What Is a Biomimetic Matrix (BMM) Polypeptide?

And how is it used for the treatment of diabetic foot ulcers?

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Introduction

Biomimetic matrix polypeptides (BMM) are fully synthetic compounds that can be assembled in specific ways to mimic various naturally occurring structures critical to wound healing. For example, in the laboratory, these peptides can be formed into three-dimensional matrices resembling collagen that can facilitate cellular proliferation, migration, and cellular adhesion, similar to natural collagen.

In this article, the unique benefits of these synthetic structures will be discussed, and some examples of their clinical use will be demonstrated.

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It All Starts with Polypeptides

Polypeptides are one of the foundation building blocks of a variety of materials found in our bodies. They are composed of amino acids connected together in long chains and are the building blocks for proteins and are crucial for cellular-level activities. Proteins formed from polypeptides play a role in a wide variety of functions, including the structural components of collagen and keratin, and can act as hormones (e.g. insulin), enzymes, or receptors. They can also play a critical role in cellular signaling, immune responses, and metabolism.

In a laboratory, polypeptides can be directed to assemble in a way that mimics naturally occurring structures in order to capitalize on specific dynamic and functional properties needed to promote wound healing.[1] For example, polypeptides can be self-assembled to mimic intricate collagen structures.[2] Collagen plays a critical role in wound healing, not only serving as a scaffold, but also as a competitive inhibitor of matrix metalloproteases (MMPs) and also plays a role in the signaling process essential for wound healing.

Custom-formed polypeptides differ from one another in numerous design elements that can be controlled and fine-tuned in a laboratory setting. The selection and form factor of a specific BMM is dependent on the whims of the manufacturer who selects various properties based on proven factors chosen to stimulate or enhance healing.

The BMM that is the subject of this report was developed by Gel4Med, a biomaterials engineering company founded out of the Harvard Innovation Labs/Harvard University program. The product used for wound healing, G4Derm Plus (Gel4Med, Brighton, MA) was created with several unique attributes that have been found to be desirable for wound healing.

What Is G4Derm Plus?

G4Derm Plus is a BMM polypeptide that is custom-fabricated to mimic the native dermal extracellular matrix (ECM). Besides providing structural support to the wound bed and serving as a scaffold for cellular infiltration and attachment for tissue regrowth and revascularization, the BMM in G4Derm Plus was intentionally designed to achieve additional benefits. Namely, the permeable scaffold promotes adequate oxygenation, resists MMP degradation, and delivers bioactive amino

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New Concepts and Studies

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acids, while managing bioburden via cationic peptides that physically interact with and destabilize bacterial membranes. The BMM is fully integrated into the local tissue through gradual bioresorption. Some of the bioactive amino acids that are by-products of BMM include Arginine, Lysine, and Proline. These amino acids can elicit positive metabolic effects, rejuvenating a stalled wound and promoting healthy granulation tissue formation.

Due to its unique molecular design, BMM provides strong antibacterial effects against multidrug-resistant organisms (MDRO's) with local or systemic toxicity often observed with antibiotics and antimicrobial agents. The BMM in G4Derm Plus contains cationic peptides capable of targeting and disrupting the negative charges present in bacterial membranes.[4,5] This novel mechanism of physical interaction also reduces the risk of developing antibiotic resistance.

Figure 1: BMM (G4Derm Plus) is available as a viscous gel, provided at room temperature in a sterile syringe with flexible applicator tip.

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G4Derm Plus employs a trifecta approach to treat chronic wounds: a scaffold to support healthy tissue growth, bioactive amino acids to enhance the local metabolic environment of the wound bed, and robust antibacterial protection to control bioburden and prevent biofilm reformation.

Clinical Experience with BMMs

In 2023, G4Derm Plus received FDA 510(k) clearance for use on wounds. Our institution began to explore its use on a variety of wound types. Our initial findings were published earlier this year in the *Journal of Clinical and Translational Research.*[6] The BMM is currently available in a sterile syringe and is flowable. It is provided with a flexible tip, which allows the material to be dispensed evenly over the entire wound surface, including in deep spaces such as crevices and tunneling sites. In this form, it is especially good for delivering the actions of collagen and an anti-microbial in otherwise hard to reach areas.

Initially, 10 subjects were treated in our review, but we are now up to 21 subjects. To date, all subjects were diabetic and neuropathic and had stagnant wounds that had not decreased in size for at least three months. Many of the wounds treated had recurrent biofilms and most were Wagner 2, with a few Wagner 1 and 3 wounds as well.[7] Chronic diabetic wounds are difficult,and often contaminated wounds.

All wounds in this group were previously treated with topical antibiotics, and with antimicrobial irrigation solutions to reduce or eliminate bioburden (e.g. Hypochlorous acid, Dakins solution, povidone-iodine). Appropriate off-loading was provided where indicated.

Wound bed preparation was performed on all subjects. Preparation consisted of sharp debridement using either scalpel or curette, to bleeding granular tissue when possible. Wounds exhibiting slough, exposed bone or tendon were also included. Following debridement, all wound surfaces were cleaned with a hypochlorous acid solution (Vashe; Urgo Medical) and gently patted dry with a sterile gauze pad.

BMM is stored at room temperature and is provided in a sterile pack as a syringe with a flexible needle used to disperse the material across the wound surface (Figure 1). The flexible tip is used to first fill all tunneling areas and areas where the wound margins are undercut. Next, the entire surface of the wound is covered with BMM to about the thickness of a coin. The wound is then covered with a non-absorptive dressing (Adaptic; 3M, St. Paul, MN), and backed with an absorbent sterile gauze. Depending on the level of exudate, the dressing could be left in place for three to five days, giving the BMM time to act and incorporate into the wound bed. All wounds were measured and photographed at baseline, and at subsequent follow-up visits.

BMM is stored at room temperature and is provided in a sterile pack as a syringe with a flexible needle used to disperse the material across the wound surface.

Results

This small series was intended to gain experience on how and when BMMs are most suitable for wound healing in this common population of patients. In our experience, most wounds demonstrated an initial immediate burst in healing activity, with many closing 50% or more of the total surface area in the first four to six weeks

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of treatment. None of the patients had any complaints of pain. In all cases, the wounds appeared to have less drainage and less odor following treatment. Most showed excellent progress with rapid development of granulation tissue.

In our test, patients received treatment every two to three weeks (Figures 2 & 3). Each time, they were instructed to leave the dressings in place for up to five days but could change the dressing earlier if they observed strikethrough.

In our sample, several patients had exposed tendon, muscle, and/or bone. Several of the patients initially had dirty wounds, likely accompanied by biofilms. None had purulence or ascending cellulitis, but several had localized erythema, which appeared to improve after treatment. No complications attributed to the BMM were observed. Two representative cases are presented in Figures 2 & 3.

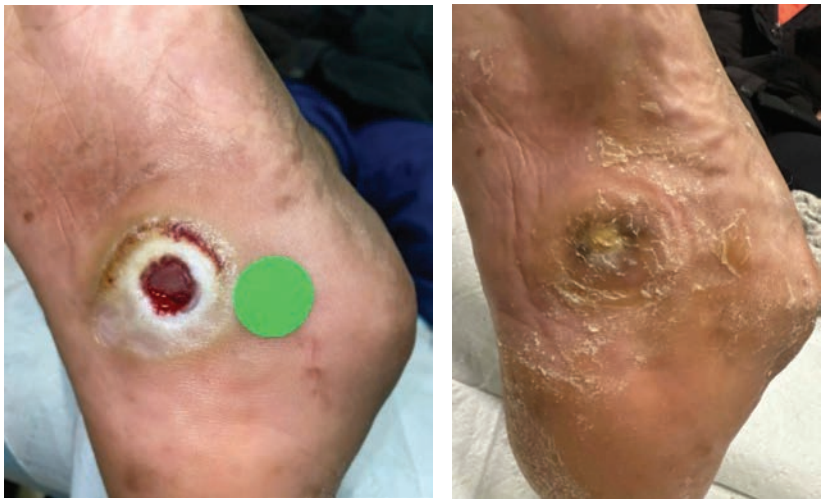

Figure 2: 63 year-old diabetic female with history of Charcot neuroarthropathy with midfoot breach developed an ulceration while wearing a Crow walker. The ulcer was present approximately 4 months before starting BMM treatment. Initially the area surrounding the ulcer was erythematous and edematous with maceration. BMM treatment was initiated approximately 10 days after administration of an oral antibiotic. Patient received 2 treatments (3 weeks apart) and fully healed in 8 weeks.

The flowable formulation of G4Derm Plus BMM is advantageous when trying to reach difficult locations within the wound bed—most notably exposed structure, tunneling and undermined wounds.

Discussion

To date, more than 100 advanced biologic products are available in the market, specifically intended for wound care. Some products are naturally derived while others are laboratory-created, and many are hybrids based on a combination of allograft, xenograft, and synthetic materials, created in a laboratory. G4Derm Plus offers a radical novel approach by offering a fully synthetic material to overcome many of the limitations of cellular and tissue-based products (CTP's).

G4Derm Plus is a SAP-based biomimetic matrix uniquely positioned to simultaneously spur tissue regrowth and control bioburden in complex and hard-to-heal wounds. The 3D matrix structure of G4Derm Plus resembles the native ECM and encourages cell attachment and proliferation, while the cationic peptides present in the BMM reduce bioburden and prevent biofilm reformation, protecting the wound bed.

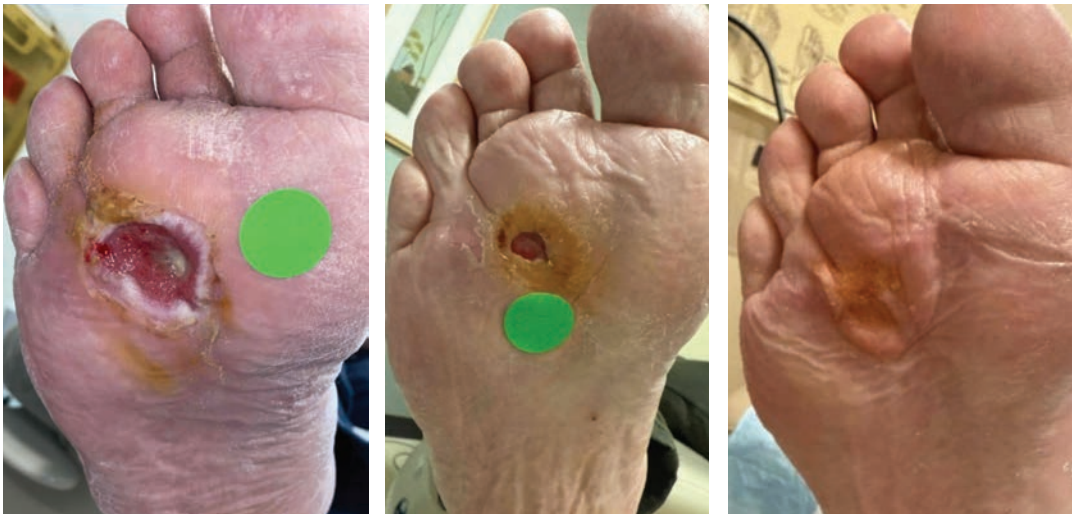

Figure 3: 62 year-old diabetic male who initially presented with a deep wound with exposed flexor tendon. The ulcer was present for 3 months before starting treatment with BMM. He initially closed the wound after 2 treatments then re-ulcerated. and subsequently closed after 11 weeks following5 applications of BMM administered 1 to 2 weeks apart.

The flowable formulation of G4Derm Plus BMM is advantageous when trying to reach difficult locations within the wound bed—most notably exposed structure, tunneling and undermined wounds. It is also beneficial for irregularly shaped areas around the perimeter of the wound, where contact with tra-

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ditional rigid sheet material has been proven to be challenging.

The broad-spectrum antibacterial activity of G4Derm Plus is also unique since it relies on the incorporation of cationic peptides into the BMM. Cationic peptides have been shown to disrupt negatively-charged membranes found in bacteria cell membranes.[8] Previous in vitro studies have demonstrated full eradication of multi-drug resistant bacteria, including Gram-positive MRSA, and Gram-negative bacteria including P. aeruginosa, on contact with cationic peptides.[9,10] Furthermore, by physically disrupting the bacteria cell membrane, the likelihood "threat" or "prospect" of bacterial mutations and developing resistance is unlikely.[9,10]

G4Derm Plus delivers a BMM with a structure similar to native extracellular matrix, combined with a strong antibacterial barrier through the introduction of cationic peptides, in a flowable and easy-to-use product.

Conclusions

BMMs are generating a great deal of interest in the wound healing community. The idea of delivering a product that combines multiple attributes not normally found together is enticing. G4Derm Plus delivers a BMM with a structure similar to native extracellular matrix, combined with a strong antibacterial barrier through the introduction of cationic peptides, in a flowable and easy-to-use product. In our limited experience, we have found this to be particularly effective in wounds that tend to be more complex, with exposed deep tissues, and signs of bioburden. It has been particularly helpful in stimulating the healing process in wounds that have been stagnant by promoting rapid granulation tissue formation and a recution in wound area within a few applications. Further clinical trials will help to validate the benefits of this innovative technology.

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