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Reviewing Advances in Skin Grafting for Diabetic Foot Ulcers

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ABSTRACT

Diabetic foot ulcers (DFUs) represent a significant health concern linked to poorly managed diabetes, affecting 19% to 34% of diabetic individuals and resulting in impaired functionality, infections, hospitalization, and the potential for amputations or mortality. Effective management involves addressing hyperglycemia, risk factors, and utilizing classification systems like SINBAD and IDSA/IWGDF for treatment. Skin grafting techniques such as split-thickness (STSG) and full-thickness (FTSG) grafts offer effective wound closure options. We acknowledged management for diabetic foot ulcers (DFUs) include autografts, cadaveric allografts, xenografts, and synthetic skin substitutes with natural polymers. Advanced techniques encompass biomaterials, nanobiomaterials, endothelial progenitor cells, and tissue engineering, while cellular therapies like mesenchymal stem cells (MSCs) show promise when properly activated. Innovations in DFU management encompass 3D bioprinting, nanotechnology, gene therapy, and photobiomodulation therapy. Positive clinical outcomes from skin grafting, including acellular fish skin (AFS) grafts, are observed, although challenges like graft rejection and limited technology awareness persist. Further research is essential to seamlessly integrate these advancements into DFU management for enhanced outcomes.

KEYWORDS: Diabetic foot ulcers, wound management, skin graft, split-thickness skin graft, full-thickness skin graft, cadaveric allografts, xenografts, synthetic skin substitutes, nanobiomaterials, endothelial progenitor cells, tissue engineering, mesenchymal stem cells, 3D bioprinting, nanotechnology, gene therapy, photobiomodulation, acellular fish skin graft

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INTRODUCTION

Diabetes, when poorly controlled over an extended period, can lead to the frequent occurrence of diabetic foot ulcers (DFUs), which represent a significantly grave health concern. Globally, an estimated 19% to 34% of the approximately 537 million individuals affected by diabetes are likely to develop diabetic foot ulcers (DFU) during their lifetime. These ulcers can impose severe consequences, including impaired functionality, susceptibility to infections, prolonged hospitalization, and the potential for lower-extremity amputations or even mortality. Shockingly, 10% of patients who develop diabetic foot ulcers (DFU) will succumb within a year of their initial diagnosis, while an additional 20% will necessitate lower extremity amputations, varying from minor (below the ankle) to major (above the ankle) procedures or a combination of both. As such, the impact of diabetic foot ulcers (DFU) on both individual well-being and the healthcare system necessitates heightened attention and targeted interventions to mitigate their devastating effects.[1]

The presence of diabetic foot ulcers (DFUs) poses significant challenges to individuals, particularly when considering the adverse effects of hyperglycemia on immune function and wound healing. Hyperglycemia not only retards the healing process of wounds but also compromises the immune system is ability to combat infections.[2] The healing of diabetic foot ulcers (DFU) is marked by complete epithelialization of previously ulcerated areas. However, the duration of this healing process and the overall rates of recovery can vary substantially, with median healing times ranging from 3 months to over 12 months. Several factors influence the healing outcome, with ischemic ulcers, larger and deeper ulcers, plantar ulcers, and infected ulcers being associated with poor or delayed healing. Moreover, non-ambulatory status further contributes to prolonged healing times and worsens the amputation-free survival rate, in addition to the previously mentioned wound and patient-level risk factors. Given these findings, it becomes evident that managing hyperglycemia and implementing strategies to address

specific risk factors are critical in optimizing diabetic foot ulcer (DFU) healing outcomes and preventing associated complications.[1]

We acknowledge that direct closure is a suitable approach to close small to medium-sized wounds with a favorable result. However, in cases of any extensive, shallow wounds, skin grafting has proven to be a viable and effective therapeutic choice. Such option is also recommended for diabetic chronic wounds,[3] including those with predominant arteriopathic conditions, provided that revascularization is undertaken beforehand. By employing skin grafting techniques, clinicians can enhance wound closure and promote healing in diabetic patients, addressing the specific challenges posed by chronic and complex wounds associated with diabetes.

TYPES OF DIABETIC FOOT ULCERS (DFUS) For individuals with diabetic foot ulcers (DFUs), the utilization of standardized classifications and staging systems is essential for effective communication among healthcare professionals regarding ulcer characteristics. Among these systems, the SINBAD (Site, Ischemia, Neuropathy, Bacterial Infection, and Depth) system has gained prominence in clinical practice. The SINBAD system offers a straightforward scoring mechanism, assigning 0 or 1 point to the assessment of area, depth, sepsis, arteriopathy, denervation, and site, resulting in a maximum score of 6 points. This systematic approach allows clinicians to precisely categorize and evaluate DFUs, facilitating enhanced collaboration and decision-making in the management of these complex wounds. By applying the SINBAD system, healthcare professionals can achieve a standardized and comprehensive evaluation of DFUs, leading to more targeted and effective treatment strategies for patients with diabetic foot ulcers.[4]

Table 1. SINBAD system

Category	Definition	Score
Site	Forefoot Midfoot and hindfoot	0 1
Ischemia	Pedal blood flow intact: at least one palpable pulse Clinical evidence of reduced pedal flow	0 1
Neuropathy	Protective sensation intact Protective sensation lost	0 1
Bacterial infection	None Present	0 1
Area	Ulcer <1 cm2 Ulcer ≥1 cm2	0 1
Depth	Ulcer confined to skin and subcutaneous tissue Ulcer reaching muscle, tendon or deeper	0 1
Total possible score		6

The Infectious Diseases Society of America (IDSA) and the *International Working Group on Diabetic Foot* (IWGDF) have developed a comprehensive classification system that categorizes diabetic foot ulcer (DFU) infections into distinct grades: uninfected, mild, moderate, and severe infection. This classification system serves as a valuable framework for healthcare practitioners to effectively manage and treat infected DFUs. By employing this standardized approach, clinicians can accurately assess the severity of infection, enabling them to tailor appropriate interventions and therapeutic strategies. Not only the IDSA/IWGDF classification enhances communication and collaboration among healthcare professionals but it also facilitates the delivery of targeted and timely care for individuals with diabetic foot infections. Embracing this classification system is vital in optimizing patient outcomes and reducing the burden of diabetic foot complications on the healthcare system.[4]

Table 2. IDSA/ IWGDF system

Clinical Manifestations	Infection Severity	PEDIS Grade
Wound lacking purulence or any manifestations of inflammation	Uninfected	1

Presence of more than or equal to two manifestations of inflammation (purulence or erythema, tenderness, warmth, or induration), but any cellulitis/erythema extends ≤2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild	2
Infection (as above) in a patient who is systemically well and metabolically stable but that has more than or equal to one of the following characteristics: cellulitis extending >2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint, or bone	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (eg, fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycaemia, or azotaemia)	Severe	4

Initially designed as a guideline to aid in decisions concerning hospital admission, the *Infectious Diseases Society of America*/*International Working Group on Diabetic Foot* (IDSA/IWGDF) classification system underwent subsequent evaluation as a predictor of lower extremity amputation (LEA), encompassing both major and minor amputations, rather than its original purpose. However, it is worth noting that this assessment might have inadvertently influenced outcomes due to potential self-fulfilling prophecies.[4]

In contrast, there is also an alternative classification approach, the *Wound, Ischemia, and Foot Infection* (WIFI) system (see **Figure 1**, **Table 3**), which evaluates the risk of major amputation within one year and predicting the need for revascularization to facilitate wound healing and limb salvage. This system was specifically designed to provide a more accurate depiction of the burden of limb-related diseases, thereby enabling improved outcomes assessment and targeted therapy selection.[4] By embracing the WIFI system, healthcare professionals gain valuable insights into the limb is threatened status, allowing for more informed and precise treatment decisions and potentially contributing to better patient outcomes.

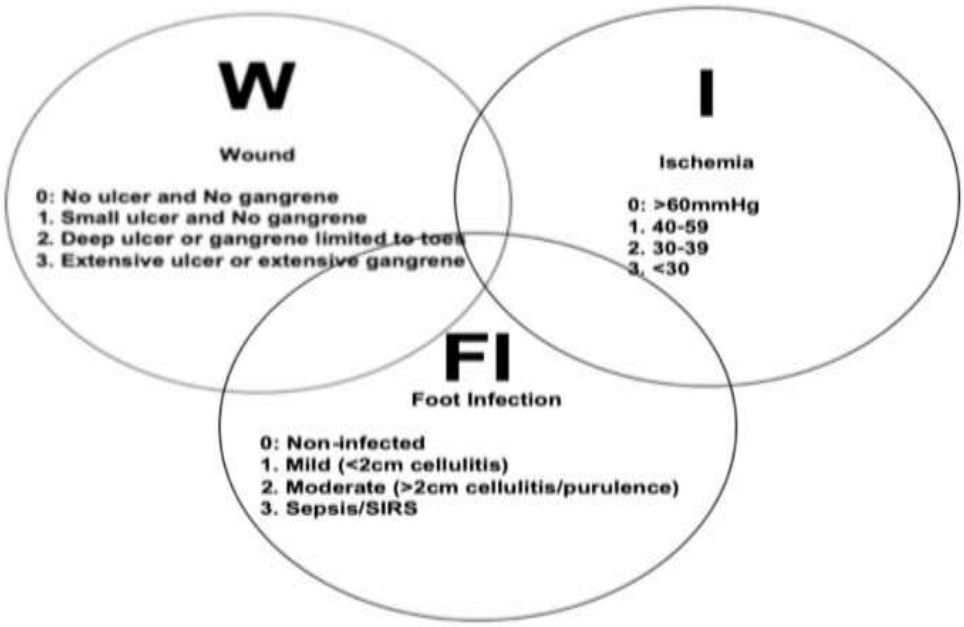

Figure 1. Parameters of the WIFI system

Table 3. The WIFI system

Wound		
Grade	**Diabetic Foot Ulcer (DFU)**	**Gangrene**
0	No ulcer	No gangrene
	Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.	

1	Small, shallow ulcer(s) on distal leg or foot; no exposed bone, unless limited to distal phalanx	No gangrene	
	Clinical description: minor tissue loss. Salvageable with simple digital amputation (1 or 2 digits) or skin coverage.		
2	Deeper ulcer with exposed bone, joint or tendon; generally not involving the heel; shallow heel ulcer, without calcaneal involvement	Gangrenous changes limited to digits	
	Clinical description: major tissue loss salvageable with multiple (≥3) digital amputations or standard transmetatarsal amputation (TMA) ± skin coverage.		
3	Extensive, deep ulcer involving forefoot and/or midfoot; deep, full thickness heel ulcer ± calcaneal involvement	Extensive gangrene involving forefoot and/or midfoot; full thickness heel necrosis six calcaneal involvement	
	Clinical description: extensive tissue loss salvageable only with a complex foot reconstruction or non-traditional TMA (Chopart or Lisfranc); flap coverage or complex wound management needed for large soft tissue defect		

Ischemia			
Grade	Ankle-brachial index	Ankle systolic pressure (mmHg)	Toe Pressure, transcutaneous oxygen pressure (mmHg)
0	≥0.80	>100	≥60
1	0.6-0.79	70-100	40-59
2	0.4-0.59	50-70	30-39
3	≤0.39	<50	<30

Foot Infection	
Grade	Clinical manifestations
0	No symptoms or signs of infection Infection present, as defined by the presence of at least two of the following items: • Local swelling or induration • Erythema >0.5 to ≤2 cm around the ulcer • Local tenderness or pain • Local warmth • Purulent discharge (thick, opaque to white, or sanguineous secretion)
1	Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). Exclude other causes of an inflammatory response of the skin (eg, trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, and venous stasis)
2	Local infection (as described above) with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, and fasciitis), and No systemic inflammatory response signs (as described below)
3	Local infection (as described above) with the signs of SIRS, as manifested by two or more of the following: • Temperature >38C or <36C

	• Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO2 <32 mmHg • White blood cell count >12 000 or <4000 cu/mm or 10% immature (band) forms

There may never be a single diabetic foot ulcer (DFU) classification system, since the specification of any classification will depend heavily on its purpose and clinical setting. It should be emphasized that classifications may also be useful for continued surveillance and some should be repeated following an intervention and periodically to detect changes in the DFU, either improvement (healing) or worsening (eg, infection occurrence).[4]

SKIN GRAFT

Autologous skin grafting procedure, or simply named **autograft**, is a process of harvesting a graft of skin tissue from one point and transferring it onto another place with a skin defect within the same individual is body. It is the most often used skin graft technique to aid the skin regeneration due to the low risk of immunological rejection[5] and its ability to cover large skin defects. When performing coverage of large defect, a surgeon stretches and makes slices or mesh to facilitate a wider stretching.[6] (see **Figure 2**)

Conventional autograft techniques have some significant limitations despite being essential for the treatment of large and severe skin lesions. First, autologous skin grafting causes secondary wounds in the donor area. Second, should the local blood supply in the defect area be compromised, the skin grafting procedure will fail. The latter is the case in any chronic ulcers, including diabetic ulcers.[6]

Clinicians classify autologous skin grafts into two major categories based on their anatomical makeup: split-thickness skin grafts (STSG) it the thickness does not or only partially include the dermal layer, and full-thickness skin grafts (FTSG) if the thickness includes the whole thickness of dermal layer.[5] Very thin split-thickness skin grafts (STSG) which consist of only epidermal layer are sometimes called epidermal skin grafts (ESG).

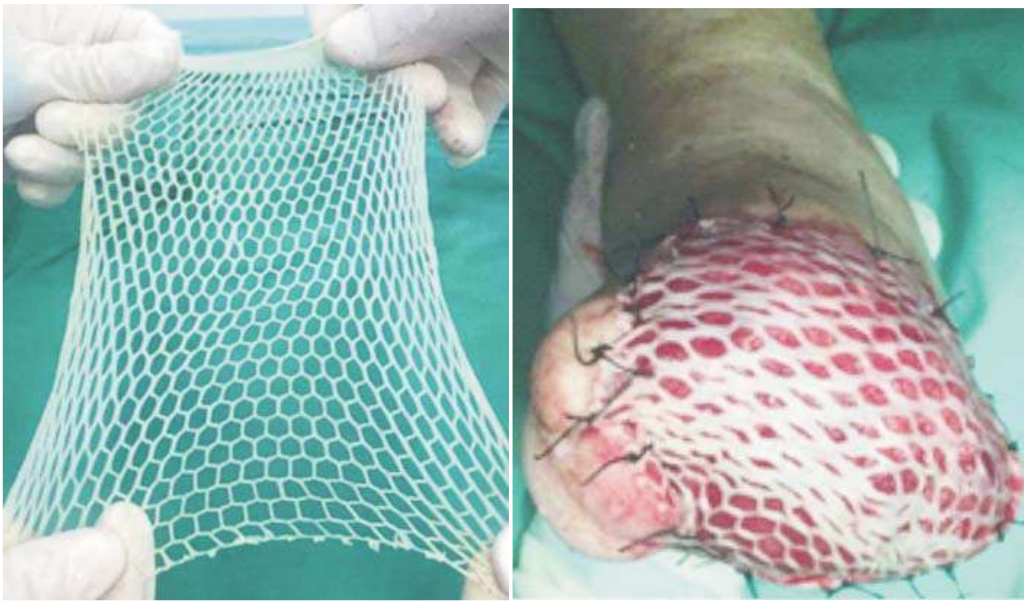

Figure 1. Meshed skin grafts to cover large defect.

Split-thickness skin grafts (STSG) have long been acknowledged as a therapy option for difficult ulcerations. From a retrospective study, Anderson and colleagues reported that split-thickness skin grafts (STSG) coverage for diabetic feet or leg ulcerations showed an average healing time of 5.1 weeks (3 to 16 weeks0 and 90% of the ulcers had healed by the 6th week. They also discovered that skin grafting on ulcers with specific comorbidities like smoking, diabetes, and end-stage renal disease had an average of 7-week healing duration.[7]

In comparing and selecting between split-thickness skin grafts (STSG) and full-thickness skin grafts (FTSG) for diabetic foot ulcer coverage, surgeons need to weigh the advantages and disadvantages based on individual patient factors, wound characteristics, and desired outcomes. The choice should align with the patient's functional needs, aesthetic concerns, and potential for graft take, considering both short-term and long-term implications.

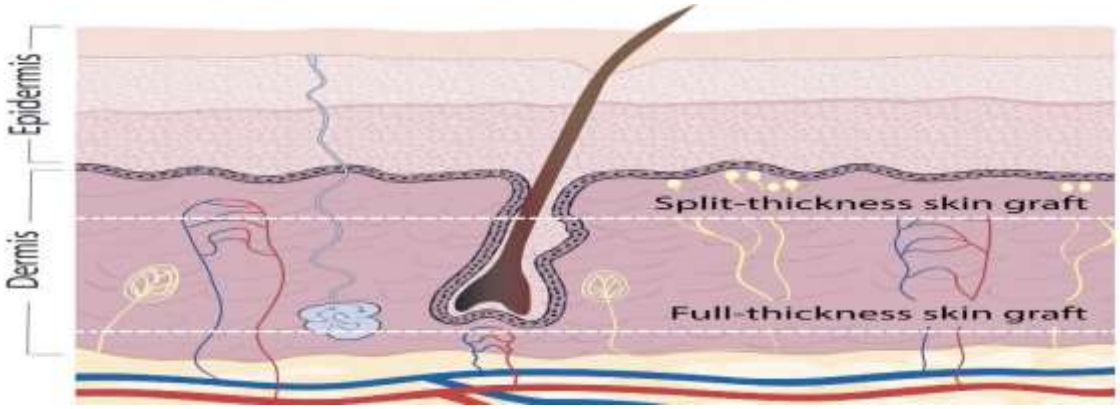

Figure 3. Split-thickness skin grafts (STSG) and full-thickness skin graft (FTSG).

Split-thickness skin grafts (STSG) have demonstrated a higher graft take rate in comparison to full-thickness skin grafts (FTSG). This is attributed to their thinner nature, allowing better integration with the recipient wound bed. The broad availability of donor sites permits split-thickness skin grafts (STSG) to cover extensive wound areas effectively. Split-thickness skin grafts (STSG) are commonly harvested using Humby knives or dermatomes, leading to an easier and quicker harvesting procedure compared to excision and defatting of full-thickness skin grafts (FTSG). Considering the depth of injury, the donor site of split-thickness skin grafts (STSG) heals spontaneously with epithelialization. The disadvantages of split-thickness skin grafts (STSG) are related to its thickness. Split-thickness skin grafts (STSG) are more prone to shear forces and mechanical injury, compromising their durability over time. Over time, split-thickness skin grafts (STSG) may undergo contracture, leading to restricted joint movement and potential functional impairment. Split-thickness skin grafts (STSG) also yield a suboptimal aesthetic appearance due to post-surgical discoloration and an uneven texture.

Full-thickness skin grafts (FTSG) offer superior aesthetic outcomes due to their thickness, closely resembling natural skin (see **Figure 4**). The thicker nature of full-thickness skin grafts (FTSG) provides greater mechanical strength, rendering them more resistant to shear forces and external trauma. Also, full-thickness skin grafts (FTSG) have shown a lower tendency for contracture formation compared to STSGs, contributing to functional preservation. The disadvantages of full-thickness skin graft (FTSG) are related to its demand for greater blood supply and richer vascularization: full-thickness skin grafts (FTSG) exhibit a relatively lower graft take rate compared to split-thickness skin grafts (STSG), and their thicker nature makes vascularization and incorporation into the recipient wound bed more challenging. Moreover, the harvesting process for full-thickness skin grafts (FTSG) involves excision, defatting, primary closure for donor defect, causing a slower harvesting period.

Yet, certain parameters favor split-thickness skin grafts (STSG) implementation. The important thing to remember in cases of chronic foot and leg ulcers like diabetic foot ulcers is the poorly vascularized condition of the defect tissue that will be covered by skin grafts. A split-thickness skin grafting (STSG) will have a better chance of survival and enhanced take rate than a full-thickness skin graft which, due to its thickness, requires a vascular bed with a richer supply.

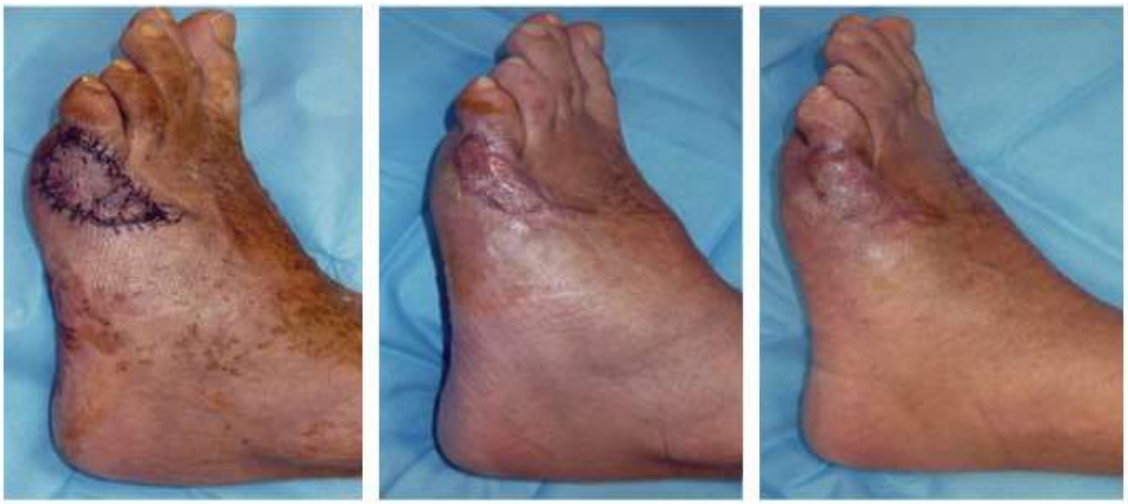

Figure 4. A full-thickness skin graft (FTSG) resembles natural skin appearance.

ALLOGRAFT

Although using autologous skin grafts to cover wounds or skin defects is the gold standard, clinicians often meet the situation in which the patient has limited availability of healthy skin and requires biological or synthetic skin substitutes. The best option for short-term treatment of chronic non-healing wounds such decubitus ulcers, venous leg ulcers and diabetic ulcers continues to be cadaveric allografts.[8] **Allografts**, also called allogenic transplant or homografts, are the skin tissue harvested and transferred between genetically non-identical members of the same species –e.g. from human to human. In recent years, fresh or cryopreserved cadaveric skin allografts have stood out among the options as the best choice due to their availability, affordability, and rapid revascularization. Regarding the cadaveric donor, it is crucial that they have healthy epidermal and dermal cells. The dermal non-cellular components from the allograft are transferred to the wound bed, where the cells then release a number of growth factors and cytokines to foster the development of keratinocytes and skin regeneration.

In plastic surgery, the utilization of cadaveric allograft skin presents a fundamental challenge stemming from its bioavailability, as well as intricate medicoethicolegal and sociocultural considerations. The application of cadaveric allograft skin is hampered by issues regarding its accessibility, which frequently falls short of meeting the existing demands. This disparity is notably pronounced in certain countries where availability is disconcertingly low due to a confluence of factors, including resource insufficiency, logistical complexities, and underlying social and cultural influences. Resource constraints manifest as a significant impediment, as rigorous screening processes govern the utilization of cadaveric allograft skin. Essential steps involve comprehensive evaluation of the donor's medical history and meticulous skin examination. Furthermore, thorough screenings for potential infections, including cutaneous bacterial contamination, human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), human T cell lymphotropic virus (HTLV), syphilis, and cytomegalovirus (CMV), are mandatory components of the donor assessment process.[8] Additionally, it is imperative to acknowledge that allogenic grafts inherently entail the risk of disease transmission, heightened inflammatory responses, and the potential for graft rejection.[9]

Apart from medical matters, the employment of skin grafts from cadaveric donors encounters significant sociocultural and medicoethicolegal challenges. Sociocultural factors play a pivotal role, influencing public perception, religious beliefs, and cultural norms regarding organ and tissue donation. These factors can lead to hesitancy or opposition toward cadaveric skin grafts, impacting both donor availability and recipient acceptance. Additionally, regulatory frameworks govern the acquisition and utilization of cadaveric tissues, ensuring ethical practices and legal compliance. Navigating these intricate sociocultural and medicoethicolegal dimensions is integral to the successful integration of cadaveric skin grafts within the field of plastic surgery.

XENOGRAFT

Another option is **xenografts,** a process of harvesting a graft of skin tissue from one animal species and transferring it onto a skin defect within the human body.[9]

Since the mid-1950s, clinicians, particularly in China, have actively utilized pig skin xenografts to provide interim coverage for substantial wound areas. Upon transplantation, the xenograft initiates the establishment of a nutritive connection with the underlying wound bed. Although initially revascularized, the dermal component of the harvested skin undergoes rapid dissolution and is subsequently replaced by collagen structures. The application of xenografts for temporary wound coverage remains a pivotal procedure in contemporary practice, particularly in regions where ethical concerns preclude the use of allogenic grafts. Notably, these grafts have extended their utility beyond wound coverage to encompass the treatment of both acute and chronic wounds, including the management of severe burns, a role especially significant when donor sites are precarious.[10] In comparison to xenografts derived from pig and bovine sources, acellular fish skin (AFS) graft offers a range of distinct advantages. With a shelf life of three years, these grafts can be stored at room temperature. The protein and matrix structure of marine omega-3 wound matrices is remarkably akin to that of human skin, a result of the meticulous decellularization and preservation process employed. This structural integrity facilitates capillary and cellular infiltration. Acellular fish skin (AFS) grafts are notably abundant in omega-3 fatty acids, which confer additional anti-infective and anti-inflammatory properties. Given these attributes, omega-3 wound matrices emerge as a promising option for the management of complex acute and chronic wounds, representing a noteworthy advancement in wound care.[10]

However, the utilization of xenografts also engenders significant sociocultural and medicoethicolegal considerations. Sociocultural factors actively shape public perceptions and attitudes toward xenografts, given their inter-species tissue transplantation nature. The diversity of cultural beliefs, religious observances (especially the issue of pig skin in Moslem-populated countries), and ethical paradigms greatly influences the readiness of both donors and recipients to engage with xenograft procedures. Furthermore, the integration of medicoethicolegal perspectives plays a pivotal role, necessitating meticulous evaluation and ethical adherence. Xenograft employment brings forth queries about the ethical treatment of animals and introduces concerns regarding informed consent, transparency, and potential health-related hazards. Guaranteeing robust infection screening and comprehensive risk-benefit evaluations assumes paramount importance to ensure both patient safety

and ethical integrity. In addition, regulatory oversight remains a cornerstone to ensure that the practice of xenograft implementation remains harmonious with established ethical standards and legal frameworks. This comprehensive approach seeks to uphold the core principles of medical ethics and safeguard the well-being of all stakeholders involved in xenograft procedures.

ADVANCED METHODS IN SKIN COVERAGE

Synthetic skin substitutes have gained substantial traction and witnessed a surge in adoption within the field. These artificial grafts, often composed of natural polymers, have exhibited a reduced tendency to induce inflammatory responses and the likelihood of rejection, in comparison to allogenic grafts. It is important to note, however, that these synthetic skin substitutes commonly lack the presence of basement membranes and are notably distinct from authentic skin in terms of their structural composition and characteristics.[10]

Biomaterials have ushered in a revolutionary era in tissue engineering, as they enable the creation of synthetic connective, epithelial, or neural tissues. This paradigm shift represents a departure from gradual progress to a fundamentally transformative approach. A pivotal advancement supporting the integration of nanobiomaterials in medical applications is their remarkable dimensional adaptability. Ranging from one-dimensional fibrous configurations like carbon nanotubes and fibers, to multi-dimensional forms such as equiaxed symmetrical gold, platinum, and titanium nanoparticles (NPs), as well as quantum dots (QDs), their versatility becomes evident. This diversity positions nanobiomaterials as a compelling choice for materials employed in wound dressings. Notably, the profound advantage of nanomaterials lies in their substantial surface-to-volume ratio, facilitating extensive coverage of applied surfaces. This attribute presents a distinct opportunity for surface healing, allowing for the effective treatment of vast areas with minimal material consumption.[11]

Endothelial progenitor cells (EPCs) actively contribute to fostering differentiation, angiogenesis, and the mobilization of bone marrow-derived endothelial progenitor cells. This effect is facilitated by their secretion of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor 2 (VEGFR2) factors. These cells have gained prominence within intelligent biomaterial composites, enabling the modulation of microenvironmental cues. Circulating endothelial progenitor cells (EPCs) from the human fetal aorta (HFA) exhibit pivotal expression of CD133 protein, CD34 protein, and vascular endothelial growth factor receptor 2 (VEGFR2). Notably, these endothelial progenitor cells (EPCs) possess robust self-renewal capabilities. This attribute takes on significant importance within the context of murine models for treating diabetic foot conditions. Recent investigations emphasize the critical role of transplanting EPCs derived from the human fetal aorta (HFA) in addressing the inherent microvascular dysfunction associated with diabetic vascular pathology. This pivotal discovery not only introduces an innovative avenue for diabetic foot treatment but also signifies a novel strategy applicable to a broader range of vascular disorders.[11]

Bioengineered grafts have roles to provide oxygen due to their permeability to oxygen, avoid wound dehydration, promote healing, and protect against infections.[5] The pursuit of an optimal skin replacement solution for acute and chronic wounds has yielded a plethora of skin substitutes, ranging from synthetic and natural scaffold-based options to bioengineered alternatives. Moreover, the advent of three-dimensional (3D) bioprinting technology has introduced a viable avenue for crafting skin substitutes utilizing patient-derived primary cells. While this technology is currently in its nascent phase, ongoing advancements are poised to refine its capabilities. A novel and significant concept in skin tissue engineering is prevascularization, particularly relevant for managing chronic wounds. This innovative approach seeks to establish pre-formed microvascular networks within skin substitutes before transplantation, holding substantial promise.[12]

Tissue-engineering has a major limitation considering the required time for the isolated cells to generate a sufficient number of cells, especially in the case of keratinocytes. However, epidermal keratinocytes are terminally differentiated cells that are challenging to work with in culture when feeder layers are not present, proliferate slowly, and have a propensity to dedifferentiate.[13] It is becoming obvious that the various vascularization techniques are moving closer to generating clinically useful tissue transplants. This idea is further supported by the enormous impact extracellular matrix (ECM) molecules, growth factors, and angiogenic factors, as well as their release in a healthy manner, have on tissue growth. Importantly, engineering-based methods emphasize the value of the microenvironment. Endothelial cell alignment and adhesion qualities have been demonstrated to be influenced by electrospun topographies, and the biomaterials employed in scaffolds can have an equal impact on proliferation and differentiation, which can affect therapeutic use.[14]

Cellular therapies for chronic wounds recently employ the unique biological characteristics of mesenchymal stem cells (MSCs); multipotent stromal cells that can differentiate into a variety of cell types, including osteoblasts, chondrocytes, myocytes, and adipocytes. Recent years have witnessed the application of mesenchymal stem cells (MSCs) in cell-based therapy across global experimental and clinical studies, addressing diverse disorders. These versatile cells are sourced from various adult tissues including bone marrow, adipose tissue, muscle, and lung, as well as perinatal tissues like umbilical cord, umbilical cord blood, and placenta. Despite persistent challenges linked to pre-activation of MSCs, their remarkable regenerative potential holds significant promise

in treating refractory conditions. Indeed, emerging research suggests that pre-activated mesenchymal stem cells (MSCs) often yield superior therapeutic outcomes compared to their naive counterparts across several clinical scenarios. Paving the way for a new era in mesenchymal stem cell (MSC) clinical utility, the strategic implementation of "pre-activation" techniques stands to optimize mesenchymal stem cell (MSC) therapeutic efficacy and tailor their application to specific conditions.[15]

EMERGING TECHNOLOGIES AND INNOVATIONS

Three-dimensional (3D) bioprinting - The field of tissue engineering has harnessed three-dimensional (3D) bioprinting, a subset of 3D printing, to fabricate biomimetic tissues. This additive manufacturing technique creates mechanically robust, biocompatible structures mirroring the natural microenvironment with exceptional flexibility and reproducibility. The three primary categories are inkjet-based, extrusion-based, and light/laser-based three-dimensional (3D) bioprinting methods.[16] In fostering vascularization and tissue integration, human dermal microvascular endothelial cells (ECs), neonatal human dermal fibroblasts, epidermal keratinocytes, and three-dimensional (3D) bioprinted skin substitutes are employed. These endothelial cell (EC)-containing constructs were implanted in mice with full-thickness excision wounds to assess wound healing. Compared to commercial skin substitutes and acellular matrix controls, the bioprinted endothelial cell (EC)-containing graft expedited wound healing by 17% improvement in wound contraction. Similarly, a distinct study revealed that in vitro, 3D-printed constructs incorporating human cord blood endothelial cells (ECs), placental pericytes (PCs), dermal fibroblasts, and keratinocytes exhibited biological and morphological activities akin to native human skin.[16]

Nanotechnology has enabled the creation of functional biomaterials. These materials possess surface characteristics that actively reduce device rejection rates in both injectable and implantable biomaterials. Furthermore, surfaces can be modified by grafting macromolecules, enhancing their responsiveness to stimuli. This augmentation bolsters the efficiency of applications involving drug release. Additionally, in tissue engineering, surfaces adorned with grafted macromolecules showcase a hierarchical nanostructure resembling natural nanotextured surfaces. Recent research highlights the potential of surface nanostructures in preventing thrombosis formation caused by traditional bare-metal stents. Moreover, grafting macromolecules onto fiber surfaces has demonstrated controlled medication release to support wound healing initiatives.[17]

Nanotechnology also holds promise as a transformative tool to elevate skin grafting outcomes in the context of diabetic foot ulcers. One potential application lies in the development of scaffolds and matrices that mimic the intricate structures of natural tissues. These nanotextured constructs promote cellular attachment, proliferation, and differentiation, critical factors in achieving successful graft integration. By providing a biomimetic environment, nanotechnology enhances the chances of graft success. Incorporating nanotechnology into skin grafting for diabetic foot ulcers, while promising, requires careful consideration of safety and regulatory aspects. The potential of nanomaterials to revolutionize grafting outcomes underscores the need for ongoing research to optimize their design, fabrication, and clinical implementation. In the future, the integration of nanotechnology into diabetic foot ulcer management could pave the way for more effective and tailored solutions, ultimately improving patient outcomes.

Gene therapy stands as a dynamic frontier in therapeutics, aimed at tackling conditions that face limited treatment avenues, with the overarching goal of achieving substantial enhancements or potential cures. In the domain of managing diabetic foot ulcers, a pioneering strategy centered on VM202 gains prominence. VM202 represents a plasmid DNA encoding two distinct isoforms of hepatocyte growth factor (HGF), fostering an innovative trajectory. This approach holds promise not only for diabetic foot ulcer treatment but also for addressing the vexing challenges posed by painful diabetic peripheral neuropathy, both of which pose significant dilemmas for contemporary medical interventions. A notable facet of VM202 lies in its potential to target both wound healing and the concurrent neuropathic pain component associated with diabetic foot ulcers. The progress of VM202 through phase II studies, particularly within the critical limb ischemia context, instills a sense of promise and anticipation in the realm of gene-based therapeutics. The evolution of such interventions augments the prospects of redefining diabetic foot ulcer management, concurrently aiming at mitigating wound healing impediments and assuaging pain burdens. The pursuit of VM202 and akin gene therapy modalities represents a paradigm shift toward innovative and comprehensive solutions for the intricate realm of diabetic foot complications.[18]

Gene therapy also presents an exciting path to enhance skin grafting outcomes for diabetic foot ulcers by manipulating genetic elements that govern wound healing. One avenue involves introducing genes that stimulate angiogenesis. By introducing genes encoding vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF), blood vessel formation at the graft site can be enhanced, resulting in improved nutrient supply and graft viability. Another strategy in gene therapy focuses on boosting the production of extracellular matrix components, like collagen. Genes responsible for collagen synthesis can be delivered to the graft site, promoting tissue durability and strength. Furthermore, gene therapy can manipulate the local inflammatory milieu. Introducing anti-inflammatory genes can help mitigate the chronic inflammation characteristic of

diabetic foot ulcers, thus fostering a favorable microenvironment for graft integration. Gene therapy's promise in diabetic foot ulcer skin grafting is evident, despite challenges like refining safe and targeted gene delivery methods. Rigorous research is essential to optimize gene therapy protocols, ensuring their efficacy and safety in clinical applications. In the future, the convergence of gene therapy and skin grafting could potentially revolutionize diabetic foot ulcer management, addressing the underlying molecular factors that hinder successful graft integration and wound healing.

Phototherapy also emerged as a therapeutic modality for diabetic foot ulcers. Noteworthy findings have arisen, shedding light on the potential of photobiomodulation (PBM) treatments. These interventions have demonstrated a significant enhancement in wound areas, substantiated by concurrent elevations in key prohealing factors. Specifically, heightened levels of vascular endothelial growth factor (VEGF) associated with angiogenesis and transforming growth factor-beta (TGF-β) linked to matrix reconstruction and epithelial closure were observed. Importantly, the application of photobiomodulation (PBM) therapy resulted in lower levels of tumor necrosis factor-alpha (TNF-α), indicative of reduced inflammation.[19]

Considering its prohealing mechanism, clinicians believe phototherapy also holds promising potential as an adjunct to skin grafting procedures. One of the key mechanisms through which phototherapy augments skin grafting is by promoting angiogenesis, mediated by factors such as increased production of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which later facilitates graft survival and integration. Additionally, phototherapy reduces the production of pro-inflammatory cytokines and exerts anti-inflammatory effects, thereby mitigating inflammation at the graft site, minimizing graft rejection and complications. Moreover, phototherapy modulates cellular metabolism and enhances collagen production, essential for graft strength and durability. The activation of fibroblasts and keratinocytes by phototherapy fosters granulation tissue formation, facilitating wound closure and graft integration. Its impact on collagen synthesis contributes to improved graft resilience over time. However, the optimal parameters and protocols for effective phototherapy in skin grafting contexts warrant further investigation to harness its full therapeutic potential.

CLINICAL OUTCOMES

A systematic study reviewing the outcomes of split-thickness skin grafting on diabetic leg and foot ulcers encompassing eleven studies and 757 patients with 759 foot/leg ulcers revealed a healing rate of 85.5% within an average span of 5.35 ± 2.25 weeks, accompanied by a 4.2% recurrence rate, 4.4% infection rate, and 12.1% regrafting rate over an average follow-up duration of 2 years.[20] Other study discovered that full thickness skin grafting combined with negative pressure wound therapy (NPWT) can be the recommended alternative treatment to split-thickness skin grafts (STSG) for the diabetes mellitus foot amputee.[21]

In addition to the well-known split-thickness skin grafts (STSG) and full-thickness skin grafts (FTSG), which have long established good clinical outcomes, the utilization of acellular fish skin (AFS) grafts has yielded favorable results in treating diverse wounds, including diabetic foot ulcers (DFU) and burn wounds. Its unique attributes facilitate strong adherence to wound beds, reduced dressing requirements, promotion of pro-inflammatory healing, and acceleration of comprehensive wound healing. Notably, acellular fish skin (AFS) grafts prove cost-effective compared to contemporary wound management approaches like dehydrated Human Amnion/Chorion Membrane (dHACM) allografts, collagen alginate dressings, and 1% silver sulfadiazine cream in burn wounds.[22]

COMPLICATIONS

Graft harvesting poses notable risks at the donor site, encompassing scarring, chronic pain, abnormal pigmentation, and infections. Application of allogenic skin grafts or xenografts carries substantial potential for rejection and therapeutic failure.[3] Cases of skin graft failure or necrosis have largely been linked to limited vascularization. Clinicians should never understate the significance of blood supply in guiding the suitability for skin grafting. Vascular desobstruction procedures are frequently deemed necessary prior to wound coverage in cases involving vasculopathic diabetic patients.[5]

FUTURE DIRECTIONS AND CHALLENGES

In skin grafting for diabetic foot ulcers (DFUs), the trajectory of future advancement encompasses multifaceted strategies. Personalized and biomimetic grafts, driven by advancements in tissue engineering and three-dimensional bioprinting, hold potential to closely emulate the native skin microenvironment. These grafts, customized to match individual wound characteristics, offer improved integration and healing outcomes. Stem cell-based therapies, notably utilizing patient-derived mesenchymal stem cells (MSCs), present a paradigm shift by promoting angiogenesis, dampening inflammation, and enhancing graft integration. Gene therapy augmentation introduces genes for angiogenesis, collagen synthesis, and anti-inflammatory responses, but successful implementation requires refined gene delivery methods. Nanotechnology integration enhances graft properties through nanomaterial infusion, necessitating research for safe and effective usage. Advanced imaging techniques and sensors are poised to revolutionize graft monitoring in real time, providing valuable insights into integration and tissue regeneration.

However, clinicians also face future challenges in grafting for diabetic foot ulcers (DFUs). Graft rejection remains prominent, particularly with allogenic and xenografts,

necessitating strategies to enhance graft immunocompatibility. Selecting the optimal graft type, whether autografts, allografts, xenografts, or synthetic substitutes, requires a thorough understanding of patient-specific factors. Regulatory and ethical considerations accompany emerging technologies like gene therapy and nanotechnology. The need for educating clinicians about new techniques poses a challenge, as does addressing the cost-effectiveness and accessibility of advanced methods. Fostering awareness, training, and refining cost-efficient techniques are crucial to the widespread integration of these advancements for diabetic foot ulcer management.

CONCLUSION

Diabetic foot ulcers (DFUs), prevalent among poorly controlled diabetes patients, pose significant health risks, with potential for impaired functionality, infections, and even amputations. Effective management entails controlling hyperglycemia, addressing risk factors, and utilizing classification systems for treatment. Skin grafting techniques, such as autografts, allografts, xenografts, and synthetic substitutes, offer successful wound closure. Advanced strategies involving biomaterials, nanobiomaterials, cellular therapies like mesenchymal stem cells (MSCs), and innovative approaches like 3D bioprinting, nanotechnology, gene therapy, and photobiomodulation show promise. Positive clinical outcomes from split-thickness and full-thickness skin grafting are noted, with emerging options like acellular fish skin (AFS) grafts. However, challenges like graft rejection and limited awareness of novel technologies among clinicians persist, necessitating further research to fully integrate these advancements into diabetic foot ulcer management for improved outcomes.

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