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REVIEW ARTICLE

Use of Cellular and Tissue-based Product in the Treatment of Diabetic Foot Ulcers

[1]Thomas E Serena, [2]Raphael A Yaakov, [3]Eliot N Mostow

ABSTRACT

Introduction: The prevalence of diabetes has been rising sharply and the rise in chronic wounds parallels this trend. Lower extremity ulcers present a serious complication for people with diabetes. While debridement of necrotic tissue and off-loading plays an important role in wound healing, many patients with diabetic foot ulcers (DFUs) fail to heal with standard of care (SOC) alone. Unresolved ulcers can lead to complications, such as osteomyelitis and amputation. There continues to be a need for the evaluation of novel wound therapies that can accelerate wound healing and lower the cost of care associated with DFUs. This paper presents recent evidence for the use of cellular and/or tissue-based products (CTPs) and offers an approach for selecting an appropriate CTP.

Materials and methods: A systematic literature search was conducted using PubMed, Embase, Medline, Cochrane library, and NHS Economic Evaluation Database. Full-length articles in English were assessed for relevance to select studies on effectiveness and economic evaluations. Additionally, Google Scholar was used to gather relevant literature on commonly used CTPs, including Apligraf®, EpiFix®, and Dermagraft®.

Findings: Results from randomized controlled trials (RCTs) provided evidence for the superior efficacy of CTPs over SOC alone in treatment of chronic DFUs. In recent studies evaluating commonly used CTPs, significantly higher number of DFUs achieved complete closure with EpiFix® when compared to either Apligraf® or Dermagraft®. While cost-effectiveness studies continue to be limited, current literature suggests that CTPs can decrease the long-term costs associated with the care of DFUs by increasing the healing rate, reducing recovery time, and lowering the risk of infection and complications. Cellular and/or tissue-based products (CTPs) may result in higher average number of ulcer-free months and lower average number of amputations or resections compared to SOC alone.

Keywords: Advanced wound care, Bioengineered skin, Cellular and/or tissue-based products, Cost-effectiveness, Diabetic foot ulcers, Human skin equivalent, Value analysis.

[1]CEO and Medical Director, [2]Clinical Project Lead, [3]Professor and Chair

[1,2]Department of Clinical Research, Wound and Hyperbaric Centers, SerenaGroup™, Cambridge, Massachusetts, USA

[3]Department of Dermatology, Northeast Ohio Medical University Rootstown, Ohio, USA

Corresponding Author: Thomas E Serena, CEO and Medical Director, Department of Clinical Research, Wound and Hyperbaric Centers, SerenaGroup™, Cambridge, Massachusetts USA, Phone: +6179455225, e-mail: serena@serenagroups.com

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INTRODUCTION

The prevalence of diabetes has been rising sharply among all age groups and ethnic backgrounds.[1,2] In the United States alone, over 1.4 million new patients are diagnosed every year.[3] About 4.3 million diabetic patients, representing 15% of the estimated 29.1 million diabetic patients, will develop a diabetic foot ulcer (DFU) in their lifetime.[4-6] Approximately up to 24% of the foot ulcers lead to limb amputation within a period of 6 to 18 months after the first evaluation.[7] Moreover, DFUs impose a substantial burden on the health care system. According to a recent economic study, DFUs add $9 to $13 billion to the direct yearly cost associated with diabetes itself.[8]

The standard of care (SOC) for DFUs includes debridement of the wound, off-loading of the ulcer, management of infection, and revascularization when indicated.[9] While debridement of necrotic tissue and off-loading plays an important role in wound healing, only about a third of patients with DFUs heal with SOC alone. A meta-analysis of 10 control groups from randomized controlled trials (RCTs) found that less than 30% of individuals with a DFU will heal within 20 weeks of commencing SOC.[10] Unresolved ulcers can lead to cellulitis, osteomyelitis, and eventually to amputation. If a DFU does not reduce in size by 50% or more after 4 weeks of SOC, alternative treatment should be considered.[11]

In recent years, there have been significant advances in the field of wound care. Cellular and/or tissue-based products (CTPs), in particular, have made significant gains, evolving from autograft and allograft preparations to biosynthetic and tissue-engineered human skin equivalents. Recent evidence suggests that CTPs are more effective for treating chronic DFUs than SOC alone. Moreover, by increasing the healing rate, decreasing recovery time, and lowering the risk of infection and complications, CTPs can also decrease the long-term costs associated with the care of DFUs.

There are over 70 approved CTPs; however, they have had limited clinical adoption. One of the main challenges

for providers has been securing and maintaining a reasonable reimbursement level. Given the novel nature of CTPs, there continues to be some concern regarding reimbursement decisions. Second, given the perceived complexity of CTPs compared to traditional treatments, physicians are often reluctant to transition. Moreover, the wide variety of CTPs on the market has led to considerable confusion, which has made it difficult for providers to determine which CTPs to use. This qualitative systematic review presents recent evidence for the use of CTPs and offers an approach for clinicians to select CTPs which would result in good evidenced-based clinical outcomes in a fiscally responsible manner.

MATERIALS AND METHODS

A systematic literature search was conducted using PubMed, Embase, Medline, Cochrane library, and NHS Economic Evaluation Database. The search was performed using the Boolean operator, and/or using the following search strategy: ["Diabetic Foot Ulcers" AND "Bioengineered Skin" OR "Human Skin Equivalent" OR "Apligraf" OR "EpiFix" OR "Dehydrated Human Chorion Membrane Allograft" OR "Dermagraft"]. Full-length articles in English were assessed for relevance to select clinical studies on the effectiveness of CTPs in the treatment of DFUs. Clinical studies that consisted of subjects with the following criteria were considered: (1) At least 18 years of age, (2) study ulcer size minimum of 1.0 cm^2 and maximum of 24 cm^2, (3) presence of ulcer extending through the full thickness of the skin but not down to the muscle, tendon, or bone (4) presence of type I or II diabetes, (5) adequate circulation at the ankle or affected leg, and (6) no clinical signs of infection. The clinical studies did not include any subjects with: (1) The diagnosis of cancer or undergoing chemotherapy, (2) history of treatment with immunosuppressants, (3) history of AIDS or HIV, and (4) any connective tissue diseases. Additionally, Google Scholar was used to gather relevant articles and literature on Apligraf®, EpiFix®, and Dermagraft®. Literatures on cost-effectiveness or cost–benefit analyses were also reviewed.

FINDINGS

Apligraf®

Apligraf® (Organogenesis, Canton, MA), a bi-layered tissue-engineered skin equivalent, is composed of living keratinocytes and fibroblasts anchored in a type I collagen matrix (Table 1).[12] It is produced *in vitro* from postnatal human foreskin.[12,13] Immunohistochemistry studies provide evidence that epidermal–dermal interactions suppress epidermal matrix metalloproteinases (MMP) activity.[12,13] In addition, expression of tissue inhibitors of MMPs (TIMPs) and fibronectin in Apligraf® dermis suggests that Apligraf® has the potential to counteract the imbalance between matrix production and degradation in chronic wounds and thus may support wound re-epithelialization.[12,13]

Pham et al[14] compared Apligraf® to a control treatment consisting of saline and woven gauze in patients with DFUs. All participants received SOC including debridement and weight off-loading. Sixteen patients treated with Apligraf® once a week for a maximum of 4 weeks were compared to 17 matched-control patients. Complete wound closure was achieved in 12/16 (75%) subjects in the Apligraf® group compared to 7/17 (41%) subjects in the control group (SOC only).[14] The median time to complete closure was 38.5 days for Apligraf® and 91 days for the SOC arm.[14] The results demonstrated that weekly application of the Apligraf® for a maximum of 4 weeks results in higher healing rate when compared to SOC alone.

Dermagraft®

Dermagraft® (Smith and Nephew, Largo, FL) is a cryopreserved human fibroblast-derived dermal substitute, which is cultured from human neonatal dermal fibroblasts onto a bioabsorbable polyglactin mesh scaffold (Table 1). The fibroblasts proliferate the mesh scaffold and secrete human dermal collagen, matrix proteins, growth factors, and cytokines to create a three-dimensional (3D) human dermal substitute containing metabolically active living cells.[15]

Table 1: Comparison of commonly used CTPs

Product	*Description*	*Graft size*	*Application*	*Storage*
Apligraf® (Organogenesis, Canton, MA)	Neonatal fibroblasts and keratinocytes in bovine collagen matrix	44 cm^2	Remove from liquid-filled pouch. Use within 15 minutes	Must be kept sealed in a nutrient medium and 10% CO_2/air atmosphere under controlled temperature 20–23°C. Shelf life up to 15 days
Dermagraft® (Smith and Nephew, Largo, FL)	Neonatal dermal fibroblasts cultured in a bioabsorbable polyglactin mesh	37.5 cm^2	24-step application process including thawing	Must be stored continuously at minus 75°C ± 10. Frozen 6 months shelf life
EpiFix® (MiMedx Group, Inc., Marietta, GA)	Dehydrated human amnion/chorion membrane allograft	1.5–49 cm^2	Remove from dry pouch	Stored at ambient conditions for up to 5 years

A prospective single-blind RCT across 35 centers was conducted to compare Dermagraft® to SOC in the treatment of DFUs. Complete wound closure was evaluated in subjects randomized to either Dermagraft® or SOC at 12 weeks. Subjects in both of the study arms received identical care with the exception of Dermagraft® applications for the treatment arm. 30% (39/130) of the subjects in the Dermagraft® arm achieved complete wound closure by 12 weeks compared to 18.3% (21/115) in the SOC arm.[15] Dermagraft® when used along with SOC can increase healing in patients with DFUs.

EpiFix®

EpiFix® (MiMedx Group, Inc., Marietta, GA) is a dehydrated form of human amnion/chorion membrane (dHACM) that has preserved the properties of natural membrane. It is composed of multiple layers including single layer of epithelial cells, basement membrane, and an avascular connective tissue matrix (Table 1). Enzyme-linked immunosorbent assay (ELISA) performed on samples of dHACM confirmed that quantifiable levels of the growth factors are present. The assays also established that dHACM contains at least three TIMPs, which directly inhibit the activity of MMPs.[16]

In a prospective, randomized, single-center clinical trial of 25 subjects, Zelen et al[17] evaluated wound size reduction and rates of complete healing after 4 and 6 weeks in subjects with DFUs receiving SOC alone or SOC with EpiFix®. At 4 weeks, the average ulcer surface area reduced was 97.1% for 13 subjects in the EpiFix® group compared to 32% reduction for 12 subjects in the SOC group. The average ulcer surface area reduction at 6 weeks was 98.4% in the EpiFix® group and 70.3% in the SOC group.[17] The results indicate that EpiFix® achieved superior healing rate over SOC alone.

A more recent prospective randomized study provided further evidence that a weekly application of EpiFix® is superior to application every 2 weeks.[18] During the 12-week study period, 92.5% (37/40) DFUs completely healed. Mean time to healing was 2.4 weeks for weekly application *vs* 4.1 weeks for bi-weekly application.[18] This study validates the previous findings that EpiFix® is an effective treatment for DFUs.

Comparative Effectiveness

In a head-to-head prospective randomized controlled multicenter study, Zelen et al[19] compared the effectiveness of Apligraf®, EpiFix®, and SOC in the treatment of DFUs. Percent change in complete wound was assessed after 4 and 6 weeks of treatment in subjects receiving weekly applications of Apligraf®, EpiFix®, or SOC with collagen-alginate dressing. At 4 weeks, 85% of the subjects had achieved complete wound closure in the EpiFix® group compared to 35% of the subjects in the Apligraf® group and 30% of the subjects in the SOC arm. By 6 weeks, 95% of the subjects had achieved closure in the EpiFix® group, significantly higher than Apligraf® (45%) and SOC (35%).

Another comparative effectiveness study, led by Fetterolf et al,[20] supported Zelen's et al findings. Fetterolf et al conducted a retrospective analysis of data collected and published in RCTs. Time to healing and rates of complete wound closure within 12 weeks was assessed for subjects with DFUs treated with Apligraf®, Dermagraft®, or EpiFix®. Within 12 weeks, complete wound closure occurred in 56% of Apligraf® treated ulcers, 30% in Dermagraft®, and 92% in EpiFix®. EpiFix® ulcers had the shortest time to healing with a median of 14 days.

Cost-effectiveness

In an economic analysis by Steinberg et al,[21] Apligraf® was compared to saline-moistened gauze. The benefit was measured by the number of ulcer-free months gained and the number of amputations or resections avoided. In comparison to patients in the SOC, Apligraf® had a higher average number of ulcer-free months (2.3 in the Apligraf® *vs* 1.5 in SOC) and lower average number of amputations or resections (5.4 in Apligraf® *vs* 12.5 in SOC).

Segal and John[22] used a Markov model and observational case studies to evaluate the cost-effectiveness of Dermagraft® in the management of DFUs. With SOC, the average cost per ulcer healed was $10,906 and 12,128 with the additional treatment of Dermagraft®. The observational study revealed that prior to Dermagraft®, the average cost to treat the ulcer was $12,500 but 4,682 after starting Dermgraft® treatment.[22]

In a comparative head-to-head study, Zelen et al[19] also demonstrated that the mean number of grafts used and the graft cost per patient were lower in the EpiFix® group compared to Apligraf®. Over the course of the study, the total number of applications of EpiFix® was 43 (mean 2.14 per study patient) with a total of 154 cm^2 of the product used to cover a cumulative wound area of 68.2 cm^2. The cost of EpiFix® was $1,669 at 2.15 grafts *vs* 6.2 grafts of Apligraf® at $9,216.[19]

The economic analysis suggests that while CTPs may have a higher initial cost, they can prove to be cost-effective in the long run because of shorter treatment periods and fewer complications. One of the concerns with economic evaluations included in this review is that the categories of cost differed substantially. Steinberg assessed the benefits; Segal and John provided an average cost per ulcer; and Zelen et al evaluated the cost of graft per patient. Moreover, only few studies provide sufficient

details on cost-effectiveness from which conclusion can be drawn, which further adds to the complexity of choosing an evidence-based and fiscally responsible CTP.

Value Analysis

There is pressing need for value analysis in medicine, especially, in selecting from the dazzling array of CTPs. The concept of value analysis, introduced by Lawrence Miles, describes value as the ratio of function to cost. Thus, value may be increased by either improving the function or reducing the cost.

Applying the concept of value analysis to wound care, providers can calculate the value of a particular CTP per wound type given the following equation:

$$\text{CTP Value} = (E * S) + R + (2 - A)$$

In this equation, the clinical evidence score (E) is multiplied by a Serena constant (S) and added to a reimbursement score (R). The number of graft applications required (A) also has been taken into consideration. A greater weight is given to clinical evidence in this formula (Table 2). Cellular and/or tissue-based products that have demonstrated efficacy in RCTs will be highly favored. A +1, 0, or –1 reimbursement score is assigned based on net profit or loss from the product (Table 3).

The calculation of CTP value can be performed per wound type. Potentially, it could be performed for each individual facility and clinician as well. For example, CTP "Y" has an RCT demonstrating efficacy in the treatment of DFUs. It has a single RCT giving it a CE score of +1. This is then multiplied by the S constant of 3. Cellular and/or tissue-based products "Y" is in the high bundle and the cost of a 1.5 × 1.5 sheet is $800. The reimbursement is $1,407 netting a profit to the center of $607. The reimbursement score would be +1. Finally, CTP "Y" requires an average of 2.5 applications to achieve complete closure.

$$\text{CTP Value} = (1 * 3) + (1) + (2 - 2.5) = 3.5$$

Table 2: Value analysis: Clinical evidence score

Score	*Description*
–2	Mechanism-based reasoning
–1	Case-series, case-control studies, or historically controlled studies
0	Nonrandomized controlled cohort/follow-up study
+1	Randomized trial single
+2	Randomized trial(s) and comparative effectiveness trial
+3	Systematic review of randomized trials

Table 3: Value analysis: Reimbursement score

Score	*Description*
+1	The facility profits from the product
0	The product is budget neutral
–1	The facility does not profit from the product

A total score of + 3.5 would suggest that CTP "Y" should result in a good evidenced-based clinical outcome in a fiscally responsible manner. In addition, CTP "Y" could now be compared to all of the other CTPs allowing physicians to choose the best product for his or her patient.

DISCUSSION

Chronic wounds represent a significant clinical challenge. A large number of patients with DFUs fail to heal with SOC alone. Nonhealing DFUs are at risk for lower limb amputation. Prompt treatment of DFUs is essential to prevent complications, reduce the cost of care, and lessen the economic burden on the health care system. Thus, it is essential for clinicians to comprehensively assess DFUs to see if a patient could benefit from advanced therapy.

Cellular and/or tissue-based products offer clinicians a more effective treatment option for management of chronic wounds. They have several benefits over traditional treatment options. Cellular and/or tissue-based products provide growth factors and extracellular matrix proteins, which is necessary to accelerate wound healing. Moreover, they can protect against moisture loss and offer some protection against bacteria. Additionally, by increasing the healing rate and shortening recovery time, CTPs can decrease the long-term costs associated with the care of DFUs.

A growing body of evidence suggests that CTPs when used with appropriate SOC can promote accelerated healing of chronic DFUs. Comparative effectiveness studies reviewed revealed that EpiFix® had the highest rate of complete healing when compared to Apligraf® and Dermagraft®. EpiFix® may offer additional molecular advantages as the proprietary preparation process, PURION®, allows for increased availability of growth factors, interleukins, and TIMPs. Additionally, EpiFix® requires the least number of grafts to achieve complete healing.

One of the limitations of the included comparative studies is that the off-loading devices varied. The data reported by Fetterolf et al[20] included Apligraf® patients who used crutches or wheel-chair for the first 6 weeks and then were fitted for tridensity sandal; Dermagraft® patients used extra-depth diabetic footwear with custom inserts or healing sandals; and Epifix® patients were offloaded using a removable cast walker. Moreover, compliance with off-loading devices is another factor that can influence the rate of healing. Future comparative studies should include a uniform off-loading device. Small sample size was also noted as a limitation of the comparative effectiveness study by Zelen et al.[19] The study was not adequately powered to achieve statistical

significance between the Apligraf® group and SOC at 6 weeks time period.[19] A limited number of studies were available for review and these early trials were sponsored by companies that distribute the mentioned CTPs. Nonetheless, these studies are pivotal as they provide robust evidence for the effectiveness of CTPs.

In summary, CTPs offers effective treatment options for DFU patients who have not responded to SOC alone. Cellular and/or tissue-based products can decrease the long-term costs associated with the care of DFUs by increasing the healing rate, decreasing the recovery time, and lowering the risk of infection and complications. Cellular and/or tissue-based products may result in higher average number of ulcer-free months and lower average number of amputations or resections compared to SOC alone.

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