Using Stem Cell Therapy to Enhance Diabetic Wound Healing

Here's an update on this emerging treatment.

BY MATTHEW JURIGA, DPM AND JOHN GIURINI, DPM

Scope of the Problem

The management of diabetic foot wounds continues to be a critical and challenging area within the medical field. The longer a wound remains exposed to the environment, the greater the potential for infection and ultimate amputation. Recent reports from the CDC indicate that roughly 8% of the United States population has diabetes mellitus and that the estimated lifetime risk of developing a foot ulcer is 25%.[1] Of these patients, over half will progress to amputations. It has been well established that such amputations in the diabetic population are associated with high morbidity and mortality. Five-year survival rates have been reported as low as 31%.

Complications from diabetic foot ulcers are the primary cause of non-traumatic lower extremity amputations.[2] It is estimated that approximately one-third of the 116 billion dollars spent on medical care of diabetic patients is related to the treatment of foot ulcers.[3]

Given the established multifactorial and complex pathophysiology of diabetes, a logical treatment algorithm for diabetic foot ulcerations would include multiple modalities that augment one another. This concept forms the basis for the multitude of growing treatments to address this international problem and expedite the healing process, of which stem cell therapy is one of many. Others include various local wound care products, hyperbaric oxygen therapy, negative pressure therapy, bio-engineered skin and skin grafts, laser/shockwave/ultrasound therapy, platelet therapy, and many more.

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Basic principles of diabetic wound management remain the same and include pressure off-loading, proper wound bed preparation, and infection control.

How Wound Healing Differs in Patients with Diabetes

In a healthy individual, wound healing progresses through three sequential stages: the inflammatory phase which lasts three to five days, the proliferative phase lasting approximately two weeks, and the remodeling phase which can last from several weeks to several months, depending on the wound. Just prior to inflammation, a fibrin clot forms at the site of the wound site to provide hemostasis. Leukocyte infiltration is the hallmark of the inflammatory phase, whereby polymorphonuclear cells (PMNs) arrive to remove bacteria.

Macrophages then follow and become the predominant cell by day two. Their function is antigen presentation, phagocytosis and release of various growth factors and cytokines. It is during this stage that granulation tissue formation begins. Around day three of the wound, fibroblasts begin to enter. This marks the beginning of the proliferative phase. The hallmark of this phase includes angiogenesis (neovascularization), re-epithelialization and extracellular matrix (ECM) formation.

Continued on page 184

Immature type III collagen and fibronectin are deposited and make up the ECM. This highly integrated process is mediated by various growth factors and cytokines. The remodeling phase begins when the rate of collagen degradation and deposition equalize. This is characterized by continued collagen remodeling, from type III to mature type I collagen, and cross-linking within the ECM.

In patients with diabetes, wounds remain stuck in the inflammatory phase. Neutrophils and macrophages continue to release inflammatory mediators. The critical balance between the proteases and their inhibitors is disturbed, preventing collagen remodeling and ECM formation. Certain functions of neutrophils and macrophages are inherently altered in diabetes, including cell adherence, chemotaxis, phagocytosis, and cytokine production and secretion.[4]

In addition, fibroblasts and keratinocytes display decreased response to growth factors, decreased migratory ability, and increased apoptosis.[5]

Where Stem Cells Come into Play

Stem cell therapy addresses the underlying pathophysiology of diabetic foot ulcers. Stem cells possess the ability to secrete growth factors and cytokines that promote angiogenesis and collagen remodeling, thereby creating an ideal environment for wound healing.

Delivery of stem cells to the target tissue may be accomplished by direct application to the wound, intramuscular or intra-arterial injection. Vojtassak, et al. showed that topical application can be effective and safe in the ultimate closure and healing of diabetic foot ulcers that are not complicated by critical limb ischemia.[6]

In patients with critical limb ischemia, intramuscular injection is the preferred method of delivery. This has been supported by numerous human clinical trials.[7] In addition to the mode of application, the vehicle for delivery is also of critical importance. Collagen-impregnated matrices and fibrin sealants are commonly used as scaffolds for stem cells to adhere and proliferate.

Allogenic Stem Cells

In comparison to autologous stem cells, allogenic stem cells have a greater capability to differentiate given their close resemblance to embryonic stem cells.[8] Additionally, they are easier to access and can be procured noninvasively. While large animal studies show great promise in this area, human studies pertaining to diabetic foot ulcers are lacking. Meschencymal stem cells can be harvested from human placenta, umbilical cord and embryonic sources.

Stem cells derived from placenta have been successfully used to treat chronic wounds related to critical limb ischemia.[9] Tran, et al. showed that placental stem cells significantly improved re-vascularization following lower limb occlusion in a mouse population.[10] Prather, et al. showed similar results, with improved capillary blood flow, limb function, and decreased endothelial damage in ischemic-limbed mice treated with placental stem cells.[11] In a separate study, Prather showed promising preliminary results with intramuscularly injected placental stem cells (PLX-PAD™, Pluristem Therapeutics) in patients with critical limb ischemia to stimulate angiogenesis.[12] However, there are currently no completed trials in human populations pertaining to placental derived stem cells.

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Umbilical cord-derived stem cells have also been used to stimulate wound healing in animal models. They can be derived from both the stroma and blood of the umbilical cord, although the stroma is a much more abundant source. Tark ,et al. locally injected human umbilical cord blood-derived stem cells into a mouse population with diabetic wounds and showed accelerated healing.[13] Again, there are currently no completed human trials utilizing this therapy.

Embryonic stem cells are procured from in vitro fertilized embryos and can be induced to differentiate into multiple cell lines. Obvious ethical questions make this therapy quite controversial and have limited any human studies. Lee, et al. demonstrated encouraging results of enhanced wound healing in diabetics treated with topical application of undifferentiated embryonic stem cells.[14]

Autologous Stem Cells

We have previously outlined how the cells involved in the wound healing process in diabetic patients are impaired in their proliferative and differentiation properties. It therefore makes sense that stem cells harvested from these patients may be fundamentally compromised. Also, harvest of autologous stem cells is an invasive procedure compared to allogenic harvest. However, fewer ethical concerns arise with autologous stem cell therapy, and therefore many more human trials exist to support their use. The two main sources of autologous stem cell therapy are bone marrow-derived cells and hematopoietic-derived cells. Additionally, adipose tissue-derived cells are also being investigated. However, no current human studies have been published.

Falanga, et al. applied bone marrow-derived stem cells to chronic wounds (defined as failure to heal after one year) topically and noted the beginning of closure within two to four weeks.[15] They also noted a direct relationship between the size of the wound and the number of cells used to heal the wound, suggesting that larger wounds require larger quantities of cells.

Kuo, et al. showed that bone marrow-derived mesenchymal stem cells significantly enhanced diabetic wound healing and increased biomarkers involved in tissue regeneration in streptozotocin-induced diabetic rats.[16]

In a recent randomized study, Prochazka, et al. showed a limb salvage rate of 79% in patients suffering from chronic critical limb ischemia and foot ulcers.[17] They injected intramuscular bone marrow concentrate into the

Continued on page 185

ischemic feet that they deemed to be at immediate risk of amputation. Interestingly, they identified lymphopenia and thrombocytopenia as potential causative factors in the remaining 21%, suggesting that platelet supplementation may also be beneficial.

Another recent randomized trial by Lu, et al. showed enhanced healing rates and increased flow in chronic diabetic wounds treated with bone marrow-derived mesenchymal stem cells in comparison to bone marrow-derived mononuclear cells.[18]

Endothelial progenitor cells can also be derived from bone marrow and have been used in diabetic foot wounds. These, however, have not shown promising results to date, likely due to impaired function of the cells themselves.

The CD34+ hematopoietic stem cell (HSCs) is commonly isolated from peripheral blood after administration of specific cytokines to mobilize them into the blood stream. Much of the data on this area has been done in animal studies with promising results. Ravari, et al. applied bone marrow-derived HSCs topically in a small population of humans with diabetic foot ulcers. Complete closure occurred in just under half of those treated.[19] Other trials are currently underway to further evaluate their efficacy in this patient population.

Conclusion

Adult autologous bone marrow-derived stem cells are currently considered the most accessible and reliable method for stem cell therapy in diabetic foot ulcers. When injected intramuscularly, and in some instances, applied directly to the wound, accelerated wound healing and increased blood flow have been reliably shown in human trials. The instance of adverse events is low and therapeutic potential is significant. As more research unfolds, this therapy looks to be a cornerstone in the future treatment of diabetic foot ulcers, particularly in those with concomitant critical limb ischemia. **PM**

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Dr. Juriga is a podiatric resident at the Beth Israel Deaconess Medical Center in Boston, MA and a clinical fellow in Surgery at Harvard Medical School in Boston, MA.

Dr. Giurini is Chief of the Division of Podiatric Surgery & Medicine at Beth Israel Deaconess Medical Center in Boston, MA and Associate Clinical Professor in Surgery at Harvard Medical School in Boston, MA.