Diabetes associated delay in wound healing and strategies for its management

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Diabetes one of the leading causes of deaths worldwide because of its secondary manifestations as discussed in this review. These manifestations are neuropathy, retinopathy, nephropathy, cardiovascular system related disorder and alterations in normal wound healing process. Healing of skin and foot ulcers retards which give rise to chronic conditions around ulcers due to changes in the pathological conditions of wound in diabetes. This review discuss about these pathological changes and therapies which are currently available in the market. This review also explores some important research studies based on novel drug delivery system i.e. nanoparticle in diabetic wound healing.

Keywords: Diabetes, wound healing, skin ulcers, foot ulcers, treatment, nanoparticle

I. INTRODUCTION

Diabetes is a condition in which body is unable to utilize glucose, leads to increased glucose levels in blood. This phenomenon of diabetes is rising worldwide as can be witnessed in the statistics given by WHO (World Health Organization) in 2016 stating, seventh major reason of deaths i.e. more than a million death, was due to diabetes. It also reports that number of diabetes cases registered at the ages of 18 years, has increased to 8.5 % in 2014 from 4.7 % in 1980 [1]. Considering the data, it is evident that all age group people are challenged with diabetes and its dangerous consequences. According to International Diabetes Federation in 2013, India by 2030 will lead in terms of people suffering from diabetes [2]. There are various repercussions related to diabetes. Delay in wound healing is one of them. It is observed that person suffering from diabetes shows slow healing of wound and can also worsen the situation. According to American Association of Diabetes, nearly 15% of diabetic population suffers from various types of non-healing ulcers [3].

A. Diabetes delay wound healing

The condition around diabetic wound can be distinguished in several aspects. The environment surrounding diabetic wound has low level of both enzymatic and non-enzymatic antioxidant machinery. It is difficult to retrieve those free radical scavengers ultimately which lead to delay in healing action. Collagen concentration is also low due to altered biosynthesis or degradation of produced collagen contributing to slow down of wound healing [4, 5]. The exact mechanism of disturbed pathology of wound in diabetes is not outlined clearly. But it has been reported that are some major differences including sustained state of inflammatory phase, impaired leukocyte function, down-regulation in the production of granulated mature tissue and concurrent tensile strength reduction of wound making it difficult to heal [6, 7]. Delay in wound healing is also observed because of disturbance in normal defense system of the body. Under expression of heat shock proteins and growth factors, decrease chemotaxis and phagocytosis are the consequences of disturbance [8]. It has also been seen that variation of cytokines bioavailability which are signaling molecules activated during injury/wound. These secondary signals are responsible for initiating action of various cells that perform important functions such as cell growth and division, cellular metabolism including others [9]. Under diabetic conditions it has observed an increase in activity of insulin degrading enzymes with simultaneously corresponding to level of HbA1c indication that glucose concentration affects healing of wound [10]. Another important cellular component which plays a role in delay of healing process is matrix metalloproteinases (MMPs) and tissues inhibitors of metalloproteinases (TIMPs). The function of MMPs is epithelial growth, new blood vessel formation and restructuring of scar tissue [11]. A balance between collagenous and non-collagenous matrix is required which is adjusted by MMPs and TIMPs in normal wound conditions [12]. But in diabetic situations it was found that MMPs are higher in levels than TIMPs which is generally in the case of chronic wound [13].

B. Diabetes related other impediments

Diabetes is associated with various secondary issues accounting for deaths of millions of people and this problem are categorized as macrovascular, microvascular and neuropathic complication. Retinopathy and nephropathy are complications which come under microvascular [14].

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Diabetic retinopathy is due to high level of blood glucose present in retina for prolonging period causing severe eye problems. Improper circulation makes retina blood vessels lack of oxygen, which leads to abnormal growth of blood vessels. Due to unwanted angiogenesis serious vision problem occur majorly vitreous hemorrhage, retinal detachment, glaucoma and blindness [15]. Microalbuminuria, macroalbuminuria and elevated creatinine serum levels are the markers of nephropathy caused in diabetic patients as reported in clinical studies [16, 17]. In macrovascular complications atherosclerosis and other peripheral disease are included. Atherosclerosis in diabetes is due to malfunction in endothelium cells and vascular smooth muscles. Also there is high probability of thrombosis which subsequently account for complicating atherosclerosis (18, 19). Diabetic neuropathy is another arena of consequences which makes diabetes a serious problem. Studies have found that abnormality in glucose tolerance is related to oxidative stress in peripheral nerves [20].

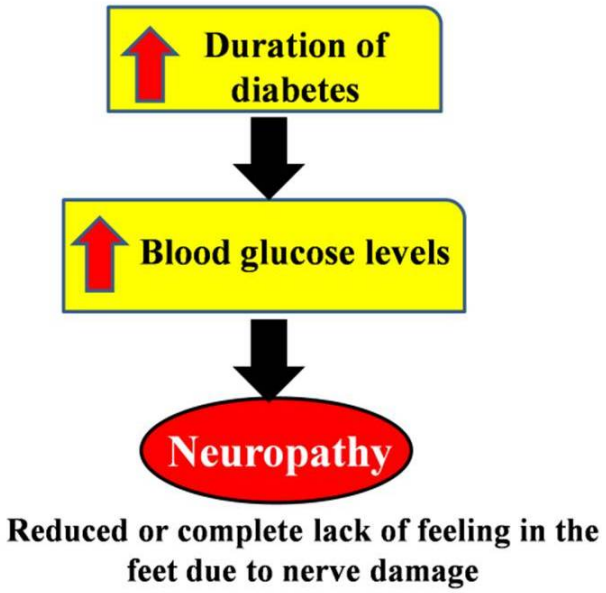

FIG. 1: Diabetic neuropathy.

C. Diabetic wound healing

There are many significant pathological events take place with this diabetic wound healing. Most of them are occurred as skin ulcers and foot ulcers. Their manifestations are mentioned here.

D. Skin ulcers

Typically diabetic wound healing comprises of many severely outbreaks of skin ulcers. We have incorporated all the clinical manifestations for these skin ulcers. Depending upon the types of diabetics with which the skin ulcers are associated, we have categorized into two parts. [21].

E. Pathological manifestations of skin arising from DM type I

- **Periungual telangiectasia:** Most of the capillary loops are lost and they become dilated. In the persons associated with DM I, they produces nail fold erythema with fingertip tenderness and ragged cuticles [22].

- **Necrobiosis lipoidica:** These are mostly predominant in the females as compared to the males. They are associated with erythematous or violaceous border without any scaling plaques. However, some yellow colour atrophic centres are found in this surface telamgiectasia. Medication with some topical steroids as well as some systemic steroids has shown the effectiveness against this pathological outbreak [23-25].

- **Bullosis diabeticorum:** These are the non-inflamed bullae on dorsa and sides of lower legs which are mostly asymptomatic. They are more common in men as compared to the women. Treatment is considered as symptomatic and conservative [26].

- **Vitiligo:** They are associated with some type of polygladular autoimmune syndrome in where occurrence of depigmentation of skin is rapidly. The diabetic patients should avoid the exposure from the sun rays. This can be avoided by the use of cosmetic treatments like the use of sunscreens etc [27].

- **Lichen ruber planus:** They are expressed as flat, erthematous lesions in the skins as well as white reticular stripes in the mouth. These are occurred mainly on the wrists and dorsa of feet and lower legs of both female and male. Treatment can be effective with the administration of topical corticosteroids with or without the use of cyclosporine [28].

F. Pathological manifestations of skin arising from DM type II

- **Diabetic dermopathy:** These are some hyperpigmented pretibial papules which are found on the extensor surface of lower legs. They are not pathognomonic for diabetes and no treatment is required [29].

- **Acanthosis Nigerians:** These velvety-looking hyperpigmented plaques are especially occurred in mostly of the body folds. Their presence may be correlated with the high levels of circulating insulin. Treatment is not required but salicylic or retinoic acid ointments may be found useful to relieve from the symptoms [30].

- **Yellow nails:** These are mainly occurred in the distal end of nail of the elderly diabetic patients. The nails become yellow coloured.

- **Diabetic thick skin:** They may produce diabetic sclererderma in where sensitivity towards the pain and touch in the affected areas of back of the neck are significantly decreased [31].

- **Acrochordons (skin tags):** They are the small, pedunculated, soft lesions, mostly observed on axillae, eyelids and neck. It may indicate the sign of impaired glucose tolerance, diabetes, and increased cardiovascular risk. Treatment is not necessary, but it can be removed with cryotherapy or electrodessication [32].

G. Foot ulcers

The diabetic patients have a tendency to develop the various pathological manifestations of foot ulcers. This is referred as Diabetic Foot Ulcers (DFU). It is predominantly occurred in the bottom of the foot as an open sore of ulcers. Approximately 15% of diabetic patients are associated with this DFU. In many of the research study it was revealed that progression of these ulcers is directly related with the consumption of alcohol and tobacco [33]. They are some important factors which may contribute in the development of ulcers are the duration of diabetes, poor blood circulation, foot deformities, lack of sensation in the foot etc. The DFU can be more complicated if the diabetic patients have any vascular disease [34]. Due to the inability to heal the wounds by the body's defence system, the risk of infection may be increased. Besides this, an elevated glucose levels can reduce the wound healing ability of body [35, 36].

II. THERAPIES

Several advancements in research have been done in the recent years to combat the pathological outbreaks of diabetic wound healing.

A. Current therapies

In this section marketed formulation used in the diabetic wound healing are enlisted.

TABLE I: List of marketed formulation used in diabetic wound healing

Sr. No.	Market Name	Composition	Company
1.	Biatain Alginate Ag	Ionic Silver complex with Carboxymethylcellulose (CMC) and Calcium Alginate	Coloplast
2.	PROMOGRAIN & PROMOGRAIN PRISMA	Collagen, sliver and Oxidised Regenerated Cellulose (ORC)	Systagenix
3.	ACTISORB PLUS 25 Dressing	Sliver incorporated in activated Charcoal layers	Systagenix
4.	FIBRACOL PLUS	Collagen and Alginate	Systagenix
5.	CalciCare™	Fibres of natural Calcium Alginate	Hollister
6.	ENDOFORM Derma template (Dressing)	Salt form of sliver (AgCl)	Hollister
7.	SilverCell hydro-Alginate with Silver Dressing	Nylon impregnated with silver, Alginate and carboxymethylcellulose	Systagenix
8.	IODOSORB & IODOPLEX Pads	Iodine	Smith & Nephew
9.	IODOSORB & IODOPLEX Gel	Cadexomer Iodine 0.9% w/w	Smith & Nephew
10.	NaturalQR® ointment	Pongamia pinnata, Lawsonia alba, Datura alba, Cocos nucifera	Apptec Group of Companies in USA
11.	PROMOGRAN PRISMA™ Matrix	A sterile, freeze dried composite of 44% oxidized regenerated cellulose (ORC), 55% collagen and 1% silver-ORC.	KCI
12.	SILVERCEL™ NON-ADHERENT Antimicrobial Alginate Dressing with EASYLIFT™ Precision Film Technology	Non-woven pad composed of alginate, carboxymethylcellulose (CMC) and silver coated nylon fibers, with EASYLIFT™ Precision Film Technology; laminated non-adherent wound contact layer	KCI
13.	Vancocin	Nancomycin	ViroPharma
14.	Fortaz	Ceftazidime	GlaxoSmithKline
15.	Maxipime	Cefepime	Pfizer
16.	Zosyn	Piperacillin-tazobactam	Pfizer

The effectiveness of current therapies is still need to be improved. Many researchers are focusing on the molecular aspects of this disease so that more prominent treatment can be developed in upcoming days. These molecular aspects are summarized below.

B. Growth Factors (GFs)

GFs play crucial role in every steps of wound healing process. They are released from the endothelial cells, macrophages, neutrophils, fibroblasts, platelets etc. Platelet-derived growth factor (PDGF) is currently employed in the treatment of DFUs due to its prominent mitogenic action on various cells like platelets, fibroblasts, skeletal myoblasts, vascular smooth muscle cells, macrophages, microvascular endothelial cells and neurons [37-39]. At present, Becaplermin which is a recombinant human-platelet-derived growth factor (PDGF) is used as GFs in the treatment of DFUs [40, 41]. Beside it, there are some other GFs which are currently

under the development stage. This includes fibroblast growth factor [42-45], vascular endothelial growth factor (VEGF), granulocyte colony-stimulating factor and hepatocyte growth factor [46-48]. More effective treatment can be approached if we combine all the different GFs with other wound healing agents.

C. Neuropeptides

In presence of diabetic neuropathy, the signaling pathways between the nervous system and immune system are impaired which leads to the development of acute and chronic wounds as well as many pathological features of ulcers. Therefore, these peripheral nerves and cutaneous neurobiology make a strong impact on the wound healing process. A crucial relationship exists between the nervous system and endocrine feedback mechanism to elicit an immunomodulatory response. These complex responses are facilitated by several neuromodulators such as neuropeptides, neurotransmitters, neurotrophins, and neurohormones. These neuromodulators act on the specific receptors on cutaneous cells including microvascular endothelial cells, keratinocytes, mast cells, fibroblasts, and immune cells. Behind the impaired diabetic wound healing, the most important neuropeptides are reported as substance P and neuropeptide Y [49, 50]. So our current research targets to develop some neuropeptide based medicines which can control the neuropeptide-immunomodulatory signaling pathways in order to counteract wound-healing abnormalities specific to diabetes.

D. Gene Therapy

Although GFs show the effectiveness in the treatment of diabetic wound healing, but several difficulties arising from its development and administration which may complicate its therapeutic approach. For example, purified and large amount of GFs is required which is very troublesome and tedious. Apart from this, the half -life of GFs are reduced due to its degradation by proteases which are present in the place of wounds [51]. Therefore, gene therapy may be a good alternative for diabetic wound healing for targeted delivery of GFs to eliminate these hurdles. There are some methods commonly employed including genetically modifying autologous cells *in vitro* using replication deficient viral vectors, liposome, or naked DNA, and transplanting the modified cells back to the host tissue. Mostly viruses are used as carrier in most of the gene therapy protocols, but it may exerts a variety of potential threats to the patient such as toxicity, immune and inflammatory responses, and targeting action. In addition, there is always a possibility of regaining the replication ability of these viral vectors used in the gene therapy [52- 55]. This is why, although it is very promising in the treatment of wound healing but still, not a single drug has been clinically approved so far.

E. Cell-based Therapies

From the investigation of many cell based studies, it is significantly evident that the contributory role of stem cells, fibroblasts, keratinocytes among others is very much crucial in the effective treatment of diabetic wound healing. Thus, Cell-based therapies are coming as an emergent player in the modern context of wound healing treatment [56, 57].

F. Silver based therapy

Over many decades, silver has been used as one of the effective antimicrobial agents mainly Silver Nitrate. Its effectiveness is proved against a broad range of aerobic, anaerobic, Gram-negative and Gram-positive bacteria, yeast, filamentous fungi and viruses. But due to its tissue irritant property, some new silver-impregnated dressings such as Acticoat were developed [58]. Some of the incorporated silver first interacted with target cells and after being inactivated by protein and anion complexes present in wound fluid, additional silver is released from the dosage form, thus producing a sustained, steady supply of active silver. Molecular mechanistic study of silver reveals that it directly interferes with the respiratory chain at the cytochromes as well as interferes with components of the microbial electron transport system (ETC). In addition to the antimicrobial properties, silver also appears to have anti-inflammatory properties, as suggested by the loss of redness in chronic wounds treated with colloidal silver [59-61].

III. NOVEL DRUG DELIVERY SYSTEM IN DIABETIC WOUND

Now-a-days, chronic wounds have becoming a major healthcare burden. As the days are going on, conventional therapies for the diabetic wound healing are becoming inefficient to combat all the pathological manifestations occurred within the diabetic patients. At present, researchers emphasize on the crucial exploration of nanotherapies and develop a varying number of nanoparticle strategies in the effective treatment of diabetic wound healing [62].

These nanotherapeutic based drug design can efficiently control the different stages of wound healing and minimize any possible complication. For the nanosize of these therapeutic active particles, the penetration into the wound site can be enhanced and thus provoking a high probability of selective interaction with the biological target of our interest. As a result, a sustained and controlled release of therapeutics is occurred over the stipulated time which facilitates an accelerated healing process. Thus, the nanocarriers or nanodelivery systems are gaining significant importance, as they help to in-

crease the therapeutic potential for biological and synthetic molecules [63].

The nanoparticle strategies were explored for treatment of diabetic wound healing and some of the important strategies are discussed below.

A. Silver Nanoparticle

Silver nanoparticles are one of the important promoters in wound healing process. AgNPs facilitate wound healing by inducing the myofibroblasts from fibroblast differentiation. As well as, it acts through the proliferation and migration of keratinocytes [64].

B. Curcumin loaded chitosan nanoparticle

Curcumin (CUR) which is reported in the treatment of diabetic wound healing for its well-known anti-inflammatory and antioxidative property. CUR loaded chitosan nanoparticles impregnated into collagen-alginate scaffolds produce a novel nanohybrid scaffold which is prepared by incorporating CUR in chitosan nanoparticles (CSNPs). The stability and solubility profile of these CSNPs is significantly improved when CUR impregnated CSNPs are incorporated into collagen scaffold. A complete epithelialization with thick granulation tissue formation is occurred for the presence of the nanohybrid scaffold which further facilitates better tissue regeneration application. Thus, it shows an 'all-rounder' role of biocompatibility, anti-inflammatory, cell adhesion and proliferative activity which are considered as very much crucial aspects for tissue engineering study in the impaired wounds of diabetics.

Hence, the present study suggests that the synergistic combination of CUR (anti-inflammatory and antioxidant), chitosan (sustain drug carrier, wound healing) and collagen (It is already established as wound healer scaffold) will pose a very promising strategy to address various pathological manifestations of diabetic wounds [65].

C. Fibrin-based scaffold incorporating VEGF- and bFGF-loaded Nanoparticles

Recombinant human vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are reported for the cell proliferative activity in wound healing process. In order to directly deliver the VEGF and buff at the wound site, a poly (ether) urethane-polydimethylsiloxane/ fibrin-based scaffold containing poly (lactic-co-glycolic acid) (PLGA) nanoparticles is developed. These scaffold/GF-loaded NPs can exert the desired biological effects in a sustained and controlled fashion without loss of bioactivity. They can induce a complete re-epithelialization with enhanced granulation tissue formation/maturity and collagen deposition. The ability of the scaffold/GF-loaded NPs to promote wound healing in a diabetic mouse model suggested us that it can be administered for the effective treatment of patients with DFUs [66].

D. Topical administration of rhEGF-loaded lipid nanoparticles

Lipid nanoparticles are currently receiving increasing interest because they permit the topical administration of proteins, such as recombinant human epidermal growth factor (rhEGF), in a sustained and effective manner. The topical administration of rhEGF-loaded lipid nanoparticles, namely solid lipid nanoparticles (SLN) and nanostructured lipid carries (NLC), significantly improved chronic wound healing in terms of wound closure, restoration of the inflammatory process, and re-epithelisation grade. Thus, it may be a suitable approach for the treatment of chronic wounds.

Overall, these findings demonstrate the promising potential of rhEGF-loaded lipid nanoparticles, particularly NLC-rhEGF, for the promotion of faster and more effective healing and suggest their future application for the treatment of chronic wounds [67].

E. Nitric oxide-releasing nanoparticles

The physiological role of nitric oxide i.e. NO is very important in different molecular action such as stimulation of fibroblasts, keratinocytes, and endothelial cells. Endothelial cells take part in the angiogenesis process via production of additional NO and vascular endothelial growth factor (VEGF). NO imparts its crucial contribution in the wound healing process by generating all the required angiogenesis factors such as TGF-β and VEGF. These factors facilitate blood vessels formation by providing adequate blood supply toward the wound area.

In immunocompromised states, the process of wound healing can be interrupted as a result of decreased numbers of immune cells, impairing the production of effector molecules such as nitric oxide (NO). So, in order to provide a sustained release of NO (NO-NPs), nanoparticle platform can be better option to select for accelerating wound healing process.

From the clinical data of mice treated with NO-NPs, it is quite evident that these NO-NPs accelerate wound closure by reducing the inflammatory cell infiltration as well as increasing fibroblast cells, collagen deposition, and neovascularization in the wound parts. These results suggest that this NO-releasing platform has the potential to serve as a novel topical wound healing therapy in the treatment of chronic wounds [68].

F. Gold nanoparticles in wound healing with antioxidant epigallocatechin gallate and -lipoic acid

In recent days, focus of the researchers has directed towards the topical administration of antioxidant agents in cutaneous wounds. The antioxidative effects of Gold nanoparticles (AuNPs), epigallocatechin gallate (EGCG), and -lipoic acid (ALA) are already reported. After topical AuEA (comprised of AuNPs, EGCG and ALA) treatment, CD68 protein expression is decreased and Cu/Zn superoxide dismutase is increased significantly in the wound area thereby promoting ECGF and Angiopoietin-1 protein expression.

It has been reported that AuEA significantly accelerated mouse cutaneous wound healing through anti-inflammatory and antioxidation effects. For the enhancement in absorption of AuNPs by the use of nanogold particles, these AuNPs have been shown to be capable of opening the stratum corneum and penetrating the skin barrier.

From the hypothesis results, it is very clear that topical application of antioxidants along with a mixture of AuNPs, EGCG, and ALA accelerates the wound healing process by a mechanism that may involve anti-inflammatory and antioxidation actions in the wound area [69, 70].

G. Self-assembling elastin-like peptides growth factor chimeric nanoparticles

A close relation is found between the chronic wounds and poor remodeling of epidermal and dermal tissues. There is a significant role of keratinocyte growth factor (KGF) and elastin in re-epithelialiation and dermal wound healing process respectively. Elastin is a major constituent of skin elastic fibers and may be beneficial for dermal regeneration the application of elastin containing materials for healing of chronic wounds. When these physiological players are fused into a single fusion protein, the individual activities of KGF and elastin are retained as evidenced by its enhancement of keratinocyte and fibroblast proliferation.

If the fusion protein is self-assembled into nanoparticles at physiological temperatures, these nanoparticles may potentiate the beneficial activities in the treatment of chronic wounds resulting from diabetes or other underlying circulatory conditions. Scientific study showed that, these nanoparticles when applied to wound in genetically engineered diabetic mice, the process of wound healing is improved by enhancing re-epithlialization (2-fold) and granulation (3-fold) when compared to controls [71].

H. Recombinant human epidermal growth factor (rhEGF) nanoparticles

One of the biomarkers in pathology of DFUs is thought to be the deficiency of epidermal growth factor (EGF).The local administration of exogenous recombinant human EGF (rhEGF) in DFUs has already proven its significant effectiveness. But, due to its short biological half-life, the application of rhEGF has limited in the therapeutic treatment of DFUs. Moreover, rapid dilution by tissue fluid, leakage from the wound surface, and degradation by enzymes make it very difficult for rhEGF to achieve effective concentrations to treat DFUs.

In order to overcome all these shortcomings and optimize the rhEGF treatment, we have used a modified double-emulsion method to prepare rhEGF nanoparticles. These nanoparticles have produced the highest level of fibroblast proliferation, and showed elevation healing rate. The number of proliferating cell nuclear antigen positive cells in the rhEGF nanoparticles group was higher than the other groups. Thereby, it may be concluded that controlled release of rhEGF encapsulated in the nanoparticles can enhance rhEGF effects to stimulate cell proliferation and shorten the wound healing time [72].

IV. CONCLUSION

Diabetes related obstacles in healing wound are major concern in almost every part of the world. Because diabetic condition promotes ulcers to become chronic wound for which ultimate option is amputation. There is an increase need for development of medication for enhancing wound healing activity. Researchers currently are focusing on applying innovative strategies to treat wounds. Considering this review it was studied that novel drug delivery can be considered as one of the most promising therapy for delayed wound healing in diabetes.

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