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Management of diabetic foot ulcers using advanced biomaterials and tissue engineering: A systematic overview

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Abstract

Diabetes mellitus is a significant health issue with diabetic foot ulcers (DFUs) being a major complication affecting between 15-25 per cent of patients, leading to considerable morbidity, such as amputation and increased expenditure in health care. This systematic review assesses the role of advanced biomaterials and tissue engineering in managing DFUs, considering the limitations of conventional treatment methods. Peer-reviewed literature (20152025) was clearly and comprehensively reviewed in the PubMed, Scopus, and Web of Science databases, including clinical trials and preclinical studies of biomaterials (e.g. hydrogels, electrospun nanofibers, 3D-printed scaffolds), and use of tissue engineering strategies (e.g. stem cell therapies, bioengineered skin substitutes). The interventions are designed to reduce chronic inflammation, deranged angiogenesis, and tissue regeneration deficiency, which are characteristic of DFUs. Evidence has shown that biomaterials, such as hyaluronic acid hydrogels and collagen dressings, increase the percentage of wound closure by 20% to 30% in comparison to standard care, whereas tissue-engineered products, such as Apligraf and Grafix, increase epithelialization by reducing the number of days it takes to heal. New technologies, including innovative biomaterials, 3D bioprinting, and nanotechnology, offer custom-made and adjustable solutions to treatment. Nevertheless, the problems of expensive prices, regulatory obstacles, and the absence of long-term data persist. The review indicates that these advanced therapies have the potential to revolutionize the way the problem of amputations is addressed and patient outcomes enhanced by prompting more research on how this is received in a more cost-effective and potentially scalable manner, as well as how to introduce such characteristics into digital health tools. There is a need to bridge the gap between these innovations and clinical practice, and a multidisciplinary approach can help address the challenge of the global burden of DFUs.

Keywords: Diabetic Foot Ulcers; Biomaterials; Tissue Engineering; Wound Healing; Regenerative Medicine

1. Introduction

1.1. Background and Significance

Diabetic foot ulcers (DFUs) are a serious and widespread problem of diabetes mellitus, which is a long-term condition impacting more than 537 million individuals all over the world, and this number is estimated to reach 783 million by the year 2045 (International Diabetes Federation, 2021). Diabetic foot ulcers (DFUs) can be identified as a severe and more common issue of diabetes mellitus, a chronic condition found in over 537 million people globally, and is projected to increase to 783 million by the year 2045 (International Diabetes Federation, 2021). DFUs are slow-healing wounds typically located on the plantar side of the foot. The result is often a combination of peripheral nerve insufficiency and inadequate flow system function, which is frequently associated with persistent hyperglycemia. The impact these ulcers have on the quality of life is enormous since it implies the limitation of mobility, constant pain, and the higher risks of the development of debilitating complications. DFU development in diabetic patients occurs in 15-25% of patients

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during their lifetime (Armstrong et al., 2017). The higher the prevalence is in the regions with low access to care (Armstrong et al., 2017). DFU pathology becomes complex, and the processes of dysfunctional angiogenesis, persistent inflammation, and the inability of the extracellular matrix (ECM) to function properly prevent wound recovery. Conventional treatment modalities, including debridement and offloading, are ineffective in ameliorating these predisposing defects, resulting in prolonged healing and even recidivism. In this case, the article systematically reviews new biomaterials and tissue engineering approaches — such as hydrogels, electrospun nanofibers, and stem cell-based therapies — that offer novel ways to manage diabetic foot ulcers (DFUs) by targeting the molecular and cellular processes of wound healing. By providing stronger clinical evidence, these innovations aim to improve treatment effectiveness and help reduce the burden of this debilitating condition.

DFUs pose a significant cost and burden to the economy and society, ultimately increasing pressure on healthcare systems globally. The annual expenditure on diabetes administration in the United States is estimated to be between $9 billion and $13 billion, which accounts for a significant portion of the overall cost of diabetes in the United States, calculated to be $327 billion (American Diabetes Association, 2018). As shown in Europe, there are equal issues. A 2008 study revealed that the average cost of DFU treatment, including hospitalization, wound care, and wound-related amputation, in different countries was approximately 10,000 euros per patient (Prompers et al., 2008). Management of unhealed and DFUs included was estimated to cost more than 5 billion a year in the UK, of which diabetic wounds comprised a large percentage because they took more time to manage (Guest et al., 2018). The foremost distressing aspect is that the prevalence of DFU is increasing all over the world, particularly in the low- and medium-income countries where the patients are being subjected to an unacceptable level of difficulty because they do not get readily available access to highly developed care, which, in its turn, negatively affects the level of infection and amputations. Through DFUs, amputations in the lower limbs may reach up to 20%, and the death ratio within 5 years of implementing the amputation is almost 50%, close to some cancer rates (Armstrong et al., 2020). Such enormous figures underscore the relevance of the next stage of medical therapy, which could surpass traditional care, offering better therapeutic effects and generating a lower economic impact on citizens by utilizing new technologies, such as bioactive bandages and cultivated skin.

The adverse outcomes of DFUs, such as chronic infections and amputations, demonstrate the importance of new interventions. A perpetual wound caused by a maladjusted inflammatory process, diminished/deformed vascularization, and the presence of biofilms tends to expand chronic wounds of DFUs, making them vulnerable to infections, such as methicillin-resistant Staphylococcus aureus (MRSA) (Lipsky et al., 2016). The incidence of infectious disease of DFU is 50-60 percent, severe cases lead to osteomyelitis or sepsis, and the risk of mortality drastically increases. DFUs have a high recurrence rate, with 40% of patients experiencing a recurrence within a year and 60% within three years (Prompers et al., 2008). Besides the mechanical ones, DFUs create an overwhelming psychosocial burden, such as social isolation, depression, decreased quality of life due to persistent pain, and inability to move freely. The inefficiency of traditional treatment methods in actively inducing tissue healing and combating infection necessitates the use of novel biomaterials and tissue engineering strategies. Developments such as 3D-printed scaffolds, mesenchymal stem cell treatments, and innovative biomaterials with controlled drug delivery systems offer potential solutions to these problems. In this article, the evidence base of clinical trials and preclinical studies (2015-2025) is utilized to assess the efficacy, challenges, and future outlook of these innovative treatments, which must be integrated into a clinical therapeutic regimen to alleviate the burden of DFUs in the modern world.

1.2. Purpose of the Article

This article presents an extensive and thorough survey of emerging, promising biomaterials and advanced tissue engineering methods for treating diabetic foot ulcers (DFUs), highlighting the shortcomings of conventional techniques for managing these ulcers. It considers how new materials, such as hydrogels, electrospun nanofibers, and stem cell-based therapies, are potentially effective in the wound healing process and reducing the possibility of amputations, based on a review of published peer-reviewed articles in PubMed and Scopus (2015-2025). Its discussion evaluates such clinics in terms of their improvement of clinical outcomes, e.g., wound closure rates and healing time, as well as their shortcomings, e.g., adverse financial burdens and regulatory issues. It also examines the potential of these technologies in a clinical setting, promoting not only their implementation but also emphasizing the importance of enhancing patient outcomes and reducing the burden of DFUs worldwide.

1.3. Scope and Methodology

This literature review paper systematically examines the literature on advanced biomaterials and tissue engineering in the management of diabetic foot ulcers, with a primary focus on the period from 2015 to 2025. The sources include peer-reviewed journals (e.g., PubMed, Scopus, Web of Science), clinical trial databases (e.g., ClinicalTrials.gov), and news about new technology. Inclusion criteria include studies that evaluate biomaterials (e.g., hydrogels, nanofibers, 3D-

printed scaffolds) and tissue-engineered products (e.g., stem cell therapy, bioengineered skin substitutes) in preclinical or clinical studies for the treatment of DFUs. The criteria used to select studies focus on efficacy, safety, and translational potential. The basis of the studies is evaluated based on rates of wound closure and the time it takes for wounds to heal. Subsequently, this stringent approach will guarantee an overall assessment of new DFU treatments.

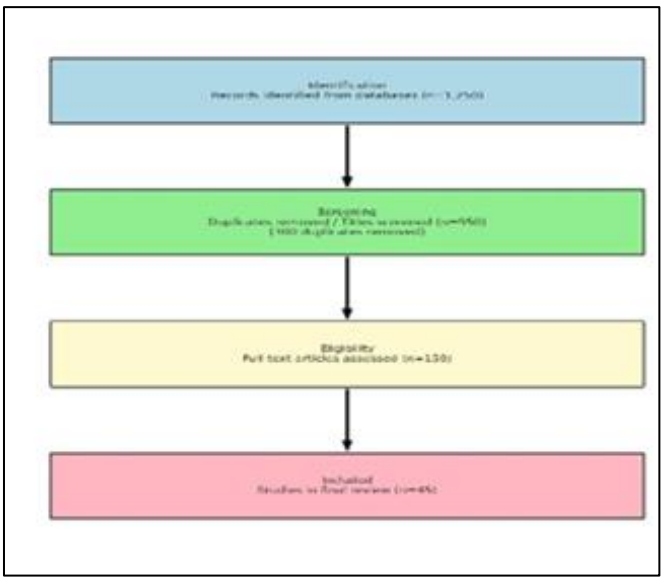

Figure 1 PRISMA Diagram

2. Pathophysiology of Diabetic Foot Ulcers

Diabetic foot ulcers (DFUs) arise from complex pathophysiological mechanisms, including hyperglycemia-induced inflammation, neuropathy, and vascular dysfunction. This section explores these processes, highlighting impaired wound healing and infection susceptibility driving chronicity and complications in DFU management.

2.1. Mechanisms of DFU Development

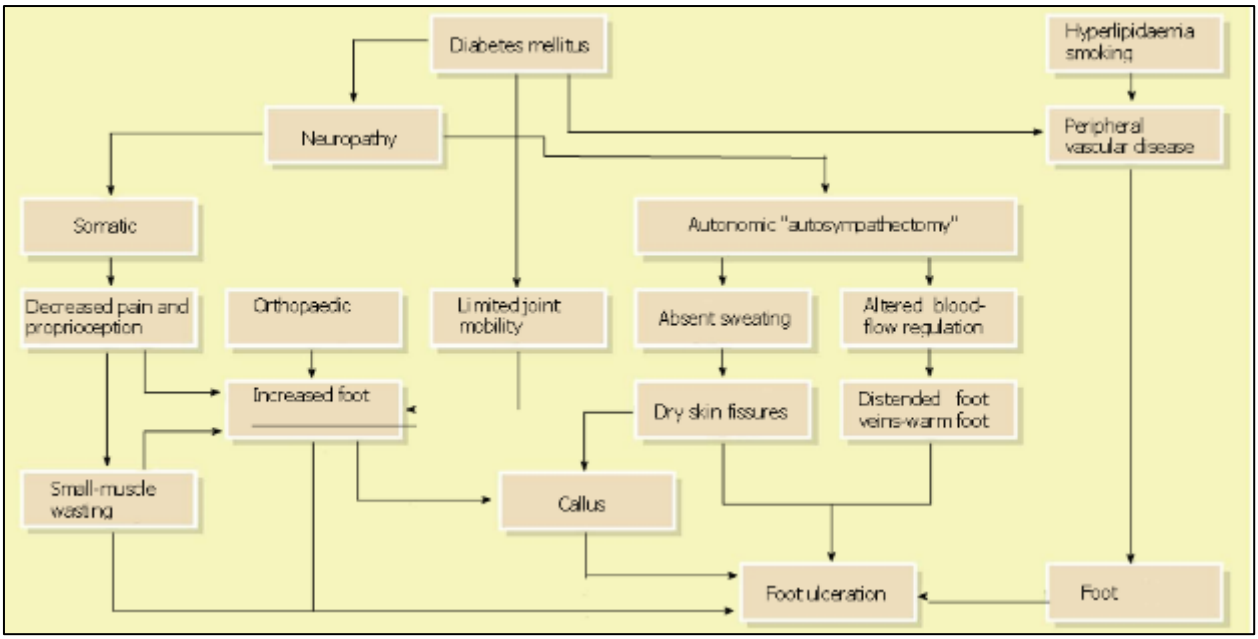

Figure 2 Contributing factors to diabetic foot ulceration, including somatic and autonomic neuropathy, peripheral vascular disease, joint immobility, and altered pressure distribution. These systemic and mechanical abnormalities

converge to cause callus formation, skin breakdown, ischemia, and eventual ulceration. Adapted from Boulton et al. (2005)

Diabetic foot ulcers (DFUs) occur due to a series of hyperglycemia-related pathophysiological dysfunctions where wound healing falls out of step. Oxidative stress is caused by chronic hyperglycemia, which generates excessive reactive oxygen species (ROS) that damage cellular components, harm neutrophils and fibroblasts, and inhibit the function of fibroblasts and keratinocytes (Falanga, 2005). Non-enzymatic glycation of proteins results in an increase in the level of advanced glycation end-products (AGEs), which stiffen the extracellular matrix (ECM) and contribute to inflammation through receptor-mediated pathways (Singh et al., 2014). The AGEs also interfere with angiogenesis by decreasing vascular endothelial growth factor (VEGF) signaling, thereby hindering the development of new blood vessels that are crucial for tissue repair. As a result, the wound microenvironment becomes hostile, cellular migration and proliferation are impaired, and this factor leads to the complications of DFUs becoming chronic, making the treatment process more complicated.

DFU also aggravates further in the presence of peripheral neuropathy and arterial disease. Up to 50 percent of diabetic individuals experience peripheral neuropathy, and it results in the loss of sensation; thus, trauma can go unharnessed, and the foot can be put under unnecessary pressure repeatedly (Boulton et al., 2005). Abnormal foot biomechanics, such as uneven weight distribution due to motor neuropathy, create sites of high pressure that are vulnerable to malfunction. Concomitantly, peripheral arterial disease (PAD) in 20-30 percent of DFU patients decreases the speed of blood flow and tissue oxygenation, which impede the processes of nutrient delivery and immune response (Armstrong et al., 2017). This reduced circulation aggravates injury by increasing the trauma (slows wound healing), and a person becomes susceptible to infection. All of these processes create a vicious cycle of tissue injury, impaired healing, and development of chronic ulceration, and thus, this confirms that these pathophysiological gaps have to be bridged using specific treatments.

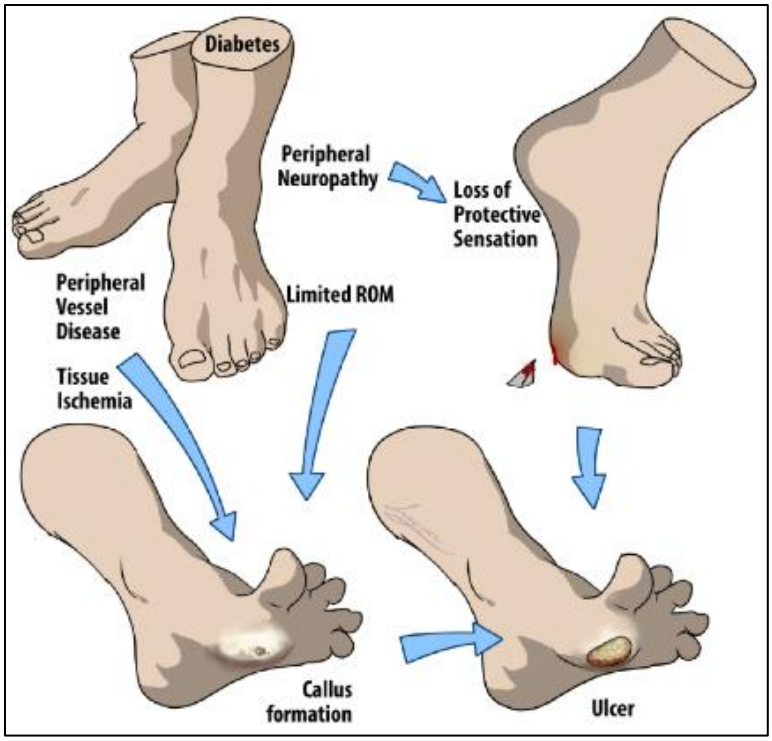

Figure 3 Progression of diabetic foot ulcers due to underlying diabetes-related complications such as peripheral neuropathy, vascular disease, limited joint mobility, and tissue ischemia. These factors contribute to loss of protective sensation, callus formation, and eventual ulceration. *Adapted from Primous et al. (2024)*

2.2. Wound Healing Challenges

Diabetic foot ulcers (DFUs) are characterized by pronounced wound healing complications caused by unbalanced inflammatory stage and defective extracellular matrix (ECM) remodeling. Chronic hyperglycemia is associated with the sustained secretion of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1β), which extends the inflammatory process and facilitates the transition to proliferation (Eming et al., 2014).

Such a dysregulation is caused by macrophage dysbiosis, where the balance shifts toward pro-inflammatory M1 phenotypes instead of reparative M2 phenotypes, thereby preventing the resolution of inflammation (Boniakowski et al., 2018). At the same time, the reduced deposition of collagen and dysfunction of fibroblasts are the factors that lead to impaired ECM remodeling. The proliferation and migration of fibroblasts, as well as the production of collagen and the integrating aspects of the extracellular matrix, which affect the strength of the granulation tissue, are adversely affected by hyperglycemia and advanced glycation end-products (AGEs) (Falanga, 2005). These shortages create an environment in which wounds fail to heal.

Susceptibility to infections also becomes another impediment to the healing of DFU, as biofilms and weakened immune systems complicate the chronicity of DFU. The presence of biofilms, multicellular colonies of microorganisms embedded in a polysaccharide layer, was detected in 6070 percent of chronic DFU, where they lower the efficiency of antibiotics and maintain the persistence of inflammation (James et al., 2008). Pathogens such as Staphylococcus aureus and Pseudomonas aeruginosa are prevalent in the hyperglycemic wound microenvironment. Moreover, diabetes also affects immunity, resulting in a decreased response in the form of neutrophil chemotaxis and phagocytosis, which can lead to infections, such as methicillin-resistant Staphylococcus aureus (MRSA) (Lipsky et al., 2016). This immunosuppressive state, together with impaired vascularization, slows down the clearance of pathogens and increases the risk of osteomyelitis and sepsis. Such issues shows the importance of developing innovative treatments, including biomaterials and tissue engineering, capable of regulating inflammation, repairing the ECM, and preventing infections efficiently.

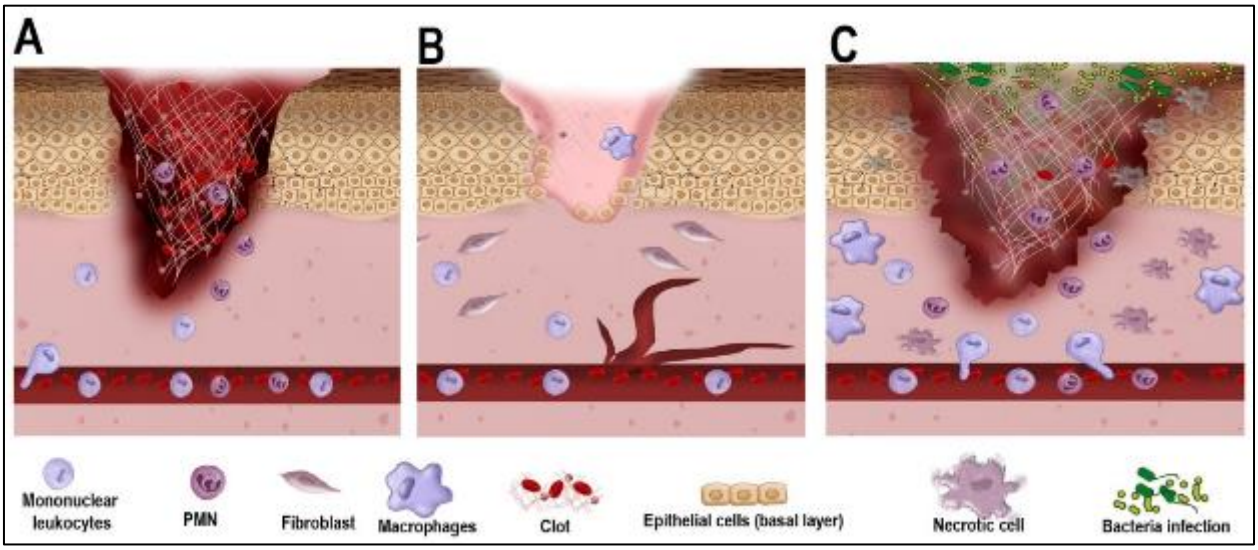

Figure 4 Progression of wound healing and pathological disruptions in diabetic foot ulcers. (A) Acute wound phase with clot formation and leukocyte infiltration. (B) Normal wound healing with re-epithelialization and fibroblast migration. (C) Chronic diabetic wound with necrotic tissue, macrophage imbalance, and bacterial infection. Adapted from Primous et al. (2024)

2.3. Clinical Implications

The chronic nature of diabetic foot ulcers (DFUs) is a significant impediment to the process of healing, predisposing to the emergence of such severe complications as osteomyelitis and sepsis. Chronic hyperglycemia, uncontrolled inflammation, and the overwhelming effect of pro-inflammatory cytokines, combined with the impaired functionality of macrophages, create an environment that hinders wound resolution, with the healing process taking longer than 12-20 weeks in most cases (Armstrong et al., 2017). DFUs can have 50–60% infection, 20% developing into osteomyelitis, which is a bone infection that only complicates the medical situation and increases the risk of amputation (Lipsky et al., 2016). In severe cases, sepsis is a life-threatening systemic infection, and it is among the causes of a 5-year mortality rate of roughly 50% within 5 years after amputation, similar to some cancers (Armstrong et al., 2020). Such complications underscore the importance of interventions that target the chronic nature of DFUs to enhance positive patient outcomes and minimise healthcare burden.

The multifactorial nature of DFU pathophysiology precludes the use of simple remedies. It requires specific interventions to address the underlying pathogenesis, which involves inflammation, defective angiogenesis, and a dysfunctional extracellular matrix (ECM). The more common treatment modalities, such as debridement and antibiotics, often fail to consider these etiologic factors, resulting in long-term recurrence rates of the condition within one year of

up to 40 per cent (Prompers et al., 2008). New biomaterials, such as hydrogels and bioactive dressings, as well as tissue repair strategies like stem cell therapies and 3D-printed scaffolds, provide attractive prospects for modulating inflammation, stimulating neo-vascularisation, and re-establishing ECM integrity (Falanga, 2005). The purpose of such therapies is to facilitate the faster closure of wounds, reduce infection rates, and prevent amputations, which is why it is imperative to incorporate them into clinical practice to overcome the pathophysiological gaps that contribute to DFU chronicity and complications.

3. Conventional Management of Diabetic Foot Ulcers

3.1. Standard of Care

The management of diabetic foot ulcers (DFUs) with standard of care employs a multidimensional treatment regimen, which facilitates healing and prevents the progression of chronic wounds, as they have a multifaceted pathophysiology. Cornerstone interventions include debridement, which entails the removal of necrotic tissue, callus, and biofilm, restoring tissue repair, through using surgical (sharp excision), enzymatic (collagenase-based agents), or autolytic (moisture-retaining dressings), of which surgical debridement is commonly used due to its accuracy of deep wounds (Armstrong et al., 2017). It is essential to decrease mechanical loading pressure on the ulcer area through offloading, which can be achieved using total contact casts, removable orthotic braces, or shoes with cushioned footwear to redistribute the load and reduce pressure (Bus et al., 2016). The weight of the foot does not feel as much upon these casts, which fit the foot perfectly, making the foot heal faster, as nothing more is being destroyed at risky spots.

The most important consideration is to manage infections by focusing on their healing. 50 to 60 per cent of DFUs are infected, thus predisposing patients to osteomyelitis and amputation (Lipsky et al., 2016). Moderate or severe infections are treated with systemic antibiotics that target the disease-causing agents, such as Staphylococcus aureus, and topical antimicrobials for simple, localized infections. Saline irrigation and the use of antiseptics can be used in wound irrigation to help reduce the bacterial burden, thereby increasing the effectiveness of other therapies. Hydrocolloids, foams, and alginates are types of wound dressings that maintain wound moisture while facilitating exudate absorption and protecting against contamination. Clinicians choose the type of dressing based on the wound's depth, the amount of exudate, and whether there is an infection (Wu et al., 2007).When used together, these interventions form the core of DFU management, overcoming short-term obstacles to healing; however, they typically do not address underlying chronic inflammation and impaired angiogenesis.

3.2. Limitations of Conventional Approaches

Current modalities of DFU also have significant pitfalls, especially in the treatment of chronic inflammation and persistence of angiogenesis. Conventional treatment regimens, including debridement and dressings, are ineffective in regulating the continued release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β) that characterize DFUs, thereby perpetuating inflammatory states and hindering healing (Eming et al., 2014). The presence of hyperglycemia and advanced glycation end-products (AGEs) affects vascular endothelial growth factor (VEGF) signaling mechanisms, thereby inhibiting angiogenesis and exacerbating tissue ischemia, which slows down tissue regeneration (Falanga, 2005). Consequently, such methods yield low curative rates, with fewer than 50 percent of DFUs achieving healing after 12 to 20 weeks (Margolis et al., 1999). The poor effectiveness of these points highlights the need for more advanced treatment methods that can address the underlying pathophysiological processes to enhance wound healing and tissue regeneration.

Standard treatments are also unable to cope with the complicated wound environment and eliminate the biofilms, contributing to high rates of recurrence and the constant risk of amputation. Antibiotic-resistant biofilms, which are found in 60-80 percent of chronic DFUs, cause the extension of inflammation and infection (James et al., 2008). The potential drawbacks of clearing biofilms in diabetic patients include compromised immune responses and inadequate vascularization (Lipsky et al., 2016). In addition, the recurrence rate of DFUs is up to 40 percent within one year and 60 percent within three years, indicating that DFUs fail to heal with regular care (Prompers et al., 2008). The recurring risk of amputation imposed because 20 of every 100 cases of infected DFU become amputated further demonstrates why more novel treatment interventions like the use of biomaterials and tissue engineering are required to enhance long-term patient outcomes and decrease DFU burden.

4. Advanced Biomaterials in DFU Management

4.1. Overview of Biomaterials

Biomaterials are any materials that are purportedly biocompatible and designed to interact with a biological system in a manner that facilitates healing, playing a key role in managing diabetic foot ulcers (DFUs). Such materials are designed to replicate and support microenvironments that aid tissue by regulating angiogenesis (O'Loughlin et al., 2013). In 20 trials, repair pathophysiological deficits associated with DFUs by providing bioactive molecules that support structures and enhance extracellular matrix (ECM) formation, thereby reducing chronic inflammation. They can be customized to the needs of specific wounds and carry better results in wound healing than typical dressings (Frykberg & Banks, 2015). This section explores how they promoted the treatment of DFU by utilizing novel therapeutic solutions.

Depending on the type of origin and composition, biomaterials can be either natural or synthetic. The sources of the materials are biological, and they are called natural biomaterials, including collagen and hyaluronic acid, which are much like native ECM, facilitating cell adhesion and tissue re-growth (Boateng et al., 2008). The synthetic biomaterials include polylactic-co-glycolic acid (PLGA) and polyethylene glycol (PEG), which can control drug release independently of the material's strength and degradation rates (Langer & Tirrell, 2004). Both are customized to enhance the healing of DFU by addressing challenges such as infection and poor vascularization, making them a necessity in next-generation treatments.

4.2. Types of Biomaterials for DFUs

4.2.1. Hydrogels

Hydrogels are highly hydrated materials with a large amount of water content, flexibility, and promote a moist wound environment, which makes them well-suited for the management of diabetic foot ulcers (DFUs). This is due to their biocompatibility and a porous structure that allows the diffusion of nutrients and the infiltration of cells during the healing process (Boateng et al., 2008). Examples include hyaluronic acid hydrogels, which stimulate angiogenesis, and peptide-based hydrogels with antimicrobial effects to combat infections. Tissue repair, growth factor delivery (e.g., VEGF), antibiotics, or stem cells are some examples that can be applied to the wound site to stimulate tissue repair and decrease inflammation (O'Loughlin et al., 2013). The hydrogels help achieve the ideal moisture for the healing of chronic DFUs.

4.2.2. Electrospun Nanofibers

Electrospun nanofibers are nanoscale fibers designed to mimic the extracellular matrix (ECM), supporting cell migration and proliferation in DFU treatment. Their high surface area and porosity enhance wound coverage and tissue integration (Jayarama Reddy et al., 2013). Examples include polycaprolactone (PCL), chitosan, and gelatin-based nanofibers, which provide structural support and biocompatibility. Applications include controlled drug release for sustained delivery of antimicrobials or growth factors, as well as tissue scaffolding to promote granulation (Langer & Tirrell, 2004). These nanofibers improve wound healing by facilitating cellular adhesion and guiding tissue regeneration in complex DFU environments.

4.2.3. Bioactive Dressings

Bioactive dressings incorporate bioactive agents, such as silver nanoparticles or growth factors, to enhance DFU healing. These dressings provide antimicrobial activity and stimulate tissue regeneration, addressing infection and poor granulation (Frykberg & Banks, 2015). Examples include collagen-based dressings (e.g., Integra), which support ECM formation, and silver-impregnated dressings for bacterial control. Benefits include reduced infection rates, enhanced granulation tissue formation, and accelerated wound closure compared to standard dressings (Veves et al., 2001). Bioactive dressings are critical for managing chronic DFUs by targeting inflammation and promoting a regenerative wound microenvironment.

4.2.4. 3D-Printed Scaffolds

3D-printed scaffolds offer patient-specific customization, tailored to the unique shapes and sizes of DFUs, enhancing treatment precision. Using biodegradable polymers or bioinks with embedded cells, these scaffolds support complex wound repair and vascular network formation (Murphy & Atala, 2014). Materials like polylactic acid and cell-laden hydrogels promote tissue integration and angiogenesis. Applications include reconstructing damaged tissue and facilitating vascularization, critical for ischemic DFUs (O'Loughlin et al., 2013). By providing a tailored structural

framework, 3D-printed scaffolds improve healing outcomes and address the challenges of chronic, non-healing DFUs effectively.

4.3. Mechanisms of Action

Advanced biomaterials modulate inflammatory cytokines and macrophage polarization to enhance diabetic foot ulcer (DFU) healing. By reducing pro-inflammatory cytokines like TNF-α and IL-1β, biomaterials such as hydrogels and bioactive dressings mitigate chronic inflammation, a hallmark of DFUs (Eming et al., 2014). They promote a shift from pro-inflammatory M1 macrophages to reparative M2 phenotypes, facilitating resolution of inflammation and tissue repair (Boniakowski et al., 2018). This modulation creates a healing-conducive microenvironment, counteracting the dysregulated inflammatory response driven by hyperglycemia and advanced glycation end-products (AGEs), thus accelerating the transition to the proliferative phase of wound healing.

Biomaterials also promote angiogenesis, fibroblast activity, and extracellular matrix (ECM) deposition while supporting cellular adhesion, proliferation, and differentiation. Materials like collagen scaffolds and electrospun nanofibers mimic the ECM, enhancing fibroblast migration and collagen synthesis, critical for granulation tissue formation (Boateng et al., 2008). They deliver growth factors, such as VEGF, to stimulate angiogenesis, improving blood supply to ischemic wounds (O'Loughlin et al., 2013). Additionally, their porous structures facilitate cellular adhesion and proliferation, enabling differentiation of stem cells or keratinocytes into functional tissue. These mechanisms collectively address DFU pathophysiology, promoting tissue regeneration and faster wound closure.

4.4. Clinical Evidence

Advanced biomaterials, currently under clinical trial as a method of treating diabetic foot ulcers (DFUs), show significant improvement compared to conventional studies. Integra, Apligraf, and PriMatrix are examples of advanced biomaterials that exhibit remarkable differences. The collagen-glycosaminoglycan matrix Integra facilitates tissue regeneration, resulting in a wound closure of 50 to 60 percent in 12 weeks, compared to 30 to 40 percent under usual care (Driver et al., 2015). Apligraf is a bilayered skin replacement that hastens healing with growth factors and viable cells. Measures of reduced healing time indicate a 20-30 percent faster healing rate in randomized trials (Veves et al., 2001). PriMatrix: fetal bovine collagen matrix is conducive to cellular infiltration and bears the same effectiveness as a granulation and closure facilitator. The supporting angiogenesis and ECM remodeling are the significant steps of DFU healing, supplemented with the following products.

However, such advancements have not resolved the problems that persist, including high costs, insufficient long-term evidence, and variations in patient responses. The cost of using bioprosthetic products, including Apligraf, exceeds $1,000 per procedure, and it is unaffordable in low-resource settings (Frykberg & Banks, 2015). There are also a few studies with long-term results; however, most trials have been implemented with short-term intervals (12-24 weeks), which raises uncertainty regarding durability and the prevention of recurrence (Prompers et al., 2008). The responses vary based on patient-specific factors, such as glycemic control and vascular status, resulting in 20-30% of patients experiencing poor healing. Such limitations underscore the need for cost-effective strategies, prolonged follow-up, and individualization to achieve biomaterial efficacy across diverse populations of people with DFU.

4.5. Tissue Engineering Approaches for DFUs

To overcome the deficiencies of currently used conventional therapies, tissue engineering is employed to produce functional skin tissue and heal wounds in diabetic foot ulcers (DFUs) by combining cells, scaffolds, and bioactive signaling molecules. It addresses the challenges of inflammation and inadequate vascularization, which are chronic and significant obstacles to DFU healing. The regeneration is mediated by cells, which include mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs) and induced pluripotent stem cells (iPSCs), which work by paracrine activities, releasing vascular endothelial growth factor (VEGF) that facilitates angiogenesis, differentiation to skin cells and control inflammation (O'Loughlin et al., 2013). The delivery/methods of delivery can be direct injection, scaffold implantation, or encapsulation in hydrogels to afford flexible platforms of therapeutic intervention, and the survival and performance of the cells in the hostile DFU microenvironment.

Bioengineered skin substitutes, such as Apligraf and Dermagraft, are composed of keratinocytes and fibroblasts, which enhance epithelialization and shorten the healing process by 20 to 30 percent compared to standard care (Veves et al., 2001). To mimic native skin architecture, scaffolds that support cell adhesion and migration are utilized (e.g., decellularized extracellular matrix (ECM), synthetic polymer scaffolds, and collagen matrices) (Murphy & Atala, 2014). Paper Smart scaffolds are dynamic, pH- or thermoresponsive. They can precisely respond to the wound environment by stimulating fibroblast activity and the deposition of extracellular matrix (ECM), promoting the formation of

granulation tissue (Boateng et al., 2008). The scaffolds enhance vascularization and help overcome the issue of ischemia in DFUs. Additionally, complex tissue repair, which is also essential in resolving chronic wounds, is required.

Growth factors, including platelet-derived growth factor (PDGF), VEGF, and transforming growth factor-beta (TGF-β), stimulate angiogenesis and ECM remodeling, but maintaining bioactivity in chronic wounds is challenging (Barrientos et al., 2008). Delivery systems like nanoparticles, liposomes, and gene therapy vectors ensure controlled release, improving efficacy. Clinical applications of tissue-engineered products, such as Grafix (placental membrane) and OrCel (cultured skin substitute), have shown success in case studies, reducing healing time by 25–40% and complications (Snyder et al., 2020). However, high production costs, regulatory complexities, and limited accessibility impede widespread adoption, underscoring the need for research to enhance scalability and affordability of these therapies (Frykberg & Banks, 2015).

5. Emerging Technologies and Innovations

The complex pathophysiology of chronic wounds is being transformed by emerging technologies, which have led to advancements in the management of diabetic foot ulcers (DFUs). The wound healing patterns in innovative biomaterials, such as pH- or temperature-dependent hydrogels, respond to wound conditions by depositing growth factors or antimicrobials where they are most effective (Mostafalu et al., 2018). The materials incorporate sensors that measure the properties of the wound in real-time, including pH, oxygen levels, and signs of infection. This allows for immediate intervention when these changes are noted, preventing complications from occurring. Nanotechnology enhances DFU treatment by facilitating the easy distribution of drugs to affected regions, where there is minimal dispersion, thereby combating infection. The use of silver nanoparticles and other materials to reduce bacterial numbers and inflammation has been demonstrated (Gurtner et al., 2008). These technologies perform wound closure more effectively and reduce the risk of infection, which also yields significant benefits in chronic DFUs.

Gene therapy, CRISPR, and bioprinting also advance DFU treatment. Specific gene editing can positively impact genes related to healing, such as vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF), thereby encouraging angiogenesis and tissue repair. However, there are issues with safely delivering the treatment and ensuring long-term safety (Eming et al., 2014). 3D bioprinting has produced patient-specific skin that contains a vascular network and utilizes cells derived from the patient to enhance biocompatibility and reduce the risk of rejection (Murphy & Atala, 2014). The use of artificial intelligence (AI) in wound healing will enable the optimization of biomaterial design, as the distinctive features of wounds and the likelihood of wound healing outcomes can be leveraged to develop and design more effective wound treatments (Frykberg & Banks, 2015). Their potential is hampered by their high expense and regulatory complexity, which makes them still inaccessible. However, they require studies that will increase their scalability and clinical integration into the advanced future of treatment.

6. Challenges and Future Directions

Most advanced products and biomaterials employed in the management of diabetic foot ulcers (DFUs) suffer from issues such as high costs and low scalability, making these treatments inaccessible not only due to their high prices but also due to their unscalable nature (Frykberg & Banks, 2015). Regulatory issues, such as the rigor of the FDA approvals process and EMA approvals, do not make it easy to adopt clinically. The absence of long-term data and unpredictability of patient responses due to variability in glycemic control and comorbidities are other factors that delay clinical adoption (Prompers et al., 2008). A subsequent process involves scaling up and advancing the biomaterials towards further affordability through production. One opportunity to enhance the healing process is to integrate multimodal therapies, which combine biomaterials, cell therapies, and bioactive molecules (Murphy & Atala, 2014). Personalized medicine, tailored to the characteristics of individual wounds and utilizing real-time machine learning tools, can lead to improved outcomes. It will take a considerable number of studies before the concept of personalized medicine can be developed and applied in clinical practice (Gurtner et al., 2008).

7. Conclusion

The treatment of diabetic foot ulcers has seen significant improvement with the help of advanced biomaterials and tissue engineering, as it not only helps to manage the problem of chronicity but also regeneration, as clinical evidence has documented that the application of products such as Apligraf and Integra closes the wounds faster and decreases the frequency of amputation. However, accessibility and scalability seem to be somewhat of a problem, as high costs and regulatory issues are present. The innovations have the potential to improve the quality of life for patients diagnosed with diabetes, as instances of their complications, such as osteomyelitis, decrease. Primary multidisciplinary

approaches that should be combined to achieve the best outcomes include biomaterials, tissue engineering, and clinical care. Additional efforts must be made to scale up cost-effective solutions, collaborate with researchers, clinicians, and industry to translate those innovations into everyday clinical practice, and reduce costs to transform the management of diabetic foot ulcers worldwide.

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