Counteracting the Consequences of Diabetic Feet

Here's another approach using collagen matrix.

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Introduction

Peripheral neuropathy secondary to diabetic conditions raises the risk of foot trauma or injury that will go unnoticed or untreated by patients. As it is a chronic condition, the power of prevention in diabetic foot disease mostly lies in the hands of the patient in terms of their education and understanding towards their own body's condition and symptoms. The less cooperative and compliant patients are, the less likely they are to maintain proper blood glucose control and Hemoglobin A1C levels, leading to nerve and blood vessel damage.

Figure 1: The painting "A Clinical Lesson at the Salpêtrière" by Pierre Aristide André Brouillet. Jean-Martin Charcot was a prominent neurologic physician who first described the anatomic changes associated with the osteoarthropathy, now described as Charcot foot, Charcot osteoarthropathy or diabetic osteoarthropathy.

Non-compliant patients will also be less likely to practice proper foot hygiene or utilize proper footwear to protect their feet from trauma. As neuropathy leads to a reduction of sensitivity in the foot region, it becomes increasingly difficult for patients to assess the severity of problems on their own. This issue further compounds risk for future wound formation. Peripheral neuropathy is the most important factor leading to ulceration; it is a condition present in greater than 80% of diabetic patients who have developed foot ulcerations.[1-3]

Infection has been a common and major complication in diabetic wounds. It may be difficult for patients to assess signs of infection, when nerve pathways for pain have been compromised due to a neuropathic process. Symptoms of fever, chills, or leukocytosis may be absent in up to two-thirds of patients with limb-threatening infections, even though they are common criteria used to assess for soft tissue infections or sepsis.[4] Thus, it is imperative to have proper support from a caregiver or family member to examine the feet of a diabetic patient daily.

At times, ulcerations and infections may go untreated, until discoloration or discharge due to the development of cellulitis occurs, eventually leading to the more severe situations, specifically sepsis, necrosis, and/or gangrenous conditions. 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. Major clinics report amputation rates exceeding 50% among diabetic patients with lower extremity infection.[5]

When a patient presents with diabetes, it is essential to thoroughly evaluate the current status of the patient using a multitude of diagnostic exams. A thorough history to understand other medical history, drug use, specifically cigarette smoking, family history, and current living conditions including socioeconomic status can

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be vital. Laboratory tests must be performed to assess the patient's current health condition, nutritional status, and the control of their diabetic condition including glucose levels, hemoglobin A1C, as well as creatinine and blood urea nitrogen (BUN) levels to assess renal function.[6]

Wounds should be cultured in order to provide proper and adequate antibiotic coverage based on the type and severity of infection, if present. Of course, pending the patient's co-morbidities and current medications, any other relevant diagnostic testing should also be performed to get a thorough analysis of the patient's condition to ensure proper treatment.

There are instances that may lead to further damage in the foot by compounding these issues with poor anatomical structure. In Charcot osteoarthropathy (otherwise known as diabetic osteoarthropathy or simply Charcot foot), (Figure 1) the underlying structure of a person's midfoot undergoes drastic and destructive changes. The pathophysiology behind this disease process is still somewhat unclear based on current evidence; however, there is a strong correlation to uncontrolled diabetic conditions. Uncontrolled diabetic conditions lead to a trifecta of neuropathic, vascular, and metabolic bony changes that all contribute to the damage involved in the structure of the foot. With these underlying conditions weakening the structure of the foot, it is prone to collapse with even minor trauma or due to abnormal weight-bearing over time. Trauma to the area can be especially devastating as it can exacerbate the underlying inflammatory response to these conditions, further catalyzing damage to the bones.[7]

As this process of anatomical change progresses, individuals are more likely to experience outer foot damage and wounds that are produced as more underlying pressure is placed upon the midfoot with every step. When wounds begin to form on the plantar aspect of the foot due to poor underlying structure, there is a nidus for infectious processes and soft tissue damage. If proper preventative treatment like good glycemic control and offloading of the foot with individualized orthotic equipment are not performed, wounds and ulcerations are likely to occur and can become very cumbersome to attempt to treat once present.

In severe cases, amputation may be required as a last resort to remove damaged and infected areas of a patient's feet. In diabetics, amputation occurs most often due to trauma, peripheral neuropathy, and infection.[8] The procedure is required more often in men, and African-American and Native American individuals.[9,10]

Amputation has a significantly detrimental effect on individuals' quality of life, not only in an obvious physical sense, but in terms of their emotional and mental state as well. It has been found that most individuals fear amputation more than any foot infection, sepsis, end-stage renal failure, or even death itself.[11] In a physical sense, amputation of the lower extremity leads to severe complications in a patient's health and future, as mobility and circulation become severely limited. If the wound involves a small area or the toes, the lower extremity can be salvaged with aggressive treatment, including distal amputation or remodeling with consistent debridement.

It has been reported that the long-term salvage of 73% of threatened limbs can occur with aggressive foot debridement and necessary revascularization, even in high-risk patients such as those on dialysis.[12] Ulcers may not heal properly despite proper metabolic control, debridement, and antibiotic therapy. Scar tissue from properly healed ulcers in high-risk patients is often not strong and susceptible to re-injury.[13] Off-loading is thus imperative for diabetic patients to prevent the development of both initial and recurrent ulceration. To further increase the efficacy of any aggressive treatment of severe infection and ulceration, collagen dressing of the wound can also help facilitate the healing process while the region is still vulnerable to complications and in need of immediate care.

Collagen

Early wound healing is essential in curtailing the risk of further complications in diabetic feet. Collagen has been used as a catalyst for wound healing in patients who are at risk of having hindered recovery due to problems such as severe infection and neuropathy. 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 not only in rebuilding skin, but it is also involved in the debriding effects and in reducing the bacterial bio-burden during healing to help jump-start the process and prevent subsequent infections or damaging inflammatory proliferation from occurring.

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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 trauma, a wound, or ulceration. During wound healing and 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]

In patients experiencing chronic wounds, an accumulation of enzymes that typically play a role in the degradation of the ECM, matrix metalloproteinase-2 (MMP2)and matrix metalloproteinase-9 (MMP9), can occur. The

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degradation of the ECM would naturally slow the healing process, making it difficult to reach proliferation. In abundance, however, collagen can play a role as an inhibitory substrate to facilitate the regulation of MMP2 and MMP9, reducing the breakdown of the ECM, regulating the imbalance of enzymes and their respective substrates, and driving the healing process towards proliferation.

MMPs and Angiogenesis

The cleavage of these MMPs also activates promoter enzymes for angiogenesis. This angiogenesis leads to the delivery of cells, platelets, and macrophages to the region to protect the wound from infection via inflammatory reactions and deliver more growth factors and nutrients to the area. 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]

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.[18] Collagen has become increasingly used in the practice of wound care and can be delivered as a topical cream or powder for use as needed in dry or wet wounds in the acute or chronic setting.

Case Presentation

A fifty-nine-year-old Caucasian male initially presented in 2014 with plantar calcaneal-cuboid erythema. Within a year, we were consulted for immediate follow-up for treatment of a stage III ulceration with cellulitis and potential osteomyelitis in the same region after he approached his primary care physician and received Keflex 500 mg as an antibiotic regimen. He had a pertinent medical history including uncontrolled diabetes mellitus Type II on insulin with lower extremity neuropathy and Charcot foot deformity.

His Charcot foot deformity had been present for over 10 years at the point of presentation. He had experienced multiple cyclic episodes of wound development and resolution with some complications of overlying drug-sensitive cellulitis in the same midfoot region as a result. Even though he had significant anatomical changes due to his diabetic osteoarthropathy, he had never experienced osteomyelitis. The patient had additional co-morbidities including hyperlipidemia, hypertension, hypothyroidism, and gout treated with gemfibrozil, lisinopril, levothyroxine, and allopurinol, respectively.

This patient reported that he had chronic ulcerations in the midfoot plantar region of his left foot that would "never fully resolve." He was very frustrated with his healthcare up to this point, claiming that he previously had surgeries to try to correct his foot deformities. A midfoot fusion was performed in 2006 to attempt to re-establish proper foot remodeling and prevent complications such as chronic ulceration, infection, and future amputation.

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Three years later, his left foot was re-stabilized using an Ilizarov apparatus to fixate his foot so that he could re-establish a fortified structure for induction of proper gait. Despite the attempts to improve his deteriorating anatomical situation both surgically and through conservative methods such as offloading, rest and elevation, he claimed that ulceration was a persistent problem for him. He explained that even if an ulcer would heal, it would simply return due to the poor underlying structure and soft tissue of his foot.

He continued to utilize proper footwear and/or braces before and after his surgical procedures, but there was still significantly appreciable bony destruction in his midfoot. He had a beefy, red, stage III ulcer measuring 3cm x 3cm x 0.5cm on initial presentation (Figures 2 and 3). Care was immediately provided including soaking and cleaning of the wound and debridement of necrotic debris. He reported that he had difficulty with compliance to his medications and was not properly maintaining his glucose levels within a consistently tolerable range.

Over the course of our care for him, his diabetes was poorly con-

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Figure 2: Presentation of a Stage III ulceration on plantar aspect of midfoot due to Charcot foot deformity, after initial debridement of necrotic debris.

Figure 3: Initial application of Kollagen Medifil II Collagen Matrix wound dressing powder after debridement of the ulcer.

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trolled evidenced by consistently elevated hemoglobin A1C levels between 8% and 9% despite treatment with insulin. Left foot radiographs and CT scans confirmed post-surgical structural changes consistent with attempted surgical correction of his Charcot arthropathy (Figures 7-11).

After multiple procedures and consistent follow-up, in April of 2018, the patient began receiving treatment with Kollagen Medifil II wound care regimen to dress his wound (Figure 4). He continued to receive the same level of care in terms of offloading techniques, cleaning, debridement, and wound dressing, but with the usage of the complementary collagen on his dressings as well.

Upon follow up a few months later, his foot was clear of any infection or inflammation, completely superficial (lacking depth) and measured 1 cm x 1 cm (Figure 5). That had been significant progress for him and the smallest his ulcer had measured since he began receiving treatment and care. Over the next several weeks later, his wound fully healed and is showing positive signs of regression and return to healthy tissue (Figure 6A, 6B). The patient has expressed significant satisfaction with his healing over the course of only several months with the aid of collagen use.

Figure 4: Ulcer fully dressed with Kollagen Medifil II Collagen Matrix powder.

Figure 5: Improvement of ulceration from initial presentations in Figures 1, 2. Ulceration has reduced in all dimensions and has more healthy soft tissue concurrent with appropriate wound healing.

Discussion

The treatment options for wounds in diabetic and other neuropathic feet have greatly improved in recent years. More emphasis has been placed on educating patients, as it is imperative for them to understand the consequences of not properly controlling the blood glucose levels and remaining adherent to their treatment regimens. 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 developed.

To properly treat patients with diabetic feet who have developed neuropathic and osteoarthropathic conditions, a three-pronged treatment is necessary. 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 aspects to ensure prevention of wound development. If a wound does develop, due to a deficiency in any of these aspects of preventative care or factors such as patient non-compliance, it becomes crucial to aggressively treat the patient to salvage their lower extremity. 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.

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 treatment options are known to be effective in skin repair. However, these treatment options are expensive due to the difficulty of manufacturing skin substitutes or grafts. We used Medifil II Kollagen powder, a collagen-specific product, due to its cost-effectiveness and efficacy as a purely collagen-based treatment.

This case history clearly demonstrates that topical collagen treatment combined with good podiatric and medical care can be an important part of our medical armamentarium. Collagen is the basis of our musculoskeletal structure and it has an integral relationship to healing and rebuilding tissues.[19] This material is highly efficient and effective as demonstrated in this case with a very high-risk patient with many risk

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Figure 6a: Fully healed plantar aspect of the patient's foot.

Figure 6b: Close-up of fully healed ulceration of patient's foot.

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factors contributing to the poor status of the structure of his foot regarding both his bony and soft tissues. Collagen, however, is thousands of dollars cheaper in comparison to the other conventional treatments such as skin grafts or aggressive debridement on its own, significantly reducing the healthcare cost burden both on a micro level for the patients and at a macro level for the national healthcare cost burden at large.

Our collagen product of choice was Medifil II Kollagen, and it led to outstanding results in the care of this patient and other patients. In this and many cases, this product has led to full healing of their diabetic foot wounds and has led to great satisfaction among patients. In this specific case, the usage of this collagen prod-

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Figure 7: A dorsoplantar radiograph of the patient's left foot. There is bony destruction and fragmentation at the base of the metatarsals with additional fragmentation of the three cuneiforms. There is also lateral subluxation of the fourth and fifth metatarsals with cystic changes compatible with Charcot arthropathy.

Figure 8: A lateral radiograph of the patient's left foot. This exhibits a post-surgical tibio-talar articulation with a pin placement. At the level of the midfoot, there is bony proliferation dorsally and inflammatory changes at the midfoot consistent with Charcot arthropathy.

Figure 9: An anterior-posterior radiograph of the patient's left ankle. This displays the attempted surgical correction of the patient's Charcot arthropathy. There is fixation via a medial ankle screw.

Figure 10a: A CT image in the lateral view of the patient's left ankle. This exhibits the post-surgical changes of the midfoot with correction at the level of the base of the metatarsals after attempted surgical correction of the patient's Charcot arthropathy.

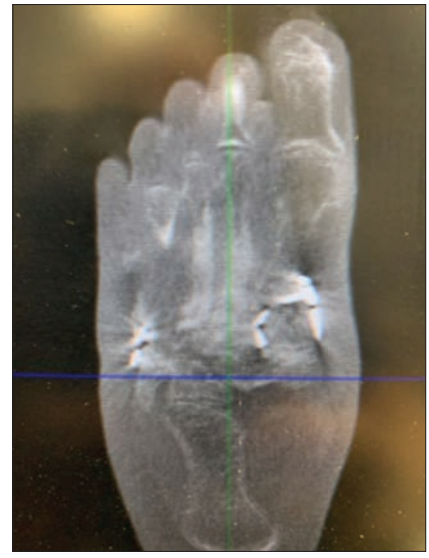

Figure 10b: A CT image of the patient's left foot in an axial view, further confirming significant post-surgical changes of the midfoot.

Figure 10c: A CT image of the patient's left foot in a coronal view, further confirming significant post-surgical changes of the patient's midfoot.

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uct led to results better than we had seen in comparison to other treatments and has been a source of wound resolution for this patient and his chronic foot ulcers.

As our knowledge of the treatment of wounds expands, there is clearly a place for the usage of collagen and collagen-containing products in wound care. We recommend further exploration into the potential uses of this product not only as a treatment option but also through other applications such as scar healing, treatment of burns, or preventative care in lower stage ulcerations. This is a small example of a situation in which a conservative treatment led to healing of a chronic wound that would not otherwise have been able to heal on its own.

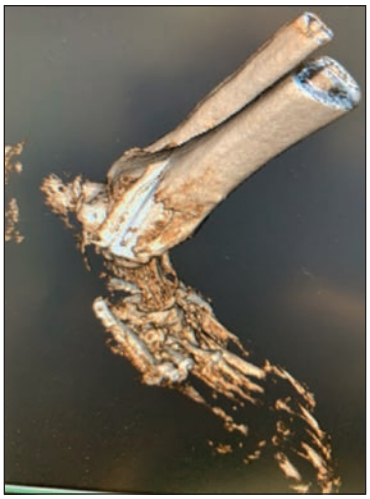

Figure 11: Remodeled 3D image of patient's foot based on obtained CT imaging. Bony degeneration of the midfoot (cuboid-calcaneal and metatarsal) region evident with soft tissue inflammatory changes present.

With that in mind, it is important to replicate such findings in other cases and continue to explore options for patients to resolve these chronic issues to improve their quality of life not only physically but also for emotional well-being. There is great potential for the use of Kollagen Medifil II Collagen matrix in wound and skin care and, therefore, it is an exciting new option that is recommended in the treatment of ulceration in diabetic feet. **PM**

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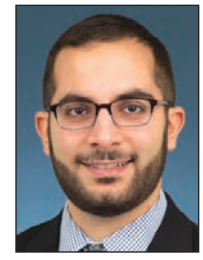

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