Original article

Adverse events generated by acellular dermal matrix in treatment of diabetic foot ulcers: A Literature Review

Eventos Adversos Generados por Matrices Dérmicas Acelulares en el Tratamiento de Ulceras de Pie Diabético: Una Revisión de Literatura

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ABSTRACT

Background: The purpose of this review was to highlight the acquired complications when acellular dermal matrix is grafted in chronic diabetic foot ulcers.

Methods: Different information sources, Pubmed, Researchgate and Scielo databases were reviewed to summarize different contributions for the past 20 years.

Results: Adverse events reported by application of acellular dermal matrix were infection, seroma, peri-wound erythema, maceration, hematomas, liquefactions, necrosis, gastrointestinal disorder, ischemia, malodor and matrix resorption.

Conclusions: The acellular dermal matrix as dermal substitute generates adverse events when treating diabetic foot ulcers; however, there are optimal allografts that did not register adverse events after application. Regardless the adverse events generate by acellular dermal matrix, they may improve the healing process of uninfected, non-ischemic and full-thickness diabetic foot ulcers. In fact, it is evident that the acellular dermal matrix has advantages compared with standard of care.

Keywords: Diabetic foot ulcer, Acellular dermal matrix, Adverse events, Diabetes.

RESUMEN

Antecedentes: El propósito de esta revisión fue describir las complicaciones adquiridas cuando se injerta la matriz dérmica acelular en las úlceras crónicas de pie diabético.

Métodos: Se revisaron diferentes fuentes de información y bases de datos como Pubmed, Researchgate y Scielo para resumir las diferentes contribuciones de los últimos 20 años.

Resultados: Los eventos adversos comunicados por la aplicación de la matriz dérmica acelular fueron infección, seroma, eritema peri-herida, maceración, hematomas, licuefacciones, necrosis, trastorno gastrointestinal, isquemia, mal olor y reabsorción de la matriz.

Conclusiones: La matriz dérmica acelular como sustituto dérmico genera eventos adversos en el tratamiento de las úlceras del pie diabético; sin embargo, existen aloinjertos óptimos que no registraron eventos adversos después de la aplicación. Independientemente de los eventos adversos generados por la matriz dérmica acelular, estas pueden mejorar el proceso de curación de las úlceras del pie diabético no infectadas, no isquémicas y de espesor total. De hecho, es evidente que la matriz dérmica acelular tiene ventajas en comparación con el tratamiento estándar.

Palabras clave: Úlcera del pie diabético, Matriz dérmica acelular, Eventos adversos, Diabetes.

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Introduction

According to the American Diabetes Association, diabetes mellitus belongs to a set of metabolic diseases featured by the increase of plasma glucose, resulting in alteration of insulin secretion.[1] A chronic complication of diabetes mellitus is the diabetic foot ulcer (DFU), a pathology considered as ulceration, infection and/or

gangrene of the foot. This disease is associated with diabetic neuropathy and different degrees of peripheral arterial pathologies that are the result of the interaction of different metabolic factors.[2] In fact, DFU is an alteration of the lower limb integrity, which is exposed to chronic pressures.[3] The DFU syndrome is a neuropathic alteration that may trigger an ulceration by a resulting traumatism. Here, the ulcer may be infected due to the injury is exposed to external agents, as the hyperglycemia provides an optimal media for the proliferation of microbial agents. This favors the necrosis of adjacent tissues and hinders the healing process.[4] Given that DFU is a chronic pathology, there are different treatments focused on its healing. Debridement is a treatment used when the DFU has not a favorable evolution either by a lack of vascularization of the affected limb or the absence of an adequate treatment of the infection. The debridement consists in wash the injury and extract the necrotic and infected tissue, such an antibiotic treatment is started.[5] The negative pressure wound therapy is other healing procedure, that uses controlled negative pressure using vacuum-assisted closure device to help promote wound healing by removing fluid from open DFU through a sealed dressing and tubing, which is connected to a collection container.[6] Ozone therapy is another treatment that directly applies to the DFU a mixture of ozone and oxygen, which aims to saturate the tissue with oxygen.[7] As a last treatment alternative, when DFU is in an advanced degree of limb involvement, limb amputation is applied.

Currently, acellular dermal matrix (ADM) are applied for the treatment of DFU, where these allografts can be obtained from the skin of tissue donors of the same species.[8] The fabrication process of the ADM is based on the removement of biological components such as cells, epidermis and dermis from the tissue donor throughout freezing and drying processes. These processes help to maintain the integrity and natural biochemistry of the tissue. The ADM is characterized by having two surfaces, a basal membrane opaque in appearance and rough and a connective tissue surface bright in appearance capable of absorbing blood.[9] The basal

membrane allows the cell migration, while the connective tissue surface promote the cell growth favoring the angiogenesis process.[10] A study developed by Kavros et al, evidenced that the PriMatrix ADM achieved a complete wound closure was around of 76% of treated ulcers. Of these healed ulcers, 57.1% healed with 1 application of PriMatrix, and 22.9% healed with 2 applications of PriMatrix.[11] A similar study evaluated the safety and efficacy of two ADM (DermACELL and Graftjacket) against the conventional care of DFU. Results elucidated that after 16 weeks of treatment, patients treated with DermACELL had a significantly higher proportion of completely healed ulcers (67.9%) compared to the conventional care (48.1%), while patients treated with Graftjacket evidenced a non-significantly higher proportion of healing (67.9%) compared to the conventional care (47.8%).[12] In a case report study the ADM MatriDerm was used to treat DFU. Results showed that after 15 days from the surgical treatment the treated ulcers were reduced. Moreover, the ulcers presented a reduction secretion, a complete restoration of the missing volume and good quality of skin.[13] In a study carried out by Campitiello, et al., they observed the efficacy of an acellular Flowable Matrix in comparison with a wet dressing for the treatment of patients with DFU. Both groups were assessed once a week for 6 weeks to value the degree of epithelialization and granulation tissue of the wound. Complete wound healing occurred in 20 patients (86.95%) of the Integra Flowable Wound Matrix group and in 12 patients (52.17%) of the control group. Amputation and rehospitalization rates were higher in the control group compared to the treated group.[14]

As mentioned above, the ADM have been widely used to treat DFU to enhance the healing stages of wounds. However, it has been evidenced that application of the ADM generates adverse events (AEs), which can be subject to different factors. Although several studies have elucidated the advantages of ADM compared to conventional care, highlighting the benefits of this biomimetic materials, there are studies that have evidenced the AEs that this kind of allografts produce. Accordingly,

a review of literature of the past 20 years was performed to highlight the AEs generated by the application of ADM to treat DFU. The information presented not only summarizes the current understanding about the role of the ADM in the healing process of DFU, but also provides information about the possible AEs process to produce allografts and to increase the healing rate of the DFU treated.

Methods

Search strategy

Pubmed, Researchgate and Scielo were searched from 2000 to 2020 for comparative studies involving ADM in the management of DFU. Keywords such as DFU, ADM, AEs, diabetes were implemented using boolean operators (AND and OR). Initially, the studies that enrolled one variable by separately were selected: DFU or ADM, Thereafter, studies that included both variables (DFU and ADM) were included. A total of 85 studies were found during search; however, a total of 37 articles were discarded due to duplication. This left 48 possible articles to be included, but 37 of these were excluded, since they did not show any AEs. Therefore, 11 studies were analyzed to evidence the AEs generated by the ADM when DFU were treated.

Data abstraction and quality assessment

Data was recorded by a bibliographic matrix considering variables such as country, author, year, aim of the study, methodology, results, conclusions and database. Data were classified by colors where red was used to show the studies that are not useful; yellow was implemented to classify studies that used ADM to treat DFU, but they did not mention AEs; finally, green to select the studies that mentioned the AEs when ADM were applied to heal DFU. Data were obtained by tabulation to organize the information and identify the relevant information about AEs generated. Additionally,

the ADM used by different studies were identified and listed. This characterization consisted in classify the ADM by name, manufacturer and main features.

Results

Characterization of ADM

This review allowed to identify the AMD used by different studies to treat DFU (Table 1). General features of the ADM, regarding to their components, were identified such as presence of submucosa of small intestine, collagen, bovine, amnion, human chorion or human skin allograft dermis components. It was identified that ADM are submitted to decellularization processes to extract the cellular component and leave just the extracellular matrix of the donor tissue. Several ADM are composed by either bilayer or three-layer, hydrated and dried, to be located directly into the injury to promote tissue regeneration. However, matrix such as Integra Flowable Wound Matrix and CG Paste are in paste form, and they are applied by syringe favoring the coverage of areas of difficult access or very deep. Overall, ADM act as three-dimensional structure that provide an optimal environment for tissue regeneration, reducing tissue inflammation and promoting stimulation of cellular dynamics such as proliferation, migration, differentiation and molecular synthesis. This kind of allografts are indicated to be implemented in acute, chronic, partial or total wounds, pressure ulcers, venous ulcers, diabetic ulcers, among others.

Table 1. Description of the commercial ADM

ADM	Manufacturer	Features
OASIS Wound Matrix	Smith + Nephew, Inc.	Natural extracellular matrix derived from porcine small intestinal submucosa. Matrix are processed into an acellular

OASIS Ultra Tri-Layer Matrix		template in which cells can grow, and it is comprised of collagen, glycosaminoglycans, proteoglycans, fibronectin, and growth factors, such as basic fibroblast growth factor and transforming growth factor-beta. These matrix are indicated for the management of wounds including partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, tunneling and undermining wounds, diabetic ulcers, trauma wounds, draining wounds and surgical wounds.[15]
GraftJacket Regenerative Tissue Matrix	Wright Medical Technology, Inc.	It is a human acellular dermal wound matrix derived from human tissue and processed from screened donated human skin. This matrix is processed to remove the living cells while preserving dermal structure and also it serves as a scaffold to support cellular repopulation and revascularization.[16]
AlloDerm Regenerative Tissue Matrix	Biohorizons.	It is an allograft derived from human skin that has been screened for transmissible pathogens. Cells were removed without affecting epidermal components. This matrix maintains tissue integrity and it supports tissue regeneration by allowing rapid revascularization, fibroblast repopulation and a minimal inflammatory response.[17]
Integra Flowable Wound Matrix	Integra	It is an advanced wound care paste-matrix composed by granulated cross-linked bovine tendon collagen and glycosaminoglycans. The matrix is mixed with sterile saline solution for gelling. This flowable wound matrix is designed for use in deep soft tissue or tunneling wounds such as diabetic ulcers, pressure ulcers, venous ulcers and chronic vascular ulcers.[18]
Integra Bilayer Wound Matrix		It is an advanced wound care bilayer allograft composed by a porous matrix of cross-linked bovine tendon collagen, glycosaminoglycans and a semi-permeable polysiloxane (silicone layer). This silicone membrane controls water vapor loss, provides a flexible adherent covering for wound surface and adds increased tear strength to the device. The collagen-glycosaminoglycan mixture promotes cell migration and proliferation, and capillary growth.[19]
PriMatrix Dermal Repair Scaffold		It is a cellular collagen matrix derived from fetal bovine dermis. This matrix is rich in collagen Type III, which is a protein crucial in developing and healing process. The matrix processing technology preserves the beneficial properties of natural

		dermal collagen fibers and removes lipids, carbohydrates and other constituents that can induce inflammation. The matrix is also free of artificial chemical crosslinkers. When applied to the patient's wound, the allograft fills with blood, binding both cells and growth factors. The enriched dermal collagen fibers support cellular repopulation and revascularization processes critical in wound healing.[20]
Omnigraft Dermal Regeneration Matrix		It is a matrix comprised of bovine collagen and chondroitin-6-sulfate, that is designed with a controlled porosity and defined degradation rate. The temporary epidermal layer is made of a thin polysiloxane (silicone) layer to provide immediate wound coverage and control moisture loss from the wound.[21]
MatriDerm	MedSkin Solutions	It is an acellular dermal substitute composed by native bovine collagen used to promotes rapid cell migration, proliferation and revascularization. This matrix contains elastin to encourages early vascularization and elastin synthesis.[22]
AlloPatch Pliable Allograft Dermal Matrix	MTF Biologics	It is a donated human allograft dermis. The matrix is processed to remove dermal cells, preserving the extracellular matrix of the dermis. The allograft supports cellular repopulation and vascularization at the surgical site. This matrix contains the deeper reticular portion of the dermis without the papillary layer.[23]
Belladerm		It is human allograft skin minimally processed to remove epidermal and dermal cells. This allograft serves as a framework to support cellular repopulation and vascularization at the surgical site.[24]
Hyalomatrix	MEDLINE, Corius Tissue Regeneration	It is a flexible wound device consisting of a non-woven pad of HYAFF, an esterified hyaluronan-based biodegradable polymer, and a semipermeable silicone membrane. HYAFF fibers promotes healing process in slow-healing and chronic wounds, while the silicone membrane controls water vapor loss, provides a flexible covering for the wound surface and adds increased tear strength.[25]
DermACELL	LifeNet Health	It is matrix which is decellularized to remove at least 97% of donor DNA without compromising the desired biomechanical structure or biochemical properties of the extracellular matrix. The matrix is also terminally sterilized to a sterility assurance level of 1×10^{-6}, consistent with medical device regulations.[12]
Omega3 Wound	Kerecis	It is an acellular fish skin graft rich in Omega3, for the

		treatment of various wounds including diabetic ulcers.[26]
Cytal Wound Matrix	ACELL	This matrix, derived from the porcine urinary bladder mucosa, is based on the MatriStem UBM (Urinary Bladder Matrix) technology. This matrix maintains an intact epithelial basement membrane, promoting neovascularization, cell migration, adhesion and proliferation.[27]
Endoform Dermal Template	Aroa Biosurgery	It is an ovine-based collagen extracellular matrix dressing. This kind of matrix are comprised of collagens I, III, and IV; they have been shown to retain the complex collagen architecture of native tissue as well as extracellular matrix associated secondary molecules including laminin, fibronectin and glycosaminoglycans.[28]
Promogran	Systagenix or Johnson & Johnson Advanced Wound Care	It is a lyophilized, sterile, porous and absorbent matrix that is composed of 55% collagen and 45% regenerated oxidized cellulose. This protease modulating matrix is an advanced topical treatment for chronic wounds that has the ability to positively alter the wound environment to facilitate healing.[29]
Talymed	Talymed, Marine Polymer Technologies Inc.	It is a matrix composed of shortened fibers of poly-N-acetyl glucosamine (pGlcNAc) isolated from microalgae. pGlcNAc is wafer-thin matrix consisting of nano-fibers for management of wounds, including diabetic ulcers, venous ulcers, pressure ulcers, ulcers of mixed vascular causes, partial- and full-thickness wounds, among others.[30]
CG Reallo Putty Paste	CGBIO	It is a micronized human ADM with sterile distilled water. This matrix promotes cell ingrowth and granulation tissue formation. This matrix facilitates cell migration, proliferation, differentiation and angiogenesis.[31]

AEs generated by ADM in the treatment of DFU

Several AEs generated by the application of ADM to treat DFU were found (Table 2). The most common AE was the infection reported in five studies. Other AEs such as seroma, erythema, cellulitis, maceration, liquefaction, necrosis, hematoma and ischemia were reported by the studies where the ADM was applied in the DFU treated. Although matrix reabsorption is not considered as AE, it was presented in 2 studies. Given that AEs are linked to different causes, it was reported that some of

them could be generated by patient non-compliance, triggering ADM failure. It is noteworthy to mention that some studies mentioned AEs generated during treatment of the DFU; however, it was elucidated that AEs were not related to the application of the ADM.[11,14,32–34]

Table 2. Recompilation of AEs generated by ADM in the treatment of DFU

Reference	AEs	ADM used	Study time
[35]	• Drying of the superficial portion of the graft in 4 patients. • Seroma in 1 patient.	GraftJacket Regenerative Tissue Matrix	4 weeks
[36]	• Infection at the wound site either peri-wound erythema or local cellulitis occurred 3 patients.	GraftJacket Regenerative Tissue Matrix	16 weeks
37	• Maceration of the peri-wound area in 1 patient.	OASIS Ultra Tri-Layer Matrix	12 weeks
[38]	• They did not specify the AEs; however, there were significantly more subjects with severe AEs (15.6% inactive and 26.8% in control group; *p = 0.016*) and moderate AEs (31.8% in active and 42.5% in control group; *p = 0.053*).	Omnigraft Dermal Regeneration Matrix	16 weeks
[39]	• 2 infections, 2 hematomas, 3 liquefactions, 5 necrosis, 10 overall.	Human acellular dermal matrix	12 months
[40]	• Partial paste resorption in 2 patients and complete in 2 patients. *	CG Reallo Putty Paste	4 weeks
[41]	• Pain/discomfort in 2 patients. • Wound infection in study ulcer in 9 patients. • Depression/mood disorder in 1 patient. • Gastrointestinal disorder in 1 patient. • Wound infection in non-study ulcer in 3 patients. • Death of a patient (This death was due to complications of diabetes and was not related to the matrix application).	OASIS Wound Matrix	12 weeks
[12]	• They did not specify the AEs; however, the proportion of serious AEs and general early	DermACELL and GraftJacket	16 weeks

	withdrawals were similar among 3 groups (control and 2 treatment groups).	Regenerative Tissue Matrix	
(42)	• 10 wounds, presenting in 8 patients, did not heal after initial matrix application. • Severe ischemia in 3 patients. • Infection in 2 patients. • Patient noncompliance and infection in 2 patients. • Severe ischemia and infection in 1 patient.	GraftJacket Regenerative Tissue Matrix	12 weeks
(19)	• Malodor in wounds in 3 patients. • Pain and swelling in 1 patient. • Erythema occurred in 1 patient.	Integra Bilayer Wound Matrix	12 weeks
(43)	• Wound Infected in 3 patients.	AlloPatch Pliable Allograft Dermal Matrix	12 weeks

Discussion

The ADM are used in the treatment of DFU to enhance the stages of wound healing. However, it has been shown that the application of ADM generates AEs, which may be subjected to different factors. Different studies have compared the ADM with the conventional treatment, highlighting the benefits of this biomimetic material. However, patients treated with ADM have presented some complications. For instance, the GraftJacket Regenerative Tissue Matrix was the allograft that evidenced more complications. The study developed by Brigido et al., evidenced drying of the superficial portion of the graft in 4 of 20 GraftJacket-treated patients. Additionally, a patient developed a seroma, which was aspirated at the first postoperative visit.(35) A similar study evidenced that Infection at the wound site such as peri-wound erythema or local cellulitis occurred in five patients from the debridement-only treatment group and three patients from the Graftjacket treatment group. Authors indicated that none of the patients experienced a systemic infection that required intravenous antibiotic treatment or hospital stay.(36) The study

developed by Winters et al., indicated that the main reasons for ADM failures were patient noncompliance (20%), severe ischemia (30%), infection (20%), patient noncompliance and infection (20%) and severe ischemia and infection (10%). It indicates that 10 wounds, presenting in eight patients, did not heal after ADM application; therefore, the GraftJacket successfully healed 90 wounds (90.0%) in 67 patients (89.3%).[42] It is relevant to mention that GraftJacket Regenerative Tissue Matrix manufacturer indicates that systemic infection and seroma are possible adverse reactions. An allograft called OASIS Wound Matrix was used in treatment of DFU and evidenced depression/mood disorder (1), pain/discomfort (2), gastrointestinal disorder (1) and wound infection in study ulcer (9). The study evidenced one death, but it was not related to the ADM.[41] The studies that used OASIS Ultra Tri-Layer Matrix and Integra Bilayer Wound Matrix registered a similar total wound closure at week 12 after the first application of the allografts, indicating a healing of 54% and 70%, respectively.[19,37] Regarding the AEs, the OASIS Ultra Tri-Layer Matrix evidenced that the only complication was maceration of the periwound area. Nevertheless, this AE was mild in severity and was resolved one week after cessation of treatment.[37] The study that used the Integra Bilayer Wound Matrix showed that three patients developed malodor in their wounds at week 4, one experienced pain and swelling at screening at week 1, and one patient suffered erythema at week 4.[19] The study that evidenced the most AEs was reported by Hu et al., who implemented a human derived ADM. The study indicated that the experimental group (38.5%) and the control group (26.9%) experienced hematoma (7.7%), infection (77%), liquefaction (115%) and necrosis (5%).[39] A study developed by Zelen et al., implemented the AlloPatch Pliable Allograft Dermal Matrix, which triggered infection in three patients that required hospitalization and subsequent IV antibiotic therapy.[43] However, in a similar study developed by the same author, where the same matrix was used, there were no AEs reported.[23] The analysis of the Omnigraft Dermal Regeneration Matrix, DermACELL and CG Reallo Putty Paste was performed; however, AEs generated by Omnigraft and DermACELL were not

specified.[12,38], while the use of the CG Reallo Putty Paste evidenced partial and complete matrix resorption in two patients.[40]

Based on the analysis performed above, it is evidenced the AEs generated for the ADM used in the treatment of DFU. Nevertheless, there are other allografts that can be used for DFU treatment such as AlloDerm Regenerative Tissue Matrix, Integra Flowable Wound Matrix, PriMatrix Dermal Repair Scaffold, MatriDerm, Belladerm, Hyalomatrix, Omega3 Wound, Cytal Wound Matrix, Endoform Dermal Template, Promogran and Talymed. The use of ADM in the treatment of DFU presents several AEs, where most of them are triggered by different factors such as manufacturing defects, patient metabolism and inappropriate treatment after allograft implantation. It is relevant to consider factors such as manufacturing processes to increase aspects such as matrix biocompatibility. It has been shown that the ADM functioning can be altered by inadequate manufacturing processes, which can alter both structure of the tissue and growth factors that play a pivotal role in the regeneration process of affected tissues. These defects lead to tissue encapsulation and excessive growth of scar tissue at edges of the wound.[44] According to Cornwell et al., the step followed for matrix manufacturing may degrade the growth factors that are bound to the extracellular matrix, resulting in rapid degradation and reabsorption of the matrix by the host and lead to scar tissue formation. This can promote AEs like inflammation with accumulation of cells around the edges of the matrix, preventing cellular or vascular infiltration.[45] There are other factors that affect the proper functioning of the matrix; for instance, the wound, since when it has a great extension, it has a long development time and it is draining actively and in excess with an active infection, the receptor tissue is not in optimal conditions to receive the allograft implantation.[44] The AEs in this type of procedures can be caused by different variables, some of them can occur due to non-compliance by the patient[42], due to failure in the adaptation process of the allograft, excessive manipulation and mood of the patient.[41,44] It is relevant to

mention the positive effects generated by the use of ADM such as cell proliferation, migration and angiogenesis, resulting in an adequate closure of chronic ulcers in a certain time. In this context, growth factors are crucial to reconstitute tissue following injury due to some components of the extracellular matrix bind to the growth factors, creating a reservoir of active molecules that can be rapidly mobilized following injury to stimulate cell dynamics.[46,47] In chronic wounds such as DFU, there is an increase of inflammatory cells, which raise the levels of proteases that degrade the extracellular matrix components, growth factors, protein and receptors that are essential for tissue healing.[48] For this reason, allografts such as OASIS Wound Matrix and OASIS Ultra Tri-Layer Matrix, which contain basic fibroblast growth factor and transforming growth factor-beta, are suitable for treatment of partial and full-thickness DFU.

According to the results obtained in this research, ADM were found to be suitable for the treatment of DFU, providing a shorter ulcer closing time compared to conventional treatments. Furthermore, the percentage of biocompatibility, due to its composition, is higher compared to other skin substitutes. However, it is key to clarify that this type of allografts present contraindications when used, generating different AEs. Accordingly, it is important to highlight the patient's commitment to the treatment to be followed once the allograft has been implanted, since several AEs can be derived from a poor post-surgical treatment. This is linked to the subjective view that patients have about the disease, the reliability they feel regarding the effectiveness of the treatment and how they decide to face obstacles or complications that arise when receiving the allograft implantation.

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