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Utilization of nanotechnology-based approaches to manage diabetic foot ulcer

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Abstract

Diabetic foot ulcer is a notable cause of amputation in diabetic patients. Multiple risk factors i.e. age, smoking, weight of patients, genetic basis, immunological disorders, neuroischemic, and neuropathic conditions contribute to diabetic foot ulcer. This review article covers both Polymer and non-polymer nanoparticles which are involved in pro healing of wounds by promoting the proliferation of fibroblast and collagen and by targeting pro-inflammatory cytokines and anti-inflammatory cytokines. Biodegradability and less toxicity of nanotechnology provide a new paradigm for the management of diabetic foot ulcer. In this review article we elaborate treatment of diabetic foot ulcer utilizing nanotechnology-based strategies which can be new promising candidates in pharmacology.

Introduction

Diabetes mellitus is a devastating global health issue and one of its significant and feared complications is diabetic foot ulcer [1]. Diabetic foot ulcer (DFU) is characterized by chronic non-healing lesions on foot which become the leading cause of amputation and long hospitalization in diabetic patients [2]. Among all amputations that occur globally approximately 85% are performed in diabetic patients due to diabetic foot ulcer [3]. From half a billion diabetic patients about 15% develop Diabetic foot ulcer and half of this 15% become death morsel within five years [4]. Approximately 10 to 30% of diabetic patients progress to minor and major amputation. Incidence of diabetes foot ulcer is approximately 1.0% to 4.1% annually and every one in fourth patients of diabetes develop diabetic foot ulcer [5]. The most common cause of diabetic foot ulcer is *staphylococcus aureus* [6]. According to an estimate globally, one limb is amputated within half a minute due to diabetes and causes disablement. Peripheral vascular diseases, peripheral neuropathy diseases, and abnormal immune responses are significant factors that mainly contribute to this multifactorial complication. Both intrinsic and extrinsic factors are associated with DFU [7]. Type of diabetes, patients' age, weight of the patient, food habits, smoking, neuropathy complication, genetic factors, and socioeconomic factors contribute to the severity of DFU. DFU contribute to a significant cause of mortality in developing countries due to poor clinical examination, unhealthy health care settings, poor self-care practices, and poor preventive strategies [2]. Wound size and depth are two important factors that must be considered at the initial stage to reduce the onset of ulceration [7]. Simply diabetic foot ulcer can be classified as neuropathic, ischemic, and neuroischemic **(Fig. 1)**. Within twenty-five years of onset of diabetes approximately half of diabetes patients develop peripheral neuropathy. Diabetic neuropathy solely contributes to 50% of all diabetic foot syndromes and approximately 90% of foot ulcer. Diabetic neuropathy causes muscle weakness, loss of sensation, and make the skin more vulnerable to infections [8]. Neuropathic wounds take less time to heal as compare to neuroischemic ulcer which mostly leads to amputation. According to research, most DFU patients have ischemic issues. More than 50% of patients of DFU have peripheral artery disease (PAD). PAD and kidney diseases are also possible risk factors for limb amputation in diabetic patients. Neuroischemic ulcers are the most common diabetic foot ulcer and cause infections and amputation [9-11]. DFU heal very slowly due to microbial infections and nanotechnologies are promising therapeutic options due to their antimicrobial activity. Treatment of DFU includes the use of an antimicrobial agent, administration of cell growth factors, use of surgical techniques, use of offloading devices, and amputation [12-14].

However, these methods are ongoing challenges for the treatment of diabetic foot ulcer. The use of nanotechnology research in medicine has increased considerably in the twentieth century due to their desired target characteristics in pharmacology. Nanotechnology involves the study of structures that range in size from 1 to 100 nm. The first development in nanotechnology was started in 1958 and 2011 is thought molecular era of nanotechnology. Nanotechnology works at atomic and subatomic levels and manipulation of these structure results in desired structures with distinct biological and chemical functions which have multiple applications in pharmacology; main reason due to which they are gaining popularity in pharmacology. Two main divisions of nanomaterials are nanostructured material and nanocrystalline. Polymer nanostructures include drug conjugates, micelles, and dendrimers while non-polymer nanostructures include metallic nanoparticles, carbon nanotubes, silica nanoparticles, and quantum dots. Due to their extremely small size they had revolutionized pharmacology especially in the field of novel drug delivery, early diagnosis of diseases, and in the development of small nanomedicines devices. Gold and silver nanoparticles are mostly used in nanotechnology due to their controlled size and composition and biocompatibility. Bottom-up and top-down techniques are used to develop nanoparticles [15].

For the treatment of complex diseases, nanoparticles are novel targeted options and are of significant interest due to their large surface to volume ratio and extremely small size and these characteristics have made them a central player in the field of nanotechnology. For desired uptake of drug nanoparticles manipulate intracellular uptake of drug in a controlled manner which could be a good treatment option for diverse diseases. In addition to their significant interest in disease treatment nanoparticles also serve as diagnostic agents especially due to their low toxicity and target site specificity [16].

Nanosize structures increase sensitivity and selectivity of early diagnosis such as the use of

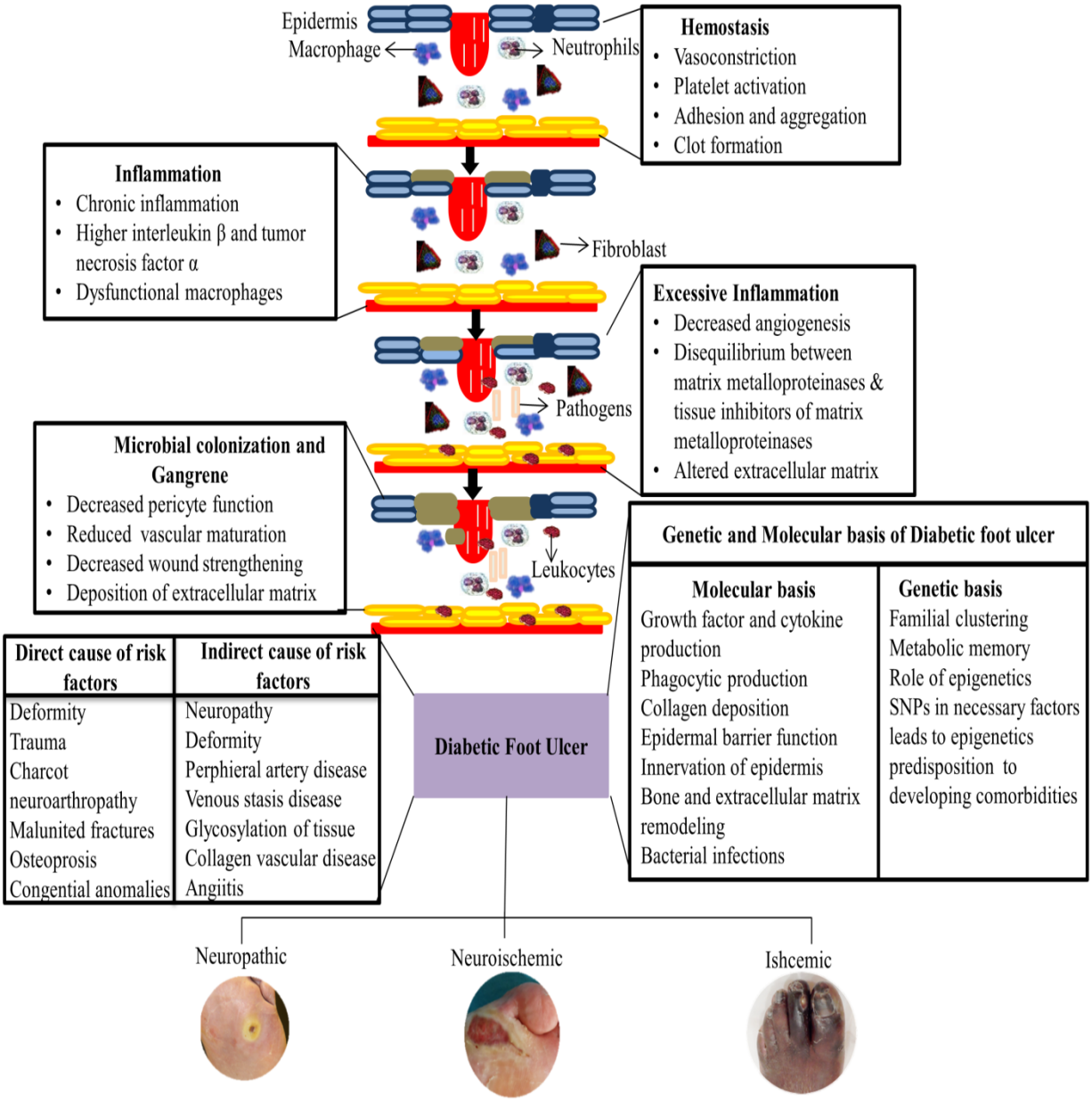

Fig. 1: Schematic representation of diabetic foot ulcer.

quantum dots, metals oxide and metals are of significant interest in better visualization of desired structures which leads to better diagnosis of disease [17]. By using nanoscale vehicles vaccines can make to prevent multiple diseases. Their unimagined ways of diagnosis and treatment have made them a promising agent for the treatment of diseases which have no specific treatment like cancer, cardiovascular diseases and diabetes etc [18]. The use of nanotechnology in the production of nanoparticles allows the controlled release of drugs. Manipulation of nanoparticles composition allows the desire release rate of drugs in a sustained manner. The release of drugs in a sustained manner enhances the likelihood of interaction of drugs to a biological target. Nanoparticles enable targeted delivery of undelivered drugs and make them ideal for topical drug delivery due to less toxicity. Many types of research support the antimicrobial activity of nanoparticles against multi resistant microorganisms as curcumin nanoparticles show antimicrobial activity against methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* in vitro experience and in vivo experiments and enhance the wound healing process. Another promising strategy presented by nanotechnology is the utilization of

wound dressing with nanoscale fibers. These dressings promote healing of wounds by targeting fibroblasts and keratinocytes which stimulate collagen synthesis (**Fig. 2**).

Nanotechnology based therapies and Diabetic foot ulcer

Although practical applications of nanomedicines for wound healing are low as compared to possible expectations however it still provides an excellent understanding of regeneration mechanism of wound healing in Diabetic foot ulcer. There are multiple types of nanoparticles i.e., carbon-based nanoparticles, ceramic nanoparticles, metal nanoparticles, polymeric nanoparticles, semiconductor nanoparticles, and lipid-based nanoparticles [19, 20]. This mini review summarizes only some pharmaceutical nano systems such as metallic nanoparticles, nanocomposite, nanobiocomposite, lipid nanoparticles, liposomes, nanofibrous structures, and carbon-based nanoparticles which would provide a possible solution to this multifactorial complication and would provide a futuristic approach to revolutionized prognosis of DFU.

Nanoparticles are not only novel target options due to topical drug delivery of undelivered drugs but they also allow topical delivery of endogenous substances such as Nitric oxide NO. NO is a gaseous molecule which is produced in less amount in diabetic wound due to abnormal immunological response and defects in the process of phagocytosis. The use of exogenous NO promotes the healing of wounds. Efficiency of topical NO-releasing nanoparticles (NO-np) is confirmed in many types of researches in which NO-np promotes re-epithelialization of wounds, increased blood vessels, increase fibroblast, organized collagen and, reduce inflammatory cells in diabetic immunodeficiency mice. In vitro studies on human dermal fibroblasts also support the pro healing activity of NO-np by proliferation of fibroblasts and collagen expression. Other endogenous molecules that reduce in diabetic wounds are growth factors [21, 22]. In one study nanoparticles incorporated with recombinant human EGF (rhEGF) accelerate fibroblast proliferation, keratinocyte proliferation, collagen expression and stimulates pro healing activity of wounds in diabetic rats. Nanoparticles encapsulated with natural ingredients such as curcumin accelerates the wound healing process by increasing the synthesis of VEGF, TGF-β epidermal growth factor (EGF), and endothelial NO synthase [23, 24]. Recombinant human vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) favor the proliferation of wounds. In an experiment in diabetic rat nanoparticles loaded with these factors promote wound enclosure [25].

In addition to the use of nanoparticles in the above stated ways nanoparticles can also use to augment gene expression. For the treatment of diabetic foot wounds GM 3synthase is a novel target. In an experiment on diabetic rat Knocked down of GM3 synthase by siRNA pathways by using gold nanoparticles accelerate wound healing by the proliferation of vascularization and IGF-1 and EGF receptor activation [26]. In biomedical research use of gold nanoparticles *(metallic nanoparticles)* has increased in recent years due to their compatibility with the biological target, small size, large size to volume ratio, and penetration into cells.

Binding of these gold nanoparticles with biological agents like chitosan and calreticulin results in the formation of *Nanocomposite* which favors the process of wound healing. Nanocomposite based on gold nanoparticles (AuNPs) functionalized with calreticulin are possible treatment options for diabetic foot ulcer and efficacy has checked in an experiment on rats. These gold nanoparticles accelerate the remolding of wounds by the proliferation of fibroblast, growth factors, collagen, and reduction of inflammatory responses [27, 28].

Excellent antimicrobial activity of Silver nanoparticles make them good wound healer in diabetic foot ulcer [29]. *Nanobiocomposites* containing bamboo cellulose nanocrystals and silver nanoparticles promote wound healing by regulating growth factors and collagen, and by reducing pro-inflammatory cytokines [30]. Other metallic nanoparticles such as copper nanoparticles, zinc oxide nanoparticles, and titanium oxide nanoparticles also use nano-bio-composites and have multiple activities like antimicrobial and anti-inflammatory [31, 32]. Nanocomposite containing antibiotics and graphene oxide-based nanocomposite are of significant interest in the treatment of chronic wounds [33, 34]. Nano-delivery routes by utilizing stem cell therapy in the future could provide more insights in biomedicines [35]. Antimicrobial properties, less toxicity and antioxidant auto regenerative ability of Cerium (Ce) oxide nanoparticles (CNPs) favors wound healing which make them novel treatment option for topical treatment of diabetic foot ulcer [36].

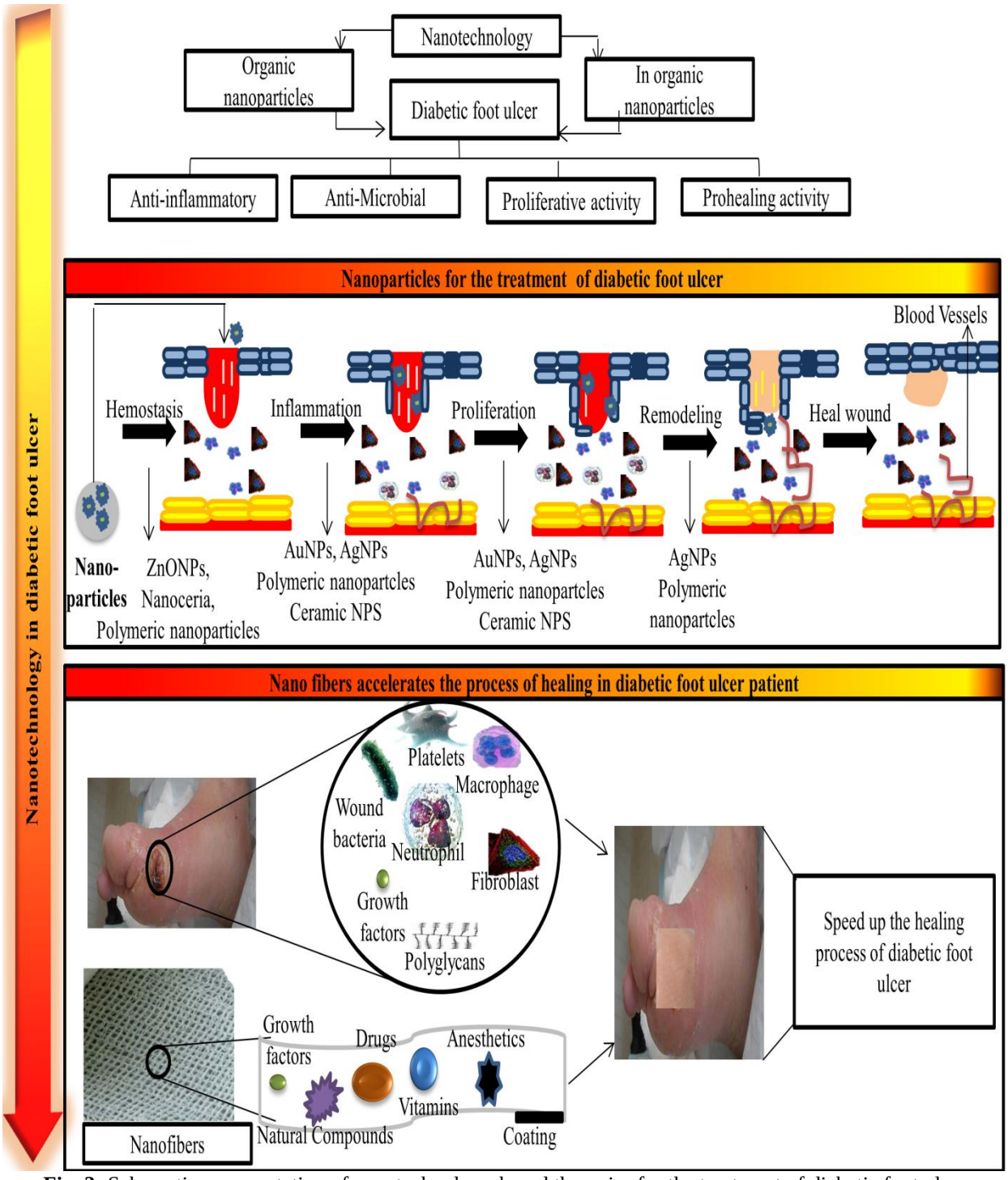

Fig. 2: Schematic representation of nanotechnology-based therapies for the treatment of diabetic foot ulcer.

Lipid nanoparticles (solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)) loaded with oil such as eucalyptus and rosemary essential oils promote wound healing by proliferation enhancement in diabetic foot ulcer. Antimicrobial activity and proliferation activity of lipid nanoparticles make them a good proliferative enhancer of wounds [10, 37, 38]. The use of SLNs and NLCs loaded with rh-EGF promotes re-epithelialization of wounds and proliferation of cells [39]. Antimicrobial activity of magnetic

nanoparticles accelerates wound healing without any damage to tissue.

Liposomes are amphipathic vesicles that are more compatible with the skin, have more penetration into the skin, and have less toxicity. Hydrophilic water cavity contains encapsulated drug (growth factors etc) and lipid bilayer is hydrophobic. Liposomes with hydrogel cover are more efficient in inducing wound healing. Deformable liposomes are emerging as innovative insight for topical drug delivery. Polymer nanoparticles are prepared with a combination of polymers to allow controlled of drugs. Polymer nanoparticles loaded with peptide LL37 accelerates the wound healing process. These polymer nanoparticles are prospects for the treatment of diabetic foot ulcer [26, 27, 40].

In tissue engineering *Nanofibrous* structures are produced by using Electrospinning techniques. High surface to volume ratio, compatibility with biological target, and favorable cell adhesion allows the transfer of multiple drugs and show promising result in skin regeneration [41-43] In some cases interaction of fibrous structures with nanoparticles stimulates the reduction of pro-inflammatory cytokine and an increase in anti-inflammatory cytokines and vascularity. In one report nanofibrous scaffold loaded with TiO2 stops bleeding of the wound and have antimicrobial activity. Scaffolds loaded with magnetic iron oxide acts as promising wound healers in skin tissue engineering [32, 44]. To speed up the wound healing process it is necessary to provide a moist environment to wound. Nano hydrogel is 3D polymeric network with fluid absorption capacity. Compatible cell adhesion, the property of absorption of fluid, and easy penetration of oxygen provide favorable conditions for wound healing and make them excellent material for wound dressing [45]. Such as VEGF-loaded nano hydrogel and baicalin-loaded nanohydrogel promote healing of wounds by inhibition of pro-inflammatory markers and promote rapid cell proliferation for wound healing [46, 47].

In tissue engineering *Carbon-based nanoparticles* (carbon nanotubes) are utilized to develop nanocarriers and nanosensors [46]. Due to biodegradability and nontoxic properties of nanomedicines it is a new paradigm for the treatment of diseases in the future [27, 48]. Silicon nanoparticles loaded with Flightless I(Flil) neutralizing antibodies hold significant promise for the healing of wounds in diabetic mice and provide new therapeutic insight for the treatment of diabetic foot ulcer [49]. Both lysine-derived CQDs (Lys-CQDs) and arginine-derived CQDs (Arg-CQDs) promote the proliferation of cells in the wound and have an antibacterial activity which makes them excellent candidates for tissue repair [50, 51]. Positively charged CQDs (Carbon quantum dots) contribute to cationic disruption of the bacterial cell membrane [52]. CODs that induce ROS promote the proliferation of wounds and possess antibacterial activity [53].

Conclusion

Diabetic foot ulcer is a leading cause of hospitalization and amputation in diabetic patients. Less toxicity and biodegradability of nanotechnology make them excellent game-changer in the management of diverse diseases. Nanotechnology has revolutionized biomedicine in the development of nanomedicines and nanodevices.

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Conflict of interest

The authors declare no conflict of interests.

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