Collagen Treatment in the Diabetic Foot

A new cost-effective collagen matrix product is showing promise in treating DFU's.

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New Concepts and Studies

"New Concepts" is a forum for the presentation of (1) new technologies and products which have been the subject of clinical study, and (2) new studies involving existing products. Readers should be aware that Podiatry Management does not specifically endorse any of the technologies, concepts, or products being discussed.

Introduction

Peripheral vascular disease and diabetes are contributing factors towards many potential complications throughout the body. Diabetic foot ulcers are a common problem for patients with these risk factors. Ulceration in feet is a problem that has been challenging people for thousands of years, as it can lead to severe consequences if untreated. Peripheral neuropathy secondary to diabetic conditions raises the risk of foot problems that will go unnoticed or untreated by patients. The power of prevention in diabetic foot disease mostly lies in the hands of patients in terms of their education and understanding towards their own conditions and symptoms. As neuropathy leads to a reduction of sensitivity in the foot region, it becomes difficult for patients to assess the severity of problems in their own feet. Peripheral neuropathy is the most important factor leading to ulceration; it is a condition present in greater than 80% of diabetic patients who had developed foot ulcerations.[1,2] In addition, infection has been a common and major complication in diabetic wounds. Symptoms of temperature elevation, chills, or leukocytosis may be absent in up to two-thirds of patients with limb-threatening infection.[3] Thus, it is imperative to have a caregiver or family member to examine the feet of a diabetic on a daily basis. Ulcerations and infections may go untreated, until discoloration due to the development of cellulitis occurs, eventually leading to more severe situations, specifically gangrene and necrosis.

In 1880, Louis Pasteur claimed, "The germ is nothing. It is the terrain in which it is found that is everything." This remains true to this day, as patients' history is very indicative of their risk of ulceration, infection, and more serious complications. Infection and amputation rates for diabetic patients far surpass that of non-diabetics. Diabetic patients are up to five times more likely to develop gangrene than non-diabetics. Moreover, major clinics report amputation rates exceeding 50% among diabetic patients with lower extremity infection.[4]

A working relationship with a vascular interventionalist is imperative.

Dr. David Armstrong explains, "Practitioners who deal with wounds of the lower extremities are always held hostage to effects of blood flow." Peripheral vascular disease additionally interferes with the body's ability to heal and combat infection. Beyond a typical physical examination, an ankle-brachial index (ABI) measurement

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should be taken to assess the extent of ischemia in the region of the ulceration. If the patient's ABI falls below the range of 0.7, angiography should be performed to determine the severity of the patient's peripheral vascular disease.[5] Other diagnostic testing to assess blood flow include duplex and Doppler ultrasonography, which allow a more accurate assessment of blood flow, but are more expensive and are not available in all practices. Conventional angiography remains the gold standard in mapping the extent of arterial pathology and allows specialists to perform endovascular therapies in the same phase of the diagnostic procedure.[6] Pending the severity of calcification or stenosis in the arteries of the limb, one or multiple stents may be necessary to re-establish proper blood flow. This is crucial, as increased blood flow aids in both fighting infection and healing ulcerations. Revascularization plays a key role in preventing amputation, prolonging survival, and improving patients' quality of life.[7] Thus, a working relationship with a vascular interventionalist is imperative.

When a patient presents with both diabetes and peripheral vascular disease, it is essential to thoroughly evaluate the current status of the patient using several diagnostic exams. Laboratory tests must be performed to assess the patient's current health condition, nutritional status, and especially the current control of their diabetic condition, including their renal function and glucose and hemoglobin A1C levels (Chart 1).[8] The wound should be cultured in order to provide proper and adequate antibiotic coverage based on the type and severity of infection. Of course, pending the patient's medical history, any other relevant diagnostic testing should also be performed to get a thorough analysis of the patient's condition to ensure proper treatment. The effects of the patient's current medications and conditions should, as always, be considered.

In severe cases, amputation may be required to remove damaged and infected areas of a patient's feet. In diabetics, amputation occurs most often due to peripheral vascular disease, peripheral neuropathy, and infection.[9] It is more often a necessary procedure in men, especially African-American and Native American individuals.[10,11] Clearly, amputation leads to severe complications in a patient's health and future, as mobility and circulation become severely limited. Toes can frequently be salvaged with aggressive treatment, including distal amputation or remodeling. It has been reported that the long-term salvage of 73% of threatened limbs can occur with aggressive foot debridement and, if revascularization is performed when necessary, even in high-risk patients, such as patients on dialysis.[12]

Ulcers may not heal properly despite proper metabolic control, debridement, and antibiotic therapy, if patients also have vascular insufficiency.

Ulcers may not heal properly despite proper metabolic control, debridement, and antibiotic therapy, if patients also have vascular insufficiency. Scar tissue from properly healed ulcers in high-risk patients is often not strong and is susceptible to re-injury.[13] Therefore, to increase the efficacy of the aggressive treatment of severe infection and ulceration, collagen dressing of the wound can help facilitate the healing process while the region is still vulnerable to complications and in need of immediate care.

Early wound healing is essential in curtailing the risk of further complications in diabetic feet. Collagen has been used as a catalyst for wound

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CHART 1:
Laboratory Exams for Wound Care[8]

Chemistry	Hematology	Nutritional
Renal	Complete blood count with differential	Albumin
Electrolytes	Sedimentation rate	Prealbumin
Glucose	Glucose-6-phosphate Dehydrogenase	Transferrin
Hepatic/Hepatitis	Protein C/S	Total Lymphocyte Count
Lipids	Fibrinogen/FDP/D-dimers	Vitamins
Hemoglobin A1C	Prothrombin Time/ Partial Thromboblastin Time	Minerals
Amylase/Lipase	Cryoglobulins/Cryofibrinogens	
Iron/Ferritin	Antiphospholipid antibodies	
Parathyroid Hormone	Antithrombin 3	
	Serum Protein Electrophoresis	
	Sickle Cell	

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healing in patients who are at risk of having hindered recovery due to problems like severe infection, neuropathy, and poor circulation. Collagen is a component of skin that allows other natural resources of the body to support wound healing at a cellular level. It is utilized as a resource in every phase of the healing process. Collagen aids in the debriding effects and in reducing the bacterial bio-burden during healing to help jump-start the process.

Collagen and Wound Healing

Collagen is also a crucial component of the extracellular matrix (ECM), especially during wound healing or tissue remodeling processes. Collagen is the most abundant of the many substances released into the ECM upon stimulation via a wound or ulceration. During wound healing and

Figure 1: Initial presentation of 3rd toe, distal on right foot

at the exact moment of injury, a complex series of events involving collagen occurs. Within the initial inflammatory phase, collagen assists with homeostasis,[14] attracts macrophages to the region via angiogenesis, and causes natural wound cleansing due to inflammatory infiltration.[15] For example, in patients experiencing chronic wound fluid, a build-up of MMP2 and MMP9 enzymes that typically play a role in the degradation of the ECM can occur. This condition would naturally slow the healing process and make it difficult for the healing process to reach proliferation.

The cleavage of these MMPs activates the promoters for angiogenesis. In conjunction with other growth factors, collagen is a key protein in establishing a scaffold for the healing process as well as bridging vascular basement membranes for angiogenesis in the ECM.[16] This angiogenesis leads to the delivery of cells, platelets, and macrophages to the region to protect the wound from infection via in-

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CHART 2:
Collagen in Wound Healing[18]

Healing Phase	Role of Collagen
Inflammatory Phase	
Hemostasis: Stop blood loss	Assists with hemostasis
Vasodilation: Migration of neutrophils to fight infection	Attracts macrophages as chemoattractant
Neutrophils: Attract macrophages, remove debris	Enhances inflammatory infiltration to improve natural wound cleansing
Macrophages: Attract fibroblasts and induce collagen synthesis	
Proliferative Phase	
Fibroblasts appear: Initiate collagen synthesis	Acts as a scaffold for fibroblast attachment
Granulation tissue develops	Attracts additional fibroblasts to the wound site
Angiogenesis: Cappillary loops aid in tissue development in a scaffold of collagen fibers	Becomes template for new tissue growth
	Primary structure presents attachment sites for fibroblasts
Maturation Phase	
Connective tissue matrix reorganizes	Enhances deposition of oriented, organized collagen fibers
Collagen fibrils consolidate into thicker fibers	Imparts strength to the tissue over time, replacing and reinforcing weaker scar tissue
Cells gain more tensile strength	

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flammatory reactions and deliver more growth factors and nutrients to the area. During proliferation, the helical structure of collagen acts as a scaffold for fibroblast attachment and attracts fibroblasts to the site of the wound. In its matrix structure, collagen becomes the template for new tissue growth, and the primary structure continues to recruit fibroblasts to the site. As the healing process reaches the maturation phase, it is suggested that it enhances the deposition of oriented collagen fibers to increase the tensile strength of the new tissue.[17] Collagen is apparent in every stage of the healing process and is an essential resource in healing wounds (Chart 2).[18]

Case Report

A sixty-seven year old African-American male patient presented with gangrene on the distal 3rd right toe, secondary to ulceration and infection of the toe (Figure 1). The patient stated an approximate two-week duration of the condition. The patient initially presented with a medical history including peripheral vascular disease, history of myocardial infarction, atrial fibrillation, congestive heart failure, anemia, hypertension, significant diabetes mellitus II with peripheral nephropathy, and has been on home dialysis for four years due to end-stage renal disease.

Figure 2: Patient's toe after aggressive debridement, excision, and cleaning

Immediate action was taken to attempt to salvage the toe and avoid complete amputation, which was the original suggestion by the patient's primary care provider. Upon examination, the patient was found to have developed cock-up toes, a common foot deformity for diabetic patients. This complication likely increased pressure on the tips of the toes, making them more vulnerable to ulceration and infection and subsequently osteomyelitis and gangrene. Lab work-up and cultures were immediately taken for analysis. Measurement of the ankle-brachial index (ABI) was approximately 0.6, confirming thoroughly reduced blood flow to the foot, further increasing the patient's susceptibility to infection upon ulceration. Moreover, the patient demonstrated poor capillary return and dorsalis pedis pulses.

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Due to suspected ischemia in the region, a vascular specialist was referred to perform peripheral angiogram of the right leg, immediately. An 80% calcified blockage was discovered in the left distal popliteal artery. The lesion was stented to allow for increased blood flow to the posterior tibial and peroneal arteries supplying blood to the anterior tibial that was previously occluded. There was no significant residual stenosis after the procedure.

Figure 3a: Patient's toe during treatment with Helix 3-CP Collagen powder

X-ray and CT scan without contrast of the right foot and toe were performed immediately to assess the potential for osteomyelitis or other complications. These methods were utilized rather than MRI, the imaging modality of choice, due to the patient's claustrophobia.

Figure 3b: Usage of collagen powder and dressing on toe

To combat the infection, the patient was prescribed broad-spectrum oral antibiotics, Augmentin (Amoxicillin/Clavluanic Acid) 500 mg and Levaquin (Levofloxacin) 250 mg daily. Levaquin was prescribed after consultation with the patient's nephrologist due to the consideration of the patient's renal disease. Initial aggressive sharp debridement of the tissue began, including excision of the necrotic phalanx (Figure 2). To properly treat the wound, daily treatment was initially necessary. Local debridements were performed using a sterile #10 blade. The area was washed using Amerigel Wound Wash (Amerx Health Care) on a ster-

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ile gauze pad. After proper cleansing of the area, HELIX 3-CP bioactive type 1 bovine collagen powder dressing (Amerx Health Care) about 1/4 inch thick was applied to the wound surface, (Figures 3 a,b). After several initial visits, the patient was seen every 3-5 days until there was full healing of the wound (Figure 4). The toe has been salvaged and recovered from ulceration and infection (Figure 5). CT scan without contrast was performed upon healing to ensure no findings of osteomyelitis or other complications (Figures 6 a,b).

Discussion

The treatments for salvaging damaged diabetic feet have greatly improved in recent years. More emphasis has been placed on education of the patients, mandating that they become part of the process as well. As patients have a better understanding of their own bodies and the severity of conditions such as diabetes, more preventative measures will be taken. To further improve our ability to provide optimal patient care and prevent foot disease, newer treatments and diagnostic testing have been developed.

Figure 4: Patient's toe mid-treatment after days of consistent cleaning, debridement, and collagen dressing.

Figure 5: Patient's toe completely healed after collagen treatment.

To properly treat patients with peripheral vascular disease and diabetic feet, a three-pronged treatment is necessary. The basics of blood flow reconstruction (better off-loading techniques, infection control, and lowering hemoglobin A1C) still become the groundwork for successful salvage. These high-risk patients must be treated in all three of these fronts to ensure that not only the original ulceration and infection are taken care of, but that future complications, including other ulcerations and infections, do not occur again. To assess and treat vascular disease, a patient's ABI should be obtained. If the ABI is below 0.7, vascular intervention is required to improve blood flow.[5] Fortunately, today there is access to more effective stents and greater numbers of skilled vascular interventionalists than were previously available to help assist with any circulatory problems. Proper control of the patient's diabetes is necessary and therefore, laboratory analysis, nutritional planning, and maintenance of the patient's hemoglobin A1C are essential towards excellent long-term outcomes. If proper control is not obtained, immediate referral to an endocrinologist is mandatory. Finally, wound cultures must be taken to determine the optimal antibiotic therapy for the type and severity of the infection.

To improve upon the treatment of the actual ulcerations many new methods and applications have been put into use. One such case is negative-pressure wound therapy, a form of dressing using vacuum pressure to help clear wounds and allow them to heal. This therapy is one of several treatment options that have been effective in treating diabetic ulcers.[19] Today, there is also more accessibility to other more "naturalistic" forms of treatment that patients may be more comfortable with. Hyperbaric oxygen chambers, for example, may be seen as an alternative natural treatment that is relatively easy for a patient to follow and has exhibited dramatic results in a multitude of cases.[20]

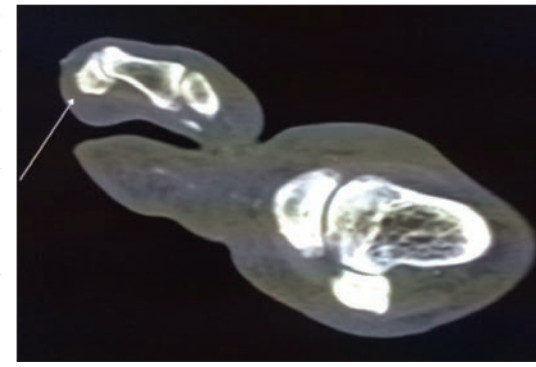

Figure 6a: CT scan depicting 3rd distal toe on right foot after debridement and excision to ensure no further osteomyelitis is present.

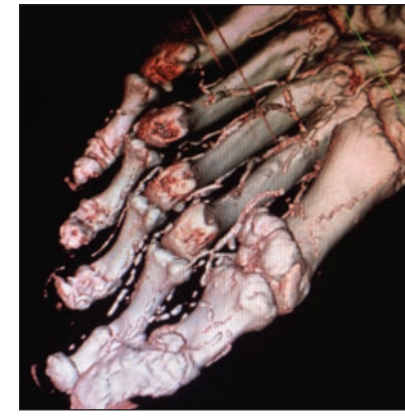

Figure 6b: This picture also depicts the foot, including the calcification of the patient's vessels consistent with peripheral vessel disease.

In a more conventional sense, however, newer and better skin substitutes are now on the market, directed towards skin and soft tissue disarray, and more effective systemic antibiotics are in place to combat infection. To treat more chronic or severe wounds, skin repair treatments such as PriMatrix (TEI Medical), Apligraf (Novartis), and Dermagraft (Organogenesis) are options known to be ef-

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fective in skin repair. However, these treatment options are expensive due to the difficulty of manufacturing skin substitutes. We used Helix 3-CP powder, a collagen specific product, due to its cost-effectiveness and efficacy as a purely collagen-based treatment.

In our experience, this case history clearly demonstrates that topical collagen treatment combined with good podiatric and medical care can be an important part of our armamentarium. This material is highly efficient and effective as demonstrated in this case with a very high-risk patient with many risk factors contributing to the poor status of the foot. Collagen, however, is thousands of dollars cheaper in comparison to the other conventional treatments with skin grafts mentioned earlier.

Helix 3-CP was chosen as an optimal type 1 collagen treatment option as it provides benefits that some other collagen treatments do not.[21] In Helix 3-CP, there is retention of its full triple helix collagen structure as a non-hydrolyzed powder product. Due to this retention of structure, not demonstrated in other collagen products, there is significantly more absorption of collagen into damaged tissue to attract more macrophages and fibroblasts during the inflammatory and proliferation phases of healing. Moreover, its unique size and structure also lead to a greater absorption of wound fluids, naturally reducing the risk of infection. Typically, other products have used fillers such as calcium alginates to improve absorption rates. The combination of efficacy and cost-effectiveness as represented by Helix 3-CP collagen powder product is crucial in progressing today's managed care environment towards optimal patient care for the wide variety of individuals.

More studies and uses of this special protein material must be indicated to further prove its effective place in today's wound healing and treatment arena, as this is a small sample displaying the effectiveness of collagen matrix upon wound healing. Helix 3-CP collagen matrix seems to have great potential in its efficacy and cost-effectiveness, and therefore is an exciting new option that should be considered in the treatment of ulceration in diabetic feet. **PM**

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