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Review article

Micro and nanoparticles for the delivery of growth factors in diabetic wounds

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ABSTRACT

Diabetic wound (DW) is one of the leading complications of diabetes patients with a long history. It also puts an economic burden on people recovering from injuries to manage medication. The critical factors in the treatment of DW are infection, inflammation, and low oxygen level. Since these non-healing injuries are linked to the extended recovery process, current treatments are studied only for a short period. The areas covered in this article are an overview of DM, Pathophysiology of DW, stages of wound healing (Hemostasis, Inflammation, Proliferation, Maturation), the role of growth factor in diabetic wound healing, advantages of micro and nanoparticles over other drug delivery systems and micro and nanoparticles for the delivery of growth factors with different studies.

Keywords: Diabetic Mellitus, Pathophysiology, wound healing, diabetic wounds, Growth factors, Micro and Nanoparticles.

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INTRODUCTION

Diabetic Mellitus (DM) ("Greek diabainein" is a complicated chronic condition with growing global incidence and it is described as copious urination, and Latin Mellitus, which is referred to as a urinary sugar "sweetened with honey". DM is an endocrine disease characterized by hyperglycemia syndrome (increased blood glucose level) [1]. Diagnosis and classification of diabetes are performed according to specific criteria, and there are two main clinical types:

Type 1-diabetes – Since the inflammatory killing of the pancreas β cells is resistant,

Type 2 diabetes - that results from a secretive insulin defect with simultaneous insulin resistance and excess of glucagon secretion [2, 3].

The most common type 2 diabetes accounts for 90-95% of adults diagnosed in the United States (4). According to the IDF's prevalence 2019 statistics, the projected global DM number (20–79) for adults is 463 million, which will grow to 578.4 million by 2030 and 700.2 million by 2045. In 2019, IDF announced that 4.2 million people worldwide had died due to DM and its complications. Global spending on DM was forecast to $760 billion per year in 2019, to $825 billion by 2030, and to $845 trillion by 2045. Thus, DM was one of the serious health risks with an immense socioeconomic effect.

If the DM progresses, diabetic foot ulcers (DFUs) are a complication. Persons with DM have a 25% chance of DFU and, unfortunately, undergo amputation if not treated well in advance. Although DFU is preventable, patients and health systems are much burdened. A precautionary lifestyle, prompt review, and high-level therapies through a multidisciplinary network of experts are optional approaches to DFU management [5].

Pathophysiology of DFU

The leading causes of DFU include peripheral arterial disorders, neuropathy, ischemia, and infection resulting from DFU production. A flow diagram showing the pathophysiology of DFU is shown in Fig. 1. [6].

Stages of wound healing

Wound healing is the mechanism that replaces the skin or any damaged organ following injury. Wound healing aims to avoid or restrict further damage and sticking the wound from infection, restoring strength, and, if necessary, functioning of the tissue. The normal function of the tissue is essential [7]. Skin wound care is a crucial biochemical mechanism consisting of several cell strains and their products in partnership [8]. In studies lasting over 100 years, wound healing, especially in the skin, was traditionally well described [9]. It is a necessary yet complicated process in the human

or animal trials, which involves a sequential and overlying multi-layered process.

Four stages differentiating the wound healing process are:

A. Haemostasis.

B. Inflammation.

C. Proliferation (growth of new tissues)

D. Maturation (Remodelling)

These phases and their bio-physiological functions must take place in the right manner, at a particular time, and continue at an ideal intensity for a certain period. Many factors can influence injury healing that interferes with one or more phases, causing improper or impaired tissue repair[10]. In general, healing wounds, including delayed, severe wounds and recurrent wounds, have not progressed through the usual healing stages. Such accidents also become pathologically inflamed because of a postponed, dissatisfied, or tedious healing method[11]. The stages of wound healing were shown in Fig. 2.

HEMOSTASIS

The first step is hemostasis, which includes the development of a fibrin plug consisting of platelets firmly enclosed in a network of fibrin, fibronectin, vitronectin, and thrombospondin. The plug activates pro-inflammatory mediators, such as cytokines and growth factors, in addition to providing mechanical protection for the wound from pathogenic microorganisms. Cytokines act to activate neutrophils, monocytes, and lymphocytes that cause the next step of inflammation[12].

INFLAMMATION

During the inflammatory process, the activation of neutrophils, monocytes, and lymphocytes has many functions: they serve as a buffer against contaminating microorganisms by releasing a wide range of proteinases and reactive oxygen species; they are involved in cell debris phagocytosis; and, most commonly, they produce growth factors and cytokines that trigger proliferatively phase of wound repair[12].

PROLIFERATION

The proliferation process begins with keratinocytes and dermal fibroblast's migration and proliferation. These cells would later transfer to the provisional matrix and deposit the ECM. During this process, the activation of angiogenesis results in new blood vessels, with nerve roots sprouting at the edges of the wound. Wound contraction occurs as ECM deposition is combined with angiogenesis and re-epithelialization. As wound contraction begins, ECM re-organization and scar tissue development with eventual wound closure define the fourth and final step of remodelling[12].

MATURATION

A great deal of study has been undertaken to identify the distinction between acute and chronic wounds. Acute wounds cure readily after the success of wound healing in the whole process. Chronic wounds including DFU appear to stagnate throughout the healing phase and present biochemical and pathophysiological anomalies culminating in the inflammatory stage of the wound becoming put. So there is no proper, trustworthy advancement of healing on the road to wound closure and hence persistent wound becomes[12].

Role of growth factors in wound healing

Growth factor

Growth factors are a cytokine subclass that promotes cell proliferation[13] explicitly. A growth factor is a polypeptide molecule found in the first three phases and regulator for cell growth, differentiation, and metabolism. Chemotaxis growth factors draw inflammatory cells and fibroblasts in the wound. Secondly, growth factors serve as mitogens to stimulate the growth of cells[13]. In just minute concentrations, they are found across the body but have a high local effect on wound healing. This is associated with specific receptor systems in the cell surface, leading to responses determined by the signal transduced by a receptor in the target cells, cell proliferation, chemotaxis, hypotaxis, angiogenesis, protein expression, and development of Enzymes are triggered by growth factors. The exact role of individual growth factors in the standard cure of human wounds remains unknown, but activities related to in vitro growth factor[14, 15].

The different stages of wound healing are difficult to control. Polypeptides that modify the production, differentiation, and target cell metabolism are biologically involved in growth factors (or cytokines). They can work through paracrine and autocrine mechanisms and influence cell behaviour by binding them to a certain cell surface. A dynamic cascade of signal transduction pathways is triggered by the receptors. All known growth reasons are pleiotropic, i.e. they control many aspects of cell behaviour and a wide range of cell population targets[16].

EPIDERMAL GROWTH FACTOR (EGF)

In 1962, EGF was found in the mouse's salivary glands. It was to be identified as the first cause of development. Interacts with the EGF receptor with epidermal cells and fibroblasts[17, 18]. This is produced by platelets, macrophages, and monocytes; and by salivary, tears, and kidney duodenal glands[19]. The key function is to activate the epithelial cells around the cut, even though it functions along with EGF on fibroblasts and smooth muscle cells.

FIBROBLAST GROWTH FACTOR (FGF)

Fibroblast growth factor (FGF) is a member of the heparin-bound growth factor family. In this FGF, they are two types, i.e., (Acidic FGF and Basic FGF), recently they have expanded extra seven additional forms. These are now named FGF1 to FGF9 [20]. FGF is formed by fibroblast, endothelial cells, smooth muscle, chondrocyte, mast cells[21]. FGF2 (Basic FGF) stimulates regenerated keratinocytes extension, differentiation, and migration. It helps to

promote angiogenesis of granulated tissue through infiltration and proliferation of endothelial cells and fibroblast migration. It stimulates them to generate collagenase, but it determines the importance during the subsequent studies of remodeling in growth factors [22-24].

C. TRANSFORMING GROWTH FACTOR-B (TGF-B)

TGF-β was first introduced in 1983 based on the ability and common renal rats to stimulate anchorage-independent development, based on mouse embryonic fibroblasts[25]. Since then, a wide variety of structurally related variables with different behaviors have been demonstrated. TGF-β1, TGF-β2, and TGF-β3 are the main types found in mammals, but TGF-β1 is dominant. TGF-β is produced with active macrophages, blasts, keratinocytes, lymphocytes, and platelets. Many cell types have TGF-β receivers. Its effects may be inhibiting or promoting according to the occurrence or association with the extracellular matrix of other growth factors. For example, TGF-β stimulates low fibroblast levels but induces high differentiation levels[26].

D. PLATELET- DERIVED GROWTH FACTOR (PDGF)

It is an autologous blood product that includes a few growth factors, not a particular growth factor, in platelet granules. This includes the PDGF, the TGF-β, the FGF, the EGF, etc. It activates the complex medium of the wound healing growth factor. Unfortunately, not all platelet stimuli promote the healing of wounds[27].

E. KERATINOCYTE GROWTH FACTORS (KGF)

Developed in 1989, Keratinocyte Growth Factor (KGF) is named for the keratinocyte function. He's a member of the FGF family (now FGF761); only fibroblasts are made. During epithelialization and proliferation and keratinocyte movement, KGF expression is increased [28, 29]. It can be the dermal/epidermal signal that activates a wound and that is necessary if a healed wound is recurrent and does not occur for diabetic foot ulcers [29]. Diabetic mouse expression of KGF Induction has been decreased and delayed, indicating that chronic diabetic sense may occur in human wounds. Nevertheless, no clinical study has been recorded and published [30].

Current treatment and limitations for diabetic wound healing

The conditions for treatment of DW care include vascular condition analysis, glycaemic control adjustment, pervasive debridement, moisture bed application, and moisture dressing[31]. The use of bone-marrow stem cells, negative pressure therapy are recent developments[32, 33] equivalents with bioengineered skin[34], and growth-factor therapy[35]. Hyperbaric oxygen treatment is the risk of significant amputation tends to be decreased, but the time for ulcer treatment or the rate of mild amputation is neutralized[36]. The routine accumulation of devitalized tissue is strongly recommended during follow-up visits, but no evidence accelerates healing[37]. Biotherapy with Maggot (larval) appears effective with degradation[38] and acceleration of healing,[39, 40] and maybe also to minimize antibiotic use and amputation risk[33].

Advantages of micro and nanoparticles for the delivery of growth factors

There are many advantages of drug delivery for micro-and nanoparticles. For example, products are typically easily produced and can be built to encapsulate a wide range of drugs by carefully selecting chemistry. They can be composed of biopolymers, lipids, metals, or chemicals, which capture the advantages of both organic and inorganic materials[41]. Further, the small size of micro and nanoparticles allows its incorporation into meshes or hydrogels and provides a multi-layered supply chain for the sustainable and sustainable release of medicines. This is particularly important for growth factors that only take effect after several hours of direct cell interaction. Nanoparticles also prohibit the use of medicines and other growth factors in chronic wound fluids against matrix metalloproteinases and other degradative enzymes[42]. They can be used for loading and/or distribution in extracellular spaces[43]. Many bio-compatible wound healing nanoparticles system composed of protein. One study produced a recombinant human epidermal growth factor (rhEGF) in solid lipid nanoparticles and nanostructured lipid carriers [44, 45]. Epidermal growth factor promotes rapid growth for fibroblasts and keratinocytes, expression and acceleration of angiogenesis for other growth factors, such as TGF-β. Increased epithelial coverage and increased devastation and reepithelization as opposed to the controls were used in the mouse diabetic model with this loaded lipid formulation considerably[46].

Micro and nanoparticles for growth factors

Studies carried out on micro particles for the delivery of GFs

M.P.Ribeiro et.al. (2013) have developed Dextran – based hydrogel containing chitosan micro particles loaded with vascular endothelial growth factor and epidermal growth factor for the enhancement of wound healing process. The macroscopic test revealed that the wound healing time is considerably less than that of the control groups for animal treatments with micro-particles loaded hydrogel. The *in vitro* experiments have shown that hydrogel filled with both the GFs are non-cytotoxic. In vivo results of dextran hydrogel and chitosan microparticles encapsulated with two GFs suggested that it offered faster-wound healing without evidence of local or systemic inflammatory reaction Its biocompatibility and by product degradation have led to skin architectural regeneration and can shortly be used in regenerative medicine to monitor the provision of other bioactive agents[47].

Feng Wang et al., (2010), studied the sustained release of insulin growth factors-1 from poly(lactide-co-glycolide) microspheres to improve Osseo integration of dental implants in type 2 diabetic rats. Twenty-two diabetic rats were split into two categories: a category obtaining Insulin-like Growth Factor 1

recombinant rat (rIGF-1) (10 rats). To achieve a sustainable release effect around titanium (Ti) dental implants of the rrIGF-1 MST community, rrIGF-1 was encapsulated within microsphere poly(lactide-co-glycoside) (PLGA). To check the release effect of microspheres and the bioactivity of rrIGF-1 scanning, electron microscopy, confocal laser scanning microscopy, and cumulative release studies were carried out. The Lower-Peterson form of evaluating protein developed rrIGF-1 release. This result shows clearly that continued emancipation of rrIGF-1 by PLGA microsphere encapsulation positively affects dental implant Osseo integration in type 2 diabetic rats[48].

Nathalie Bock et al., (2016), have prepared polymeric microparticles that are electros praying to encapsulate BMP-7 or VEGF. Before electro spraying, GFs have been lyophilized to form GF particles micron-sized. The dispersion of the lyophilized protein mixture into PLGA 85:15 solution and further electro spraying with tailored parameters obtained spherically and narrowly scattered micro-apartments with average dimensions of 1.3-5.0mm. With 1 percent wt after micronization. The marginal increase in total solid concentration and the presence, as predicted, of the additive, was observed as trehalose, similar size, and size distribution. Related, spherical, smooth morphologies were found and were not affected in trehalose incorporation. The GF EE and GF load results are presented in electro-spritzed microparticles. Solid proteins were distributed in a polymer-solvent during the electro-spraying process; thus, no aqueous dissolution of proteins is expected, with high EE values. However, all results were below 50 percent, calculated by ELISA after extraction, with high dispersion and no strong trend with trehalose[49, 50].

Evren H. Gokce et al. (2017), – the wound-healing effects in diabetic acid DPPC microparticles were examined in the collagen, which is a laminated dermal matrix impregnated with resveratrol loaded hyaluronic acid. As the number of macrophages in the region of the wound increases immediately and the number of microparticles smaller than 20μm is phagocytized by macrophages, the micro particle size has a major impact on injuries. The micro particles were distributed in the dermal matrix from the surface to the deeper layers. However, it prolonged the time for collagenase degradation by the addition of RSV loaded micro particles which degraded the dermal matrix. Release of RSV continued and reached 70 percent after 6 hours. The diabetic rat full-thickness excision model has been tested in different treatment groups with histologic changes and antioxidant parameters. The formulation was intense and enhanced with collagen fibers, without any sign of inflammation. The highest degree of healing was a dermal matrix with RSV micro particles and increased antioxidant activity. The skin-based matrix was synergistically successful with RSV micro particles due to the involvement of skin components in the formulation and controlled releases. It is safe and can be a perfect way for diabetic injuries to recover that last for a long time[51].

Recent studies on nanoparticles for the delivery of GFs

Hariharan Ezhilarasu et al. (2020), the present and prospective treatment of this challenging therapeutic dilemma can be strengthened by new drug delivery technologies (DDSs). Nanotechnology has recently become one of the most concentrated Care testing sectors and related risks for DM patients. Nanomaterials (1-100 nm in length) have advantages in the simplicity of application, controlled scale, and physiochemical properties tunability. Cell adhesion is feasible by nanomaterials with a greater surface area by volume ratio that can envelop many active components that work to accelerate those regenerative functions (52). The wound healing processes focused on nanotechnology would provide benefits, including current drug usage, cell specificity, and sustainable and controlled release for a time required for healing injuries were shown in Fig. 3.[53, 54].

Medicines are absorbed, dispersed, or dissolved in an aqueous center, shell-like, or the substance can be bound together with nanoparticles' surface matrix[55]. Diffusion, breakdown, reduction, and distension are used to release the medications loaded on nanoparticles in the biological system. Nanoparticles can also be encapsulated as a nanocomposite framework in nanofibers, hydrogel, foam, films, and nanocrystals. The Schematic of nanomaterial, from nanoparticle to Nano particulate system for wound regeneration was shown in Fig. 4.

Nano fibers facilitate the treatment of wounds mechanical properties by having characteristics of a high-volume surface area, Enhanced porosity, and capacity to encapsulate nanoparticles and regulated bioactive compounds During functionalization and release that will allow cells to effectively communicate with the matrix and [56] for restoration. To allow the topical distribution of bioactive molecules, hydrogel products with high water content, viscoelasticity, and biocompatibility were intensively explored[57, 58]. More specifically, nanoparticles and biomolecules can be integrated into hydrogels. Thus, by protecting their structural integrity, the door opens up to more modern, topical drug delivery with specific advantages, including increased localization of tissues, the reduced release of bursts, and controlled sequential release[59]. Silver nanoparticles (AgNPs) and gold non-polymeric nanoparticles Nano particles (AuNPs), most widely used as therapeutic agents for its anti-infectious and anti-inflammatory effects.

The Cell proliferation, migration, disparity and metabolism have been caused by the development of physiologically active proteins. Physiologically, each healing process is regulated by growth

factors and cytokines. The growth factors bind to a certain receptor and encourage the molecular sequence required in order to function in the cell[60]. Via promoting inflammation, angiogenesis, tissue granulation, and modeling, growth factors play an essential role in the healing process. The degradation of growth factors due to the multifactorial pathophysiology of diabetic wounds [61, 62] is well known.

Mirhamed Hajimiri et al. (2015), the conjugation is thought to protect the hydrogel from proteolysis, and mediate release of RhEGF by amylase, having produced a built-in polymer embedded polymer growth factor and nanoparticles as a diabetic wound dressing. The proliferation of fibroblasts was measured using a colorimetric assay to determine NaCMCh-biological rhEGF's activity and free rhEGF. Conjugated and free rhEGF stabilization was achieved against proteases. The results were explained about the conjugated form shows more stability in the in vitro findings. Proteolysis and its biochemical function have since been maintained. Besides, excision wound models for diabetic rats were used for in vivo research. The wound area was slightly lower than the others. The NaCMCh-rhEGF-hydrogel dressing group's histological parameter was equivalent to the positive group of wound controls after 15 days. A more functional rhEGF conjugated polymer was developed proteases and the bioactivity of the medication reserved. This dressing seems to be a capable chronic wound care candidate[63]. Yuejie the Chu et al. (2010), it is investigated that nanotechnology promotes diabetic wound healing full-thickness effects in diabetic rats through recombinant epidermal growth factors.

The transmission observed the morphology of nanoparticles' microscope photon. A laser was used to calculate the particle size distribution zeta potential meter analyzer. Analyzer. Enzyme-linked immunosorbent experiments tested the effectiveness of encapsulation and release models, and MTT was used to proliferation the mouse fibroblasts. Immunohistochemistry checked the proliferation of nuclear cell antigen. The results revealed that the rhEGF nanoparticles had a diameter of approximately 193.5nm, and the distribution of particle size was uniform and dispersible. The effectiveness of encapsulation was 85.6%, and the release of RHEGF was for 24 hours. The rhEGF nanoparticles supported the highest fibroblastic proliferation level compared to other groups, and this group demonstrated the quickest healing time. In the group of rhEGF nanoparticles, the number of cells proliferating nucleic positive antigen cells was more significant than the other groups[64].

Yu-Hsiang Lee et al. (2020), the co-loaded Chitosan composite hydrogel has been formed by novel silver nanoparticles-encapsulated growth factors, preserved anti-micro-ability, and promoted biological properties on diabetic wounds. SNPECHG incorporates silver ions (Ag +) in the chitosan composite hydrogel, which increases the effectiveness of the diabetic wound healing process. A nanoparticular growth factor (EGF) has been developed for this research. The results of the antibacterial studies, the cytotoxicity, and cell formation have first been measured using the ideal active 24 mM Ag+ and 60-µg EGF dosages for developing SNPECHG. The optimized SNPECHG also was characterized and the composite hydrogel could generate the continuous release of Ag+ and EGF in a PBS environment showing significantly higher hydration capacity, including in the deionized water level swelling and equilibrium content. One with SNPECHG demonstrates a substantially improved wound healing effect in vivo findings of a diabetic rat sample compared with others after day three, and on day 14 it may achieve a 97% ($P < 0.05$) wound healing result which is 7.4% and an 18.9% ($P < 0.05$) wounds of Heraderm and gauze classes[65].

Natural polymers for Microparticles

Natural polymer-based microparticles

Because of their non-toxic, biocompatible, and biodegradable properties, natural polymers are being investigated as possible carrier materials for site-specific drug delivery. Chitosan, alginate, and collagen are among the polymers used in microparticle-based drug delivery to wounds.

CONCLUSION AND FUTURE PERSPECTIVES

Wound healing, consisting of some concurrent and overlapping phases, is a complex operation. If the wounds are not treated, may lead to infection. Microparticles and Nanoparticles have attracted great interest as potential delivery mechanisms for drugs/growth factors due to easy manufacturing and characterization, fewer toxicity issues, and the fact that they can be adjusted with various strategies to solve some of the fundamental drug delivery problems. To greatly improve wound healing, microparticles have been designed to prevent protease-mediated degradation of growth factors at the wound sites. For the reliable and sustained release of drugs and growth factors at wounded sites, advanced drug delivery systems are required, reducing the need for wound care and improving the quality of life of the patients. In preclinical trials, both *in vitro and in vivo*, micron-sized structures have shown promising properties. More hybrid microsystems seem likely to be produced soon, use of the benefits of different individual microparticles and nanoparticles. The production of nano-sized particles for the delivery of drugs and growth factors to the wound site is a recent field of interest, capable of incorporating additional benefits associated with systems on the nanoscale. Many reasons for growth have been proven to be effective in wound healing, but their high price (US$1500–10,000 per mg), poor stability, and lack of stability, their application was prevented by the controlled release vehicles. Scientists are

focused on seeking answers, the cost variables, and in the development of advanced drug-delivery systems for applications in wound care.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest in this study. The authors alone are responsible for the content and writing of the paper.

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ABBREVIATIONS

DM	Diabetic Mellitus
DW	Diabetic Wound
IDF	International Diabetic Federation
DFU	Diabetic Foot Ulcer
ECM	Extracellular Matrix
EGF	Epidermal Growth Factor
FGF	Fibroblast Growth Factor
TGF-B	Transforming Growth Factor - B
PDGF	Platelet Derived Growth Factor
KGF	Keratinocyte Growth Factor
GF	Growth Factor
IGF	Insulin like Growth Factor
Ti	Titanium
PLGA	Poly (Lactic-Co-Glycolic Acid)
VEGF	Vascular Endothelial Growth Factor
PEG	Poly Ethylene Glycol
DPPC	Dipalmitoyl Phosphatidyl Choline
RSV	Respiratory Syncytial Virus
MP	Microparticles
DDS	Drug Delivery System
NFS	Nanofibers
NPS	Nanoparticles
HGs	Hydrogel
FMs	Films and Membrane
MC	Multicompanies
AgNP	Silver Nanoparticles
AuNPs	Non – Polymeric Nanoparticles
MTT	Molecular Targeted Therapies
rhEGF	Recombinant Human Epidermal Growth Factor
ELISA	Enzyme Linked Immunosorbent Assay

REFERENCES

1. Kasiewicz LN, Whitehead KA, 2017. Recent advances in biomaterials for the treatment of diabetic foot ulcers, Biomaterials science 5(10):1962-75.
2. Baron AD, Schaeffer L, Shragg P, Kolterman OG, 1987. Role of hyperglucagonemia in maintenance of increased rates of hepatic glucose output in type II diabetics, Diabetes 36(3):274-83.
3. Association AD, 2014. Standards of Medical Care in Diabetes—2014, Diabetes Care 2014; 37 (Suppl. 1): S14–S80 Diagnosis and Classification of Diabetes Mellitus Diabetes Care 2014; 37 (Suppl 1): S81–S90 Diabetes care 37(3):887-.
4. Control CfD, 2015. Prevention, Diabetes Report Card 2014. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services.
5. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y, 2017. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis, Annals of medicine 49(2):106-16.
6. Shaw TJ, Martin P, 2009. Wound repair at a glance. Journal of cell science 122(18):3209-13.
7. Kanitakis J Anatomy, 2002. histology and immunohistochemistry of normal human skin. European journal of dermatology 12(4):390-401.
8. Mathieu D, Favory R, Cesari J-F, Wattel F, 2006. Necrotizing soft tissue infections, Handbook on Hyperbaric Medicine: Springer; p 263-89.
9. Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF, 2007. Impaired wound healing, Clinics in dermatology 25(1):19-25.
10. Loots MA, Lamme EN, Zeegelaar J, Mekkes JR, Bos JD, Middelkoop E, 1998. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous ulcers versus acute wounds, Journal of Investigative Dermatology 111(5):850-7.
11. Sporn M, Roberts AB, 1986. Peptide growth factors and inflammation, tissue repair, and cancer, The Journal of clinical investigation 78(2):329-32.
12. McGrath MH, 1990. Peptide growth factors and wound healing, Clinics in plastic surgery 17(3):421-32.
13. Rothe MJ, Falanga V, 1991. Growth factors and wound healing, Clinics in dermatology 9(4):553-9.
14. Steed DL, 1997. The role of growth factors in wound healing, Surgical Clinics of North America 77(3):575-86.
15. Cohen S, 1962. Isolation of a mouse submaxillary gland protein accelerating incisor eruption and eyelid opening in the new-born animal, Journal of Biological Chemistry 237(5):1555-62.
16. Nanney LB, 1990. Epidermal and dermal effects of epidermal growth factor during wound repair, Journal of Investigative Dermatology 94(5):624-9.
17. Servold S, 1991. Growth factor impact on wound healing, Clinics in podiatric medicine and surgery 8(4):937.
18. Gharaee-Kermani M, Phan SH, 2001. Role of cytokines and cytokine therapy in wound healing and fibrotic diseases, Current pharmaceutical design 7(11):1083-103.
19. Reed JA, Albino AP, McNutt NS, 1995. Human cutaneous mast cells express basic fibroblast growth factor, Laboratory investigation; a journal of technical methods and pathology 72(2):215.
20. Kibe Y, Takenaka H, Kishimoto S, 2000. Spatial and temporal expression of basic fibroblast growth factor protein during wound healing of rat skin, British Journal of Dermatology 143(4):720-7.
21. Steed DL, 1998. Modifying the wound healing response with exogenous growth factors, Clinics in plastic surgery 25(3):397.

22. Sasaki T, 1992. The effects of basic fibroblast growth factor and doxorubicin on cultured human skin fibroblasts: relevance to wound healing, The Journal of dermatology 19(11):664-6.
23. Frolik CA, Dart LL, Meyers CA, Smith DM, Sporn MB, 1983. Purification and initial characterization of a type beta transforming growth factor from human placenta, Proceedings of the National Academy of Sciences 80(12):3676-80.
24. Massague J, 1990. The transforming growth factor-beta family, Annual review of cell biology 6(1):597-641.
25. Ganio C, Tenewitz F, Wilson R, Moyles B, 1993. The treatment of chronic nonhealing wounds using autologous platelet-derived growth factors, The Journal of foot and ankle surgery: official publication of the American College of Foot and Ankle Surgeons 32(3):263-8.
26. Okumura M, Okuda T, Nakamura T, Yajima M, 1996. Acceleration of wound healing in diabetic mice by basic fibroblast growth factor, Biological and Pharmaceutical Bulletin 19(4):530-5.
27. Rubin JS, Osada H, Finch PW, Taylor WG, Rudikoff S, Aaronson SA, 1989. Purification and characterization of a newly identified growth factor specific for epithelial cells, Proceedings of the National Academy of Sciences 86(3):802-6.
28. Werner S, Breeden M, Hübner G, Greenhalgh DG, Longaker MT, 1994. Induction of keratinocyte growth factor expression is reduced and delayed during wound healing in the genetically diabetic mouse, Journal of Investigative Dermatology 103(4):469-73.
29. Clayton W, Elasy TA, 2009. A review of the pathophysiology, classification, and treatment of foot ulcers in diabetic patients, Clinical diabetes 27(2):52-8.
30. Venturi ML, Attinger CE, Mesbahi AN, Hess CL, Graw KS, 2005. Mechanisms and clinical applications of the vacuum-assisted closure (VAC) device, American journal of clinical dermatology 6(3):185-94.
31. Armstrong DG, Salas P, Short B, Martin BR, Kimbriel HR, Nixon BP, 2005. Maggot therapy in “lower-extremity hospice” wound care: fewer amputations and more antibiotic-free days, Journal of the American Podiatric Medical Association 95(3):254-7.
32. Saap LJ, Donohue K, Falanga V, 2004. Clinical classification of bioengineered skin use and its correlation with healing of diabetic and venous ulcers, Dermatologic surgery 30(8):1095-100.
33. Smiell JM, Wieman TJ, Steed DL, Perry BH, Sampson AR, Schwab BH, 1999. Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies, Wound Repair and Regeneration 7(5):335-46.
34. Roeckl-Wiedmann I, Bennett M, Kranke P, 2005. Systematic review of hyperbaric oxygen in the management of chronic wounds, British journal of surgery 92(1):24-32.
35. Steed DL, Donohoe D, Webster MW, Lindsley L, 1996. Effect of extensive debridement and treatment on the healing of diabetic foot ulcers, Diabetic Ulcer Study Group. Journal of the American College of Surgeons 183(1):61.
36. Wolff H, Hansson C, 2003. Larval therapy–an effective method of ulcer debridement, Clinical and Experimental Dermatology: Clinical dermatology 28(2):134-7.
37. Horobin A, Shakesheff K, Woodrow S, Robinson C, Pritchard D, 2003. Maggots and wound healing: an investigation of the effects of secretions from Lucilia sericata larvae upon interactions between human dermal fibroblasts and extracellular matrix components, British Journal of Dermatology 148(5):923-33.
38. Rosales A, Vazquez JR, Short B, Kimbriel HR, Claxton MJ, Nixon BP, 2004. Use of a maggot motility index to evaluate survival of therapeutic larvae, Journal of the American Podiatric Medical Association 94(4):353-5.
39. Knauer D, Wiley H, Cunningham DD, 1984. Relationship between epidermal growth factor receptor occupancy and mitogenic response. Quantitative analysis using a steady state model system, Journal of Biological Chemistry 259(9):5623-31.
40. Trengove NJ, Stacey MC, Macauley S, Bennett N, Gibson J, Burslem F, 1999. Analysis of the acute and chronic wound environments: the role of proteases and their inhibitors, Wound Repair and Regeneration 7(6):442-52.
41. Kasiewicz LN, Whitehead KA, 2016. Silencing TNFα with lipidoid nanoparticles downregulates both TNFα and MCP-1 in an in vitro co-culture model of diabetic foot ulcers, Acta Biomaterialia 32:120-8.
42. Gainza G, Pastor M, Aguirre JJ, Villullas S, Pedraz JL, Hernandez RM, 2014. A novel strategy for the treatment of chronic wounds based on the topical administration of rhEGF-loaded lipid nanoparticles: In vitro bioactivity and in vivo effectiveness in healing-impaired db/db mice, Journal of controlled release 185:51-61.
43. Gainza G, Bonafonte DC, Moreno B, Aguirre JJ, Gutierrez FB, Villullas S, 2015. The topical administration of rhEGF-loaded nanostructured lipid carriers (rhEGF-NLC) improves healing in a porcine full-thickness excisional wound model, Journal of Controlled Release 197:41-7.
44. Shirakata Y, Kimura R, Nanba D, Iwamoto R, Tokumaru S, Morimoto C, 2005. Heparin-binding EGF-like growth factor accelerates keratinocyte migration and skin wound healing, Journal of cell science 118(11):2363-70.
45. Ribeiro M, Morgado P, Miguel S, Coutinho P, Correia I, 2013. Dextran-based hydrogel containing chitosan microparticles loaded with growth factors to be used in wound healing, Materials Science and Engineering: C 33(5):2958-66.
46. Wang F, Song Y-l, Li C-x, Li D-h, Zhang H-p, Ma A-j, 2010. Sustained release of insulin-like growth factor-1 from poly (lactide-co-glycolide) microspheres improves osseointegration of dental implants in type 2 diabetic rats, European Journal of Pharmacology 640(1-3):226-32.
47. Bock N, Dargaville TR, Woodruff MA, 2014. Controlling microencapsulation and release of micronized proteins using poly (ethylene glycol) and electrospraying, European Journal of Pharmaceutics and Biopharmaceutics, 87(2):366-77.
48. Bock N, Dargaville TR, Woodruff MA, 2012. Electrospraying of polymers with therapeutic molecules: state of the art, Progress in polymer science 37(11):1510-51.
49. Gokce EH, Tanrıverdi ST, Eroglu I, Tsapis N, Gokce G, Tekmen I, 2017. Wound healing effects of collagen-laminin dermal matrix impregnated with resveratrol loaded hyaluronic acid-DPPC microparticles in diabetic rats, European Journal of Pharmaceutics and Biopharmaceutics 119:17-27.

50. Mordorski B, Rosen J, Friedman A, 2015. Nanotechnology as an innovative approach for accelerating wound healing in diabetes, Diabetes Management 5(5):329-32.
51. Goyal R, Macri LK, Kaplan HM, Kohn J, 2016. Nanoparticles and nanofibers for topical drug delivery, Journal of Controlled Release 240:77-92.
52. Jackson JE, Kopecki Z, Cowin AJ, 2013. Nanotechnological advances in cutaneous medicine, Journal of Nanomaterials.
53. Gelperina S, Kisich K, Iseman MD, Heifets L, 2005. The potential advantages of nanoparticle drug delivery systems in chemotherapy of tuberculosis, American journal of respiratory and critical care medicine 172(12):1487-90.
54. Shan X, Liu C, Li F, Ouyang C, Gao Q, Zheng K, 2015. Nanoparticles vs. nanofibers: a comparison of two drug delivery systems on assessing drug release performance in vitro, Designed Monomers and Polymers 18(7):678-89.
55. Gao W, Vecchio D, Li J, Zhu J, Zhang Q, Fu V, 2014. Hydrogel containing nanoparticle-stabilized liposomes for topical antimicrobial delivery, ACS nano 8(3):2900-7.
56. Slaughter BV, Khurshid SS, Fisher OZ, Khademhosseini A, Peppas NA, 2009. Hydrogels in regenerative medicine, Advanced materials 21(32-33):3307-29.
57. Chai Q, Jiao Y, Yu X, 2017. Hydrogels for biomedical applications: their characteristics and the mechanisms behind them, Gels 3(1):6.
58. Dave HD, Varacallo M, 2018. Anatomy, Skeletal Muscle. StatPearls StatPearls Publishing. 247,(29)
59. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M, 2008. Growth factors and cytokines in wound healing, Wound repair and regeneration 16(5):585-601.
60. Ulubayram K, Cakar AN, Korkusuz P, Ertan C, Hasirci N, 2001. EGF containing gelatin-based wound dressings, Biomaterials 22(11):1345-56.
61. Hajimiri M, Shahverdi S, Esfandiari MA, Larijani B, Atyabi F, Rajabiani A, 2016. Preparation of hydrogel embedded polymer-growth factor conjugated nanoparticles as a diabetic wound dressing, Drug development and industrial pharmacy 42(5):707-19.
62. Chu Y, Yu D, Wang P, Xu J, Li D, Ding M, 2010. Nanotechnology promotes the full-thickness diabetic wound healing effect of recombinant human epidermal growth factor in diabetic rats, Wound repair and regeneration 18(5):499-505.
63. Lee Y-H, Hong Y-L, Wu T-L, 2020. Novel silver and nanoparticle-encapsulated growth factor co-loaded chitosan composite hydrogel with sustained antimicrobility and promoted biological properties for diabetic wound healing, Materials Science and Engineering: C 118:111385.

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