Original Article

Diabetic Wound Healing with Nanofibers

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Abstract

The most prevalent metabolic illness, diabetic mellitus (DM), is caused by a problem with insulin production. DM promotes the gradual degeneration of pancreatic cells, which raises blood sugar levels. Around 2.1 trillion dollars are invested in global health industries by diabetic wound repair therapies. This is a result of the difficulties that skin ulcers offer in the wound healing process, such as a shortage of macrophage and fibroblast growth factors (TGF-b1 and PDGF, respectively), all of which are required for the production of extracellular matrix (ECM). Nanofibers have been created by electrospinning with large porosity, excellent humidity absorption, a superior oxygen exchange rate, and certain antibacterial properties in response to the growth of medicinal materials and pharmaceutical technology. By including bioactive substances (such growth factors, genes, proteins/peptides, stem cells/exosomes, etc.) and nonbioactive materials, these nanoparticles/hydrogels aid in the healing of diabetic wounds (metal ions, oxygen, nitric oxide, etc.) Due to the slow wound healing process, wound care is a significant biomedical topic that presents difficulties. Malnutrition, insufficient oxygen, smoking, illnesses (such as diabetes and cancer), microbial infections, and other conditions are some of the causes of sluggish wound healing. Currently utilized wound dressings have a number of drawbacks, such as inadequate antibacterial action. Thus, we aimed to go into further depth about the NF (nanofiber) system's aforementioned characteristics for DM complications.

Keywords: Diabetes, Chronic, Wound healing, Nanofibers, Polymers, Wound dressing.

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1. INTRODUCTION

C Diabetes is a condition that affects how well glucose is controlled as well as how well protein and lipid metabolism are managed.1 The complex group of chronic metabolic illnesses known as diabetes mellitus (DM) is defined by hyperglycemia.2 An estimated 25% of DM patients have this condition. (Types 1 or 2) will develop a foot ulcer over the course of their lifetime.3 463 million people worldwide were affected by DM in 2019, with 4.2 million fatalities each year, and it is predicted that 700 million people will be affected by it by 2045.4 There are four main types of diabetes: Type I diabetes is caused by the loss of beta cells in the pancreas, which eventually causes a reduction in insulin production;5,6 Insulin resistance and the consequent decompensation of pancreatic beta-cells in type II diabetes are strongly related. (Including the shrinkage and malfunction of pancreatic beta cells);7 Heart attack, stroke, blindness, and kidney failure are only a few of the secondary problems that type II diabetes causes,8 Both types of DM are associated with protracted multisystem vascular consequences, including macrovascular endpoints like ischemic heart disease, stroke, peripheral vascular disease, and diabetic foot ulcers (DFUs), as well as microvascular endpoints like nephropathy, neuropathy, and retinopathy.9 There is a need for to overcome the issues outlined study of novel materials to aid in wound healing procedure for individuals with diabetes. presented a chitosan hydrogel to treat diabetes patients' foot skin ulcers (skin ulcer in used the remedy once every two days for the foot.10 thirty days, By the end of the research, the participant's displayed wounds have healed a good deal. Therefore, utilising a different distribution method Strategies are essential to avoid restriction or issues, and increase effectiveness and diabetics' satisfaction patients. To combat various DM-related problems, a variety of delivery strategies based on nanostructures were investigated.11 NF-based systems were used in different methods been used in recent years to treat DM. Biomacromolecules, including as insulin, GFs, and small RNA interference, anti-diabetic pharmacological compounds, one of the key characteristics of NF-based structures for the treatment of DM.12 However, several therapy alternatives that are now accessible have Several restrictions, including a significant risk of transplant skin loss, Low resistance to pressure and friction as well as serious post-operative problems such graft or flap necrosis.13 In order to cure skin ulcerations, different synthetic or biological skin substitutes have been developed. These can also be utilised to treat acute burn injuries and other skin diseases.

2. Types of wounds

2.1. IN VIVO WOUNDS

2.1.1. Diabetic wounds

A common and harmful consequence of diabetes is diabetic wounds. The antioxidant properties of curcumin are one of the key factors contributing to its reputation as a superior wound healing agent. The antimicrobial activity is a crucial component in promoting faster wound healing. Particularly their feet are prone to skin lesions and delayed recovery in diabetes patients due to neuropathy and inadequate blood flow. Chronic inflammation hinders wound healing and re-epithelialization. Tragacanthin's hydrolysis into arabinose and glucuronic acid may lead to the degradation of bacterial surface proteins and contribute to the prevention of wound infection, which would speed up the healing process.14

2.1.2. Full-thickness wounds

In investigations on wound healing, full-thickness wounds are employed as a demanding wound model. One of the polymers utilised in full-thickness wound therapy is the PCL polymer. Compared to cells cultivated with PCL/Cur nanofibers, the viability of C2C12 cells treated with PCL nanofibers is much lower. reported that compared to their other experimental groups, curcumin-loaded PCEC nanofibers demonstrated improved efficacy in full-thickness wound healing.15 Additionally, they demonstrated that the PCEC nanofiber group outperformed the control group in terms of wound healing over the course of the study as a result of the nanofiber's ability to protect the wound site.

2.1.3. Burn wounds

Common skin wounds like burns can result in infection and death. One of the most frequent side effects and a significant danger of severe trauma is infection.16 After 21 days, the wound's epidermal layer had fully developed, and after 28 days, hair follicles, appendix structures, and collagen deposition were visible.

2.2. IN VITRO WOUNDS

In order to utilise the HPG characteristics and evaluate in vitro wound healing, curcumin was added to PLA/HPG nanofibers.17 This might be as a result of HPG's hydrophilicity, which results in a larger water content, regulated curcumin release, and improved cell adhesion and proliferation.18 When compared to PHBV/Blank nanofibers, cell survival, adhesion, and proliferation were increased. By increasing the loading of curcumin, these qualities are further enhanced.

2.2.1. Optimum conditions for fabrication of beadles nanofiber

In order to offer a wound dressing, cost-effective electrospun fibrous scaffolds have been created; some of these scaffolds have combined curcumin's special properties with electrospinning technology. To transform the polymers into nanofiber using electrospinning, certain parameters must be changed.

3. Phases of Wound Healing Process

The hemostasis phase, inflammatory phase, proliferation phase, and maturation phase are all parts of the critical and intricate physiological process of wound healing.19 In hemostasis, the first stage of tissue repair, platelets are crucial. Circulating platelets get activated, aggregate, and adhere to the damaged endothelium when they come into contact with the collagen of the injured tissue.20 The neutrophils at the wound site clean the debris and eliminate germs along with reactive oxygen species (ROS), creating an ideal environment for the wound healing process during the inflammation phase.21 The neutrophils subsequently penetrate deeper into the tissue space (diapedesis) through damaged capillaries or between endothelial cells.22 The proliferation phase, the third stage of wound healing, is characterised by an accumulation of many cells and copious connective tissue. In response to tissue ischemia, a population of adult stem cells known as EPCs can convert into epithelial cells and encourage endothelial regeneration and neovascularization. About two to three weeks after the initial injury, the remodelling phase of wound healing begins, and granulation tissue eventually matures into scar tissue. Blood vessel density declines, and collagen is ordered and remodelled. Continuous new collagen synthesis and collagen degradation occur during the remodelling period, and matrix metalloproteinases (MMPs) activity mostly maintains this equilibrium. Keloids or chronic wounds can develop as a result of any interference with the stages of wound healing.23

4. Wound Dressing Classification

Materials used as wound dressings serve to keep a wound safe. Additionally, they serve as a defence against infections. There are two types of wound dressings: primary and secondary. While the secondary dressing is used to cover the primary wound dressing, the primary wound dressing is put directly to the injured area.24 Additionally, they could transmit therapeutic agents (drugs, growth factors, peptides, stem cells, and/or other bioactive compounds) and agents that promote healing.25 Bioactive substances, such as antimicrobials and growth factors, are incorporated in bioactive wound dressings made from biopolymers to speed up the healing of wounds. Collagens, alginate, hydrocolloids, and hydro fibres are a few types of biopolymers. One of the biopolymers that is frequently used in the creation of wound dressings is gelatin. Additionally, it is applied in biological and pharmaceutical fields.26 To halt bleeding and stop the wound from coming into contact with the environment again, traditional/passive wound dressings are typically applied as the first line of defence.27

5. Substances Applied in Diabetic Wound Healing

Therefore, in order to facilitate the healing of diabetic wounds, some medicines must be administered from the outside. Presently, a variety of bioactive substances, including growth factors, genes, proteins, peptides, stem

cells, and exosomes, as well as non-bioactive molecules, such metal ions, oxygen, and nitric oxide, are used to promote diabetic wound healing.

5.1. Bioactive Molecules

5.1.1. Signalling Molecules

The ability of chemokines to directly stimulate re-epithelialization, ECM development or remodelling, and angiogenesis.28 Therefore, GH hydrogel might be loaded with two different chemokine kinds (IL-8 and MIP-3). The mediating, regulating, and directing of cellular connections during typical wound healing is a crucial role for a number of growth factors.29 Because of its short half-life, VEGF (vascular endothelial growth factor) treatment to wounds alone has had minimal efficacy, according to the findings of clinical trials.30 Future controlled local distribution of several GFs by combining hydrogels with nanoparticles.

5.1.2. Proteins/genes/Peptides

A variety of damaged tissues that have been exposed to biomacromolecules in dysfunctional environments and highly oxidative, sick microenvironments can be repaired and regenerated using the recommended "seed-and-soil" method.31 Despite the fact that genes and growth factors are made to promote angiogenesis and re-epithelialization, there are still issues with cost and safety associated with their use.

5.1.3. Stem cells/exosomes

Stem cells can create a variety of bioactive compounds, including One of the most promising treatments for diabetic wounds is stem cell therapy, which can restore tissue/organ function (such as growth factors).32 Additionally, adding gingival mesenchymal stem cells (GMSCs) to a chitosan/silk hydrogel sponge effectively encourages the healing of skin wounds.33 Exosomes are thus regarded as natural RNA carriers for the therapy of illnesses and as carriers of medication delivery.

5.2. Non-Bioactive Elements

5.2.1. Metal Ion

Currently, nano-bioactive glass particles, silver, gold, copper, and other antibacterial nanoparticles are utilized in wound healing. AgNPs have two different types of antimicrobial mechanisms: (a) inhibitory effect, and (b) bactericidal action. Due to their antibacterial action against infections caused by diabetic foot ulcers, copper nanoparticles (CuNPs) have attracted more and more attention.34 Initiated by the ionic by products of bioglass disintegration, macrophages produce anti-inflammatory cytokines. This method has excellent promise for use in antimicrobial applications and tissue restoration.

5.2.2. Oxygen

Chronic diabetic wounds receive little oxygen because neuropathy and vascular dysfunction. Additionally, inflammation causes cells to consume a lot of oxygen further causes hypoxia in the wounds. In addition, macrophages and neutrophils produce greater ROS in a hyperglycemic reaction, which contributes to enhanced oxidative stress in diabetic ulcers.35 It has been demonstrated that using oxygen-producing substances in conjunction with nanomedicine can speed up the healing of diabetic wounds. These oxygen-loading nanoparticles can increase the speed of wound healing. Therefore, oxygen-producing biomaterials are necessary in the future to treat chronic diabetic wounds.

5.2.3. Nitric Oxide

NO is a broad-spectrum antibacterial agent that fights a variety of with bacteria, The physiological control of nitric oxide (NO) is essential, of vascular function, however in diabetic individuals, NO production with a decline in bioavailability, in addition to NO intake increases.

6. Current treatments of chronic wounds

chronic wound care currently being practised depends on the origin of the wound. In each situation, a thorough washing and debridement of the wound, a the usage of wound dressings and potential infections are required.36 conventional dressings made of gauze or cotton gauze composite dressings, which shield wounds from Allowing for bacterial contamination and gaseous/fluid exchange. These dressings either occlude or are semi occlusive. They can take the shape of a hydrogel, film, foam, or hydrocolloids. These materials stand out for their simplicity cheap and easy to use.37 Currently, there are novel synthetic dressings that are the responsibility of creating a suitably wet atmosphere, available. In order to acquire the best mechanical qualities, hydrogels are typically comprised of both natural polymers (like collagen and chitosan) and synthetic polymers (like PVA, PEG, etc.). Poly (vinyl alcohol), poly(lactide-co-glycolide), polyurethanes, polyethylene glycol (PEG), polycaprolactone (PCL), nylon, and silicone are only a few examples of the synthetic materials used to make them.

7. New therapeutics in the treatment of chronic wounds

In the past ten years, there have been tremendous advancements made in the creation of new medicines, including the use of additives like antibacterial compounds, immunomodulatory cytokines, GF (growth factor), and microRNA (miRNA), Antimicrobial peptides have the capacity to inhibit both infections brought on by bacteria and inflammation healing peptides for wounds. When developing fresh topical formulations, these qualities are widely desired for healing of persistent wounds.38 When it comes to GFs, numerous studies have shown that their use enhances every facet of tissue repair in animal models. The required time for some current GF techniques may not be provided Because they degrade quickly, GFs in the wound region can connect with target cells. Several GF-containing goods are permitted, including provided in the form of drugs for external usage gels, creams, ointments, and solutions. The capacity of biological dressings to interact with cells or matrix proteins in the wound bed to facilitate healing is another feature of these products. Due to the limited use of ECM-based scaffolds chronic wound treatment appears to be constrained because lack of contact with cells and tissues,

there are autologous cellular components in these struts. These biological dressings based on cells provide tremendous potential for the treatment of chronic wound care, using a variety of methods to the speed of wound healing.39 In recent years, RNA delivery methods have advanced, enabling the development of functionalized wound dressings delivering stable miRNA or anti-miRNA molecules for use in skin wound healing.40

8. Recent emerging therapy in wound healing through nanofibers

8.1. Nanofibers

The filaments known as nanofibers have sizes that are a nanoscale. Nanofibers are uniform filaments that typically have a diameter in the range of less than 0.1 m. Nanofibers have drawn a lot of interest because of their numerous uses in fields including catalysis, sensors, medicine, drug transport, biomedical and tissue engineering, diagnostics, etc. Numerous cellulose and nanocellulose-based materials can be used to make them. They are often created by the due to its low cost and ease of use, electrospinning simplicity. Its high surface area to volume ratio and adjustable porous morphology can, in fact, enhance wound homeostasis as well as permit the exchange of nutrients and gases.41 As an alternative, nanofiber meshes have also been evaluated as synthetic skin When MSCs are employed, they can release GFs to start the healing process or develop into endothelial cells.42 developed formulations based on nanofibers for oral medication delivery systems. Nanofiber scaffolds in the shape of an electro sponge for oral drug administration are among the formulations that use multi-layered nanofibers, cross-linked surface-modified nanofibers, and nanofiber scaffolds.

8.2. Fabrication methods and characteristics of Nanofibers

The current setup for making nanofibers is rather straightforward and includes a number of items such a micro pump, syringe, spinneret, voltage supply, electrode metal collector, and polymer solution. NFs are characterized by their tiny diameter, high porosity, high specific surface area, control over their composition, ability to tune mechanical and surface properties, and simplicity of synthesis as a significant matrix/scaffold.43 Additionally, by manipulating ES's typical setup and processing conditions, it is possible to create nonwoven fibers with a variety of morphologies, including ones that are randomly aligned, straight aligned, core-shell, ribbon-shaped, porous, and more. Among them, polymer solution characteristics, including as polymer concentration and molecular weight, solution conductivity, and solvent volatility, play a crucial role in the development of NFs with a wide range of sizes and morphologies. The many structural characteristics, such as fiber diameter, alignment, porosity, and spatial distribution of NFs, affect the mechanical properties of nanofibrous scaffolds and mats.44 Due to an increase in crystallinity, tightly packed lamellae, and aligned fibrillar structures, the elastic modulus and strength of nanofibers both dramatically rise with decreasing fiber diameter. Due to its biological origin, biocompatibility, and good biodegradability with minimal immunogenicity and commercial availability at cheap cost, denatured collagen, or Gel, has gained a lot of interest in NF synthesis.

8.3. Nanofibers in wound healing

When applied as a wound dressing, nanofiber layers made from biopolymers (CS, gelatin, collagen, polycaprolactone, or mixtures of these materials) can significantly speed up the healing process. Manufactured electrospun nanofibers are being used to develop a new class of active materials for the treatment of wounds. With a high global demand from patients with wounds, burns, diabetic foot ulcers, etc., the wound care industry is currently one of the most common in the medical profession. In wound therapy, it can be challenging to get satisfying outcomes, mostly because of the intricate healing process and physiological changes that take place in the skin.45 The authors showed that in order to achieve controlled release of a therapeutic substance at the wound site, wound dressing must be developed to provide the required mechanical responses to the wound and its aqueous environment. examined the characteristics of CS, their modification, and its use in biomedical engineering, especially with regard to anti-inflammatory and wound healing. Investigations into antimicrobial ciprofloxacin-loaded hydrophilic biodegradable PVA led to the development of a transdermal patch made of sodium alginate (NaAlg), an electrospun composite nanofiber. It was actively loaded with the antibiotic ciprofloxacin, and the application of the medicine was researched. examined how the immune system responds innately to a pathology like wounds.46 Depending on the chronic condition, the typical duration for wound healing is about 23 days. Nanofibers make ideal candidates for managing and treating wounds.47

9. Nanofiber for drug delivery of wound healing drug/ polymers for the treatment of diabetic wounds

9.1. Polymers for nanofibers

For each individual nanofiber, a different polymer is applied, and the decision is made based on the desired function of the nanofibers. There is no one, universal standard for this process. Properties including spinning solution viscosity, nanofibers' shape, mechanical strength, biocompatibility, and physicochemical characteristics would change noticeably amongst polymers with various components and sources. In the research of nanofibers used for DFU healing, many polymers have been created. They may be roughly divided into two groups: synthetic polymers and natural polymers.

9.1.1. Synthetic polymers

The amount of glycolic acid can be reduced, and the molecular weight can be increased, to delay the rate of breakdown.48 However, due of its water insolubility, which might result in cell toxicity and hinder the DFU from healing, organic solvents are frequently utilized to dissolve PLGA. By comparing the hydrophilic qualities of the

nanofibers made of chitosan and recombinant human platelet-derived GF to those of pure PLGA material, their research shows that the hydrophilic properties of the two materials are enhanced. Thermoplastic aliphatic polyester manufactured from poly (lactic acid) (PLA), which is frequently used in pharmaceuticals and medical technologies like stents, sutures, and drug delivery systems, is a material that is derived from natural resources. A biodegradable and biocompatible polymer with a functional ester bond, poly (-caprolactone) (PCL), may disintegrate into harmless fractions in a physiological setting. PVA has excellent mechanical properties and a high level of chemical resistance. It is aqueously soluble, nontoxic, and non-carcinogenic. Additionally, PVA is reasonably flexible and capable of swelling.

9.1.2 Natural polymers

Chitin deacetylation can produce the biodegradable polymer known as chitosan. Similar to the ECM, it contains glycosaminoglycans. The unique characteristic of chitosan, in addition to its biocompatibility, biodegradability, and hemostasis ability, is its activity against bacteria and fungus.49 This benefit helps to accelerate DFU healing by providing additional support. Chitosan's weak mechanical characteristics, however, restrict its use in the DFU therapy. The mechanical qualities can be improved by crosslinking with other natural polymers such gelatin and collagen.50 Drugs contained in the ND that are directed at the deeper tissue require it even though it may not be beneficial for the DFU wound closure. Alginate, a polymer derived from seaweed, is another biodegradable substance. It includes glycosaminoglycan, which serves as the foundation of ECM, similarly to chitosan. Alginate makes a superior wound dressing material because of its ability to absorb exudate and stop bleeding.

10. Applications of nanofibers in various phases in diabetic wounds

10.1 Inflammatory phase

Pathophysiology

The chronic inflammatory phase of DWs linked to infections is the first late stage. The prolonged build up of monocytes/macrophages and increased cytokines in DWs result in persistent inflammation.51 Matrix metalloproteases (MMPs) are more prevalent and growth factors are less abundant due to this protracted inflammation. The platelet-derived growth factor (PDGF), which draws immune cells to the wounded site, causes the poly-morphonuclear neutrophils to come first during the inflammatory phase of acute wound healing. After that, neutrophils eventually develop into monocytes, which are then followed by the production of macrophages. However, under diabetes settings, the nuclear factor kappa B (NF-B) cells that cause the development of advanced glycation end products (AGEs) are responsible for the dysregulation of macrophages M1 to M2.52

Anti inflammatory and antibacterial activity of nanofibers

The comprehensive literature review on the anti-inflammatory and antibacterial properties of nanoparticles using various polymers in DWs is summarised in this section. The scientists have come to the conclusion that fiber diameter, as opposed to fiber alignment, significantly affects in vitro macrophage activation and production of proinflammatory chemicals.53 Have investigated the in vivo effectiveness of the collagen-coated nanofibrous scaffold and its impact on pro-inflammatory cytokines and growth factors in wound healing. The poly (3-hydroxybutyric acid) was coated with a bioactive Coccinia grandis extract that was created by electrospinning using collagen that was collected from the skin of marine fish. In comparison to chitosan/PVA nanofibrous membranes, the results showed that the produced dressings had stronger antibacterial power against E. coli, P. aeruginosa, B. subtilis, and S. aureus, increased antioxidant capacity, and quicker wound healing, Due to the longer release and less side effects, they came to the conclusion that nanofibers can accelerate DW healing to a greater extent than topical doxycycline therapy.54 Overall, it has been demonstrated that the production of dressings may benefit from the use of thymol-loaded nanofibers with bactericidal and anti-inflammatory capabilities.

10.2 Proliferative and remodeling phase

Pathophysiology

In DWs, the proliferation phase is a key stage for angiogenesis. Hyperglycemia in type II diabetics significantly impairs the stimulation of blood vessel development, proliferation, and growth. Pericytes that surround the capillary wall in the wound bed and trigger the production of angiogenic and anti-angiogenic factors that maintain the balance in the wound region influence the vessel stability and development. Diabetic circumstances reduce the efficacy of endothelial cell migration and integration of endothelial progenitor cells (EPCs) into the tubular channel.55 It has been suggested that using growth factors in combination in vivo is a viable therapy for accelerating healing. Despite being the only growth factor that have successfully passed clinical trials, exudates or proteases can degrade or remove growth factors before they can reach the wound bed. For the treatment of DW healing, efforts have been made to supply growth factors by electrospun fibers. Although adult stem cells have shown promise in the treatment of wounds, access to them is frequently restricted by the sources used, the invasive methods used to collect them, and ethical, immunological, and tumorigenicity-related concerns. Therefore, the need to find a new, simple, non-invasive source of autologous stem cells is critical. As a result, they suggest that the produced mixture may affect the DWs' angiogenesis process.56 The fibrin mediates fibronectin and vitronectin for the support of ECM formation, which is essential for tissue regeneration in wounds.

11. Conclusion

The pathophysiology of diabetes makes treating diabetic wounds difficult due to altered cellular activity and

imbalanced quantities of vital biochemical healing mediators. There have been a sizable number of nanocarriers published in the literature during the past few years for use in various medication delivery applications, however some are not widely used in the commercial sector. The use of dressings for wound healing is accelerating due to an increase in global population (45.5 billion by 2024). Due to the fact that they possess all the essential characteristics, nanofibers seem to be the best option for wound dressing. Diabetes mellitus can cause impaired wound healing by affecting one or more biological mechanisms of the process. Chronic wounds have an interrupted healing process that takes time to show results. Over 40 million individuals throughout the world are affected by this invisible pandemic that continues to inflict pain, infections, financial burden, and frequently results in amputations or sepsis. The review has focused on the several advantages that stem cells, small chemicals, and plant-based materials offer when combined with natural and synthetic fibres. Nanofibers may thus be a useful treatment option for DWs in the future when taking into account the findings and benefits mentioned above.

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