of living organisms (12). HA is a linear polymer of D-glucuronic acid N-acetyl glucosamine disaccharides and it is one of the most hygroscopic macromolecules (16). It is important to point out that HA is able to absorb up to 3,000 times its molecular weight in water and this property contributes to its significant role in wound healing (16). It has been shown that HA regulates tissue hydration level in the inflammatory phase of wound healing (17). Furthermore, HA has also been shown to induce and promote angiogenesis, ECM production, as well as enhanced production and differentiation of fibroblasts and keratinocytes (18–20). In particular, HA is abundant in the skin with the dermis containing up to 50% of the total HA and the synthesis of HA by keratinocytes stimulates their differentiation (21). In addition, the most important mechanism of HA in tissue regeneration is its ability to serve as a free radical scavenger (22,23). It is well known that one of the hallmark feature of chronic wounds is the prolonged inflammatory phase caused by the formation of oxygen free radicals and matrix degrading enzymes such as proteases and matrix metalloproteinases (MMPs) (24). HA is therefore able to prevent the damage of free radicals on granulation tissue and promote wound healing (10,25).

Hyalomatrix PA is a bi-layered wound device that is an
acellular, dermal skin substitute for the temporary coverage of partial- or full-thickness wounds and functions as a three-dimensional scaffold (12). The silicone layer of Hyalomatrix PA functions as a barrier and mimics the epidermis to achieve wound coverage, reduce bioburden, and avoid vapor loss (12). Previous studies have demonstrated the in vivo bioinductive effects of Hyalomatrix PA once applied to the wound site (26).

In our experience of patients treated with Hyalomatrix PA, the combination of wound bed preparation and serial applications of this dermal skin substitute serves as a reliable and important cost-effective approach for the treatment of chronic lower extremity ulcerations in patients with multiple medical comorbidities at high risk of limb loss. As demonstrated in the clinical cases presented above, the Hyalomatrix PA is indicated for use in wounds with exposed tendon or bone, making it a useful and important treatment option for wounds that may not be suitable for negative pressure wound therapy or skin grafts. It is also important to point out that the seemingly fibrotic tissue should not be debrided following the application of this dermal substitute. Debridement and preparation of the wound base may be initiated at the periphery while leaving the degrading graft from previous application intact. The degrading graft should not be mistaken as fibrotic tissue and removed at each application of the Hyalomatrix PA, as it will eventually be fully incorporated into the wound. Further histophysiologic studies may be warranted to investigate the cellular component of the degrading graft and its role in wound healing. In our practice we commonly remove the silicone top layer at the end of week 3, followed by a new application of Hyalomatrix PA if necessary. We consider Hyalomatrix PA to be an important tool in our treatment approach for the chronic lower extremity ulcerations.

REFERENCES