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DIABETIC FOOT ULCERS AND RECENT TREATMENT BY NANOMATERIALS: A MINI REVIEW

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ABSTRACT

Diabetic foot ulcers (DFU) are one of the biggest obstacles to managing diabetes. DFUs are more difficult to treat, especially in patients with weakened immune systems. With the drugs on the market today, pathogenic bacteria and fungus might not be able to combat microbial infections at the wound site. In addition to discussing the medications, topical antibacterial treatments, dressings, and debridement techniques used for DFU, this page provides a comprehensive discussion of DFU and similar problems. The 16S ribosomal DNA sequence found in bacteria is one of the cutting-edge diagnostic methods that can help us understand the microbiota associated with DFU. By applying cutting-edge biological and molecular therapies that have been demonstrated to promote enhanced healing, decreased local inflammation, and infection prevention, this aim may be accomplished.

KEYWORDS: Foot Ulcer, Bacterial Infection, Nanotechnology.

INTRODUCTION

Diabetes is a chronic disease with symptoms influenced by blood sugar levels. Type 1 diabetes symptoms develop quickly and are more severe, including increased thirst, frequent urination, unintended weight loss, and ketones in urine [1]. The global diabetic population has increased fourfold since 1980 and is expected to continue rising [2].

For individuals with diabetes mellitus (DM), foot ulceration is a frequent consequence that can occur at any point in their lifetime—up to 25% of people will get foot ulcers. Compared to people without diabetes, diabetics have a 15–30 times higher risk of having an amputation [3]. Proteus mirabilis, Escherichia coli, and other gram-negative bacteria are among the many microorganisms that frequently cause diabetic foot ulcers (DFUs) [4]. Owing to its high pathogenicity and virulence characteristics including biofilm development, Pseudomonas aeruginosa is a major contributor to DFUs in populations with limited resources [5].

Nanotechnology offers promising antibacterial strategies through nanoparticles like silver, zinc oxide, and copper that demonstrate potent antimicrobial properties against various bacteria [6]. Silver nanoparticles could address persistent infections, limb amputations, and morbidity in DFU management due to the presence of MDR microorganisms [7].

This study aimed to isolation and identification of the most gram-positive and gram-negative bacterial species that cause DFUs and evaluate the activity of silver nanoparticle preparations on isolated multi-drug resistance pathogenic bacteria, and also determine some biomarkers associated with DFUs.

Diabetic Disease

Diabetes mellitus (DM), a prevalent endocrine disorder, is characterised by elevated blood glucose levels brought on by decreased insulin synthesis, activity, or both. The three primary types of diabetes mellitus (DM) are type 1 diabetes, type 2 diabetes, and gestational diabetes mellitus (GDM) [8]. Pancreatic β-cell loss results in the body's inability to make insulin, which causes type 1 diabetes, which is primarily inherited. Conversely, Type 2 diabetes, which accounts for 85% of cases, is mostly linked to multi-hormonal disorders and is caused by either insufficient or resistant insulin production [9, 10]. Future development of Type 2 diabetes is more common in women with a history of gestational diabetes mellitus (GDM). Insulin resistance and hyperglycemia are the results of hormones blocking the action of insulin during pregnancy in gestational diabetes mellitus (GDM) [11].

The global incidence of DM is rapidly increasing, with the World Health Organization [2], recognizing it as a worldwide epidemic. If current trends continue, the adult diabetic population will reach 700 million by 2045 - a 51% increase (IDF, 2019). Besides being a significant public health concern, diabetes also imposes considerable economic burden; annual global healthcare expenditure related to diabetes is projected to rise by 11%, from 760 billion USD in 2019 to 845 billion USD in 2045 [12].

A third of diabetic people are thought to have experienced diabetic foot ulcers (DFUs) at some point in their lives [1]. DFUs are a frequent consequence of DM. Pseudomonas aeruginosa, Streptococcus, Staphylococcus spp., Enterococcus spp., and other bacteria can cause infections in unmanaged DFUs, which can result in limb amputations and higher death rates [13-15]. Biofilm formation and virulence factors play critical roles in DFU pathophysiology, contributing to antibiotic resistance- a major public health challenge for diabetic foot infection (DFI) patients [16].

DM-related complications account for a significant portion of its direct costs, with over 50% attributed to neuropathy, nephropathy, retinopathy, foot ulcers, and atherosclerosis [17,18]. Foot ulcers are particularly prevalent among DM patients and are responsible for 20% of hospital admissions. If not properly managed, DFUs can lead to infection, gangrene, amputation, or even death [19]. The risk of amputation increases after a DFU occurs - approximately 50-70% of all lower limb amputations (LLAs) result from DFUs [18].

Diabetic symptoms

Symptoms of diabetes vary based on hyperglycemia severity, with type 1 diabetes presenting more severe symptoms than prediabetes or type 2 diabetes. Ketones in the urine, increased thirst, and unexplained weight loss are typical signs. Type 2 diabetes is more common and usually affects those over 40 years old, whereas type 1 diabetes usually starts during infancy or adolescence [19].

Diabetic Foot ulceration

Diabetic foot ulcers can result from injuries and lead to lower limb amputations. Physicians play an essential role in preventing and identifying diabetic foot complications by understanding primary risk factors for amputation, conducting regular evaluations, and providing preventive care [20]. Peripheral artery occlusive disease, dystrophic feet, and diabetic neuropathy are risk factors. Patients who meet

certain criteria can be identified by a physical examination, noninvasive testing for vascular insufficiency, and monofilament testing for neuropathy [12].

Venous ulcers are the most common leg ulcer type but lack a consistent definition [13]. They are characterized by chronic venous hypertension resulting from venous reflux or obstruction without primary arterial or systemic causes [14].

Pancreas

The pancreas is a heterocrine gland that carries out both exocrine and endocrine tasks. It secretes digestive enzymes into the duodenum and controls blood sugar levels by producing hormones like insulin [15]. In both forms of diabetes, the pancreatic beta cells are especially vulnerable to destruction.

The pancreas contains small clusters called islets of Langerhans composed of diverse endocrine cells such as beta cells producing insulin; alpha cells generating glucagon; delta cells secreting somatostatin; PP cells synthesizing polypeptide; and epsilon cells yielding ghrelin [16]. These islets are critical parts of the endocrine gland, and their distribution within the pancreas has functional consequences [17]. [18] found peri- and intra-islet inflammatory infiltrates in individuals with T1D, described as "insulitis," suggesting a potential immunological dysfunction related to diabetes' etiology.

Risk Factors predispose Diabetic

Diabetes type 2 is influenced by a wide range of risk factors, including age, race, ethnicity, and family history. While eating a healthy weight and exercising on a regular basis might help modify some of these risk factors, others cannot be modified [19]. The risk increases with age, gestational diabetes past history, and family history of diabetes [20]. Weight loss and increased exercise can prevent or delay the emergence of this significant risk factor. The body mass index (BMI) and waist circumference are used to assess body weight. A BMI of 25 or more is often associated with overweight status and an increased risk of type 2 diabetes [21].

Acute and Chronic Pancreatitis

Acute pancreatitis (AP) is a clinical condition caused by sudden injury to the pancreas resulting in inflammation that is typically self-limiting. However, up to 25% of patients can develop severe multi-system infections with a mortality rate of 30-50% [22]. Pancreatitis refers to disorders characterized by damage to the acinar cells and pancreatic inflammation [23].

Pancreas Histopathology

Acute pancreatitis is characterized by a necroinflammatory response in the pancreas due to injury of the acinar cells, with rare involvement of the duct cells. Noninfectious factors are the main causes, although infectious agents are implicated in some cases. Histologically, a scoring system has been developed to assess the severity of the lesions in both acute and chronic pancreatitis. Interstitial edema/necrosis of mesenteric fat and neutrophilic inflammation are the two lesions linked to acute pancreatitis, while lymphocytic inflammation, cystic acinar degeneration, and interstitial fibrosis are the three lesions that make up the system. In order to appropriately represent the severity of the lesions in both forms of pancreatitis, the grading system is based on a point system [24,25].

Duct Obstruction

The primary mechanism underlying pancreatitis pathogenesis is duct obstruction. This obstruction leads to the release of pancreatic enzymes into the interstitial tissue, where they can cause tissue damage and inflammation.

Obstruction of the pancreatic duct has various impacts on the pancreas. Firstly, it leads to an increase in autophagy rate in acinar cells, resulting in the extrusion of autophagic vacuoles and residual bodies into the interstitium. Secondly, it causes edema and inflammation. Finally, progressive atrophy of acini occurs after 3-4 days. Gallstones are a common cause of pancreatic duct obstruction, especially in two-thirds of the population in which Before entering the duodenum, the major pancreatic duct connects to the common bile duct [26].

Carcinoma of the Pancreas

Pancreatic cancer is the fourth most deadly kind of cancer in males, behind colorectal, lung, and prostate cancers, according to a 2014 study that analysed cancer epidemiology throughout Europe [27]. Acinar, islet, and duct cells are among the pancreatic cell types that can give birth to pancreatic cancer. Typically, the term carcinoma of the pancreas refers to neoplasms that originate in the exocrine pancreas, whereas neoplasms that originate in the endocrine pancreas are collectively referred to as islet cell tumors. The latter group is considered special due to the potential endocrine disturbances that may arise from hormone secretion by the tumors [28]. One of the risk factors for developing cancer is the consumption of red meat [29].

Cystic Fibrosis

Cystic fibrosis can have a detrimental impact on the pancreas, leading to acute pancreatitis, chronic pancreatitis, and pancreatic insufficiency, which can affect individuals of all ages with significant morbidity and mortality. In recent years, researchers have delved into identifying the cofactors that contribute to the pathophysiology of pancreatic-related disorders, which has provided valuable insights into early screening and counseling for individuals with cystic fibrosis. Despite this progress, the underlying abnormality causing pancreatic complications in cystic fibrosis remains undefined. The clinical manifestations of the disease can vary from patient to patient and may include pulmonary disease, pancreatic insufficiency leading to malnutrition, and impaired ion transport [30].

Pancreatic therapy

Prophylactic antibiotic usage during hospital admission for acute pancreatitis has not been shown to provide substantial advantages by randomised clinical studies [31]. In this context, recent studies conducted in 22 countries have revealed the widespread misuse of antibiotics. said that individuals with moderately severe or severe acute pancreatitis may benefit from antibiotic therapy since they are more likely to experience infective consequences, especially if the condition is linked to long-term organ failure or local problems. As previously discussed, [33], bacterial translocation across the injured gut and a defective gastrointestinal permeability barrier are consequences of the systemic inflammatory response, which may explain the effectiveness of antibiotic therapy in some cases of acute pancreatitis [34].

Prognosis

There are two main methods used to assess prognosis in cases of acute pancreatitis: the use of clinical scoring systems and specific laboratory tests. However, it is important to note that these markers are

not the same as measures of severity, which are used to classify the extent of the patient's illness. Measures of severity are defined in the Atlanta classification system and include local complications [35].

White blood cells and Diabetic disease

[36] examined the relationship between white blood cell (WBC) count and type 2 diabetes, finding a significantly higher average WBC count in diabetic patients compared to controls. The odds of diabetes based on WBC count were significant even after adjusting for confounding factors (odds ratio: 1.17, CI 95% 1.11-1.23). Despite numerous studies identifying a connection between WBC count and insulin resistance/type 2 diabetes, inconsistencies persist in the literature [37,38]. Infection markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) have also been linked to glucose dysregulation and diabetes [39]. [40] found WBCs as a separate risk factor for type 2 diabetes in Japan, while another study with a healthy Japanese population showed no correlation between WBC count and diabetes incidence [37].

Neutrophils, Eosin, basophil, monocyte, and lymphocyte

Asia is predicted to become the epicenter of diabetes mellitus (DM), particularly in developing nations [41,42]. With increasing DM prevalence, diabetic retinopathy (DR), a severe DM complication causing blindness among working-age populations, is also expected to rise [43]. Although DR's exact pathogenesis is unclear, inflammation is considered a critical contributing factor.

The ratios of neutrophils to lymphocytes (NLR), monocytes to lymphocytes (MLR), and platelets to lymphocytes (PLR) may be helpful indicators of inflammatory responses, according to current studies [44]. According to one study, patients with DR had considerably greater average PLR and NLR than non-DR patients. The mean MLR was higher in the non-proliferative diabetic retinopathy (NPDR) group compared to patients without DR, but no significant differences were observed among the three groups. PLR and NLR showed a significant increase in DR patients. After adjusting for confounding factors, MLR 18 was identified as a risk factor for DR, although its predictive ability was limited despite its possible pathophysiological and clinical significance in DR [44].

Red blood cells, Platelet, and its physiology

Hyperglycemia, the primary marker for diabetes mellitus (DM), causes structural and functional modifications in red blood cells (RBCs) or erythrocytes, which are the most abundant circulating cells and highly sensitive to plasma composition changes [45]. Investigating erythrocyte-related markers is essential in preventing, diagnosing, and treating DM and its complications.

Erythrocytes consume significant glucose amounts, with sustained hyperglycemia leading to changes in shape, metabolism, and function that can impact hemorheology and microcirculation [46]. Exploring these alterations in association with diabetes progression is critical for understanding their role in diagnosis, treatment, and prognosis [47].

As blood glucose levels increase, more glucose enters erythrocytes and activates metabolic pathways. Lacking mitochondria, glycolysis serves as erythrocytes' primary energy source [48]. Adenosine triphosphate (ATP), a glycolysis byproduct, is a vital energy molecule supporting regular functions like transmembrane ion/lipid exchange and erythrocyte deformability [49].

Bacterial pathogenicity and Toxins

Diabetic patients frequently experience soft tissue infections in the foot, interdigital spaces, and toenails, potentially resulting in severe complications such as sepsis, amputation, or death if left untreated. Staphylococcus aureus is the most commonly isolated pathogen causing these complications [50,51].

Diabetic foot infections (DFI) are a prevalent complication of diabetes with significant healthcare costs. They are often caused by polymicrobial agents, with S. aureus being the most common pathogen identified. Unique characteristics of DFI include fragile granulation tissue, necrosis, malodorous secretions, non-purulent exudates, and prolonged healing despite proper care [52,53].

S. aureus strains in DFI can be classified into toxinogenic and non-toxinogenic types [54]. Toxinogenic strains possess genes for toxins such as exfoliatin, EDIN, PVL, or TSST and are often linked to more severe infections. Non-toxinogenic strains mainly affect deep structures and bones associated with diabetic foot osteomyelitis [55].

The toxic shock syndrome toxin-1 (TSST-1) is the best-characterized S. aureus superantigen responsible for toxic shock syndrome. Additionally, SEl-X has been implicated in necrotizing pneumonia caused by the USA300 MRSA strain [56]. Around 88% of DFU isolates carry the SEl-X gene while a small percentage contain TSST-1 gene or both genes [57].

The main symptoms of skin in diabetic patients

Pigmented Purpuric Dermatoses

Pigmented purpuric dermatoses are a typical observation in elderly diabetes patients, and they frequently accompany with diabetic dermopathy. It is typified by non-blanching copper-colored patches that mostly affect the dorsum of the foot or the pretibial regions of the legs. Although these lesions usually don't hurt, they occasionally could [58].

This dermatosis is more commonly seen in advanced stages of diabetes in patients with nephropathy and retinopathy. The underlying mechanism is believed to be microangiopathic damage to capillaries, leading to the deposition of sequential erythrocytes [59].

Palmar Erythema

Palmar erythema is a harmless condition characterized by symmetrical redness and warmth in the palms, particularly in the hypothenar and thenar eminences. It is usually asymptomatic and considered to be associated with microvascular complications of diabetes, which contribute to its pathogenesis [60].

Periungual Telangiectasias

Periungual telangiectasias, identified by erythema and telangiectasias around the proximal nail folds, are frequently observed asymptomatic occurrences in nearly 50% of individuals with diabetes. These manifestations may coincide with irregular cuticles and sensitivity at the fingertips. The fundamental cause is believed to be venous capillary dilation resulting from diabetic microangiopathy, which can lead to capillary irregularities, such as venous capillary twisting. This represents an initial indication of microangiopathy related to diabetes [61,62].

Yellow Skin and Nails

Often, individuals with diabetes, especially older patients with type 2 diabetes, exhibit asymptomatic yellowing of the nails or skin. These benign alterations usually affect the cheeks, palms, soles, or the big toe's distal nail. The pathogenesis of these changes in complexion remains controversial, although the accumulation of various substances in patients with diabetes is thought to be responsible [63].

Onychocryptosis

Onychocryptosis, or ingrown toenails, is a condition that can afflict patients with type 2 diabetes. Most often impacted are the great toes. This condition is believed to be caused by several factors in diabetics, including as trauma, increased body mass index, impaired vascular supply, nail plate dysfunction, and subungual hyperkeratosis. These elements cause the nail to develop abnormally, which in turn causes the nail to pierce the skin around it. Diabetes-related onychocryptosis is typically excruciating and can result in cellulitis or an abscess. Thus, in order to prevent more difficulties, it is imperative that this ailment be diagnosed and treated as soon as possible [64].

Skin tissue structure and diabetic

Diabetes mellitus is a prevalent and incapacitating condition that impacts various organs, including the skin. Skin-related complications of diabetes mellitus can be found in 30-70% of patients with both type 1 and type 2 diabetes. The dermatological manifestations of diabetes differ in severity, ranging from benign to disfiguring and even potentially fatal [65].

Dermopathy, also referred to as pigmented pretibial patches or diabetic shin spots, is the most frequent dermatological manifestation of diabetes, appearing in up to 50% of patients [66]. Although its diagnostic significance is debated, dermopathy is often deemed pathognomonic for diabetes. It is more common in men and individuals over the age of 50 [67]. While it can occur before diabetes onset, dermopathy typically presents as a late complication and is frequently associated with microvascular complications like nephropathy, neuropathy, and retinopathy [68].

Xerosis, or abnormally dry skin, is among the most frequent skin manifestations in diabetic patients, affecting up to 40% of them [69]. The affected skin may display scaling, cracks, or a rough texture, with feet being the most affected area. In diabetic patients, xerosis often arises in conjunction with microvascular [70]. Emollients such as ammonium lactate can be employed to manage xerosis and prevent complications like fissures and secondary infections [71].

Chronic venous ulceration

Chronic Venous Ulceration Venous ulcers are full-thickness skin disorders associated with chronic venous disease that fail to heal spontaneously [72]. Affecting 1% of the population, these ulcers cause pain and impact patients' quality of life (Phillips et al., 2018). Advanced venous disease affects over 2.5 million US patients annually with symptoms like edema and leg ulceration [73]. The CEAP classification system ranks venous disease severity from telangiectasia/reticular veins (C1) to chronic venous ulceration (C6) through lipodermatosclerosis (C4) [74]. Venous ulcers take six to 365 days to heal but may recur in up to 70% cases within five years resulting in pain, disability, and significant workdays loss [75].

Diabetic foot bacterial infection

Diabetic foot ulcers (DFUs) are a common diabetes complication, affecting over one-third of individuals at some point in their lives. Among those with DFUs, 50% will experience diabetic foot infections (DFIs),

with 15% of patients requiring lower limb amputations to halt infection progression [76]. Addressing both intrinsic factors, such as enhanced glucose control, and extrinsic factors, primarily the eradication of bacterial infections, are essential in the treatment of DFUs/DFIs. However, the complex bacterial communities associated with DFUs/DFIs present challenges in selecting appropriate treatment approaches [77].

There are several laboratory methods with varying degrees of sensitivity and specificity for determining the bacterial makeup of DFUs and DFIs. One major obstacle still stands in the way of fully characterising the polymicrobial community across a range of severity levels [78]. The most common way for identifying bacteria is to use culture-based techniques, yet they might miss slow-growing, picky, anaerobic, and unknown pathogens and can result in false-negative findings in patients receiving antibiotic treatment. Furthermore time-consuming, these techniques make it more difficult to identify the bacterial community in DFUs and DFIs quickly and accurately. New developments in molecular technology have considerably impacted the discovery of previously unknown and uncultivable microorganisms by addressing some constraints and offering fresh perspectives on the bacterial diversity of DFUs/DFIs [79].

Diabetic foot ulcer-associated bacterial spectrum

Biofilms provide bacteria protection against external stressors, like immune responses and antimicrobial agents, and are linked to increased antibiotic resistance and recurrent infections in diabetic individuals [80]. Diabetes patients' ulcer development has also been linked to peripheral neuropathy. Both Gram-positive (such as Enterococcus and Staphylococcus aureus) and Gram-negative bacteria are frequently involved in the infections that cause these ulcers. (e.g., Pseudomonas aeruginosa, Escherichia coli, Proteus species, Klebsiella species), as well as anaerobic bacteria like Clostridium [81].

Biofilm formation is a crucial virulence factor that allows bacteria to persist in wounds and contributes to chronic infections in diabetic foot ulcers (DFUs) [82]. Identifying biofilm-producing isolates can enhance wound infection management in diabetic patients who do not respond to repeated antibiotic treatments [83].

Study by [82] found monomicrobial isolates, while other research reported the polymicrobial nature of DFUs [84]. Early antimicrobial therapy and wound care initiation could lead to a reduced incidence of polymicrobial infections; however, as the infection progresses, a polymicrobial state emerges [85].

Regarding bacterial isolates, [86] discovered that 75.6% were gram-negative and 24.4% were gram-positive. These results align with both [86] findings and those reporting the predominance of gram-negative organisms.

Bacterial biodiversity associated with DFU

Gram-positive bacteria such as Streptococcus spp., Enterococcus spp., and Staphylococcus spp. are commonly reported causative agents of diabetic foot infections (DFIs) [87-89]. Gram-negative bacteria, particularly those belonging to the Enterobacteriaceae family (e.g., Klebsiella pneumoniae, Escherichia coli, Proteus mirabilis, Morganella morganii), have been identified as predominant microorganisms associated with DFUs [90,91].

Metagenomic study has revealed the presence of less frequent bacterial species in DFUs, including Coagulase-negative Staphylococcus species and other unusual species. To determine the significance of these unusual species in the creation and longevity of DFIs, more research is needed [92,93].

Silver Nanoparticles and Diabetic treatment

Diabetic foot ulcer (DFU) patients often face multi-drug resistant (MDR) microorganisms, leading to prolonged wound healing, increased hospital stays, treatment expenses, and patient mortality [94]. Silver has been widely used as an antimicrobial agent to manage bacterial infections and prevent wound sepsis due to its strong antimicrobial properties [95]. Topical silver antimicrobials and dressings, however, have a number of drawbacks, including decreased release rates, inadequate tissue penetration, quicksilver ion depletion, and pro-inflammatory effects in cream-based formulations [96].

To address these issues, silver has been incorporated directly into dressings like Acticoat™ and Silverlon® for wound treatment. This approach minimizes the likelihood of nosocomial infections, healthcare costs, and patient suffering. Nevertheless, these dressings are typically applied before bacterial infection occurs, whereas in DFUs, wounds are already infected with various microorganisms including MDR strains. To eradicate microbial infections and encourage quick DFU healing without the negative effects of silver ions, efficient antibacterial therapies must be developed [97].

Through the creation of nanoparticles, nanotechnology opens up new possibilities in biology and biomedicine. Because of their nanoscale size, which ranges from 1 to 100 nm, nanomaterials have special physicochemical characteristics [98]. The remarkable microbicidal activity of silver nanoparticles (AgNPs) against wild-type and nosocomial strains of multidrug-resistant (MDR) bacteria in medical products like bandages, wound dressings, catheters, and textiles has drawn significant attention to them among antimicrobial nanomaterials capable of fighting infectious diseases [99].

In DFUs, polymicrobial infections are common and MDR bacteria increase the chances of persistent infection, morbidity, and limb amputation. Considering AgNPs' antimicrobial properties [100], this study aims to investigate their potential use in treating DFUs, as evidenced by photographs documenting wound healing progression during treatment, showing a visible reduction in DFU size without subsequent infections following AgNP treatment [101].

Estimation ulcer Recovery with nanoparticles

[102] examined the DFU wound healing process following AgNP treatment using photographs. The wound was cleansed, and necrotic tissue removed, leaving a 2 cm long and 1 cm deep open wound. Daily application of AgNPs (1.8 mg/ml) resulted in a decrease in the wound's diameter and depth after eight days, along with improved closure and reduced pain.

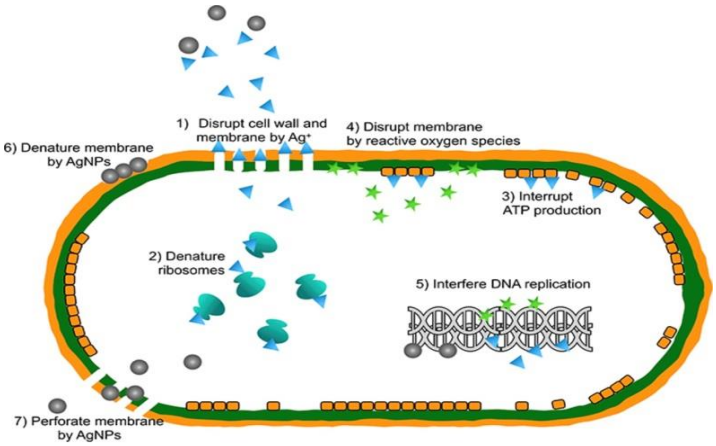
AgNPs were then administered twice weekly. A steady decrease in lesion volume was observed [103], with reduced diameter and closure without necrosis or infection. Tissue pigmentation indicated reepithelialization progress.

Nanotechnology has been explored for wound care material development, with nano-scaffolds and nanofibers promoting wound healing through various phases. Silver nanoparticles (AgNPs) have shown antibacterial and anti-inflammatory potential for diabetic wounds [104,105]. This review aims to highlight AgNPs' role in wound healing as an advanced dressing for diabetic patients' wounds and ulcers [106].

Uses silver as Nanoparticles

Metal nanoparticles such as copper (Cu), gold (Au), and silver (Ag) are increasingly used to combat infectious diseases by acting on microorganisms' protein synthesis, cell membranes, and nucleic acids [107,108]. AgNPs have medical applications but demonstrate limited antibacterial activity against specific bacteria when incorporated into polycaprolactone nanofibers, suggesting their use alongside other antibacterial agents [109,110].

Silver plays a critical role in wound healing by modulating cytokines and growth factors, while copper possesses strong biocidal properties and is essential for skin regeneration and angiogenesis [111,112]. Silver nanoparticles exhibit significant antibacterial activity through multiple mechanisms affecting bacterial cells [113,115]. [116] demonstrated silver sol's broader antimicrobial spectrum compared to antibiotics.



Schema showed Mechanism of Silver Nanoparticles Antibacterial Activity

Silver hydrogel containing Ag nanoparticles is used in dressings for various wounds, with in vitro studies showing rapid and potent antimicrobial activity against both Gram-positive and Gram-negative bacteria [117-119]. [120] found SilvrSTAT Gel beneficial for DFU healing but highlighted the need for further controlled studies. Identifying microorganisms associated with DFU is vital.

Innovative wound care approaches can speed up the healing process in place of traditional treatment methods. These include growth factor products, negative pressure therapy, maggot therapy, hyperbaric oxygen therapy, and bioengineered tissue or skin substitutes [121,122].

CONCLUSION

Diabetics put their lives and health at risk when they have infections and ulcers on their feet. The advancement of diabetic foot disease is impacting diabetes neuropathy, vasculopathy, immunopathy, and insufficient glucose regulation. Accurately diagnosing diabetic foot disease begins with a comprehensive clinical examination of the patient. This is followed by early intervention that focuses on prevention. Important preventive strategies include education, regular follow-ups, and effective coordination among a multidisciplinary team of physicians, hospitalists, endocrinologists, infectious disease specialists, and wound care experts. Suggestions for interventions and treatment choices need to come from more multicenter randomised controlled studies. Diabetes-related chronic wounds are a public health concern that significantly affects a patient's quality of life. The condition is managed using a range of effective therapies, including medicines, technological advancements, and biological approaches. Since the FDA does not approve of any of these therapies, further controlled studies are

necessary to assess their efficacy because none of them achieves the primary goal of full wound healing. For the various stages of DFUs to benefit from a mix of gene- and cell-based treatment, more research is required. Due to the several unique pathogenic mechanisms causing DFUs, a monotherapy strategy would yield a very poor percentage of recovery. As a result, a multimodal and interdisciplinary strategy is needed to treat DFU.

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