Review Article

DIABETIC WOUND MECHANISMS: PATHOGENESIS, MOLECULAR TARGETS

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ABSTRACT

Background: Healing wounds is a multifaceted process that progresses through the stages of inflammation, proliferation, and remodeling. Diabetes induces various diseases that hinder nearly all of these healing mechanisms.

Methodology: A literature search was conducted on the databases namely Science direct and PubMed with the help of different keywords such as " Diabetes Wound healing ", The search was customized by applying the appropriate filters so as to get the most relevant articles to meet the objective of this review article.

Results: Patients with diabetes may sustain wounds during or after medical treatments. The process of healing a wound comprises many phases, including remodeling, proliferation, and inflammation. Diabetes obstructs almost all of these healing mechanisms via a variety of pathological alterations.

Discussion: This study primarily focusses on the molecular pathways of inflammatory compounds, including growth stimulants and other agents that impede wound healing. It also investigates molecular targets and current progress in wound therapy and complete healing.

Conclusion: On the basis of our study, we found some useful approaches for the wound inflammation treatments and suggested that, if we use these methods together, then we may obtain the most relevant result in our research area.

Keywords- Wound healing, Diabetes, Pathological changes, Molecular targets, Inflammation.

INTRODUCTION

According to current studies on the effects and frequency of diabetes, it is still a big problem. An extra 88 million Americans had prediabetes in 2018, while 34.2 million were diagnosed with diabetes. The resultant medical costs were a staggering $237 billion, according to the CDC [1]. Ulcers of the foot and other diabetic lesions affect as many as 25% of diabetics [2]. Treatment costs for diabetes and its complications account for at least one-third of the total goes towards healing these wounds, which may be very costly [3]. A number of pathological alterations common to diabetes make wound healing less effective. Chronic hyperglycemia causes vasculature damage and impaired blood circulation. Because identification might be challenging for diabetic people due to peripheral vascular dysfunction and neuropathy. Diabetic wounds are marked by swelling, fewer new blood vessels, problems with keratinocyte migration, and fewer fibroblasts proliferating [4]. Combined, these alterations raise the risk of wound problems in diabetes patients, such as infection, wound dehiscence, and chronic, nonhealing wounds.

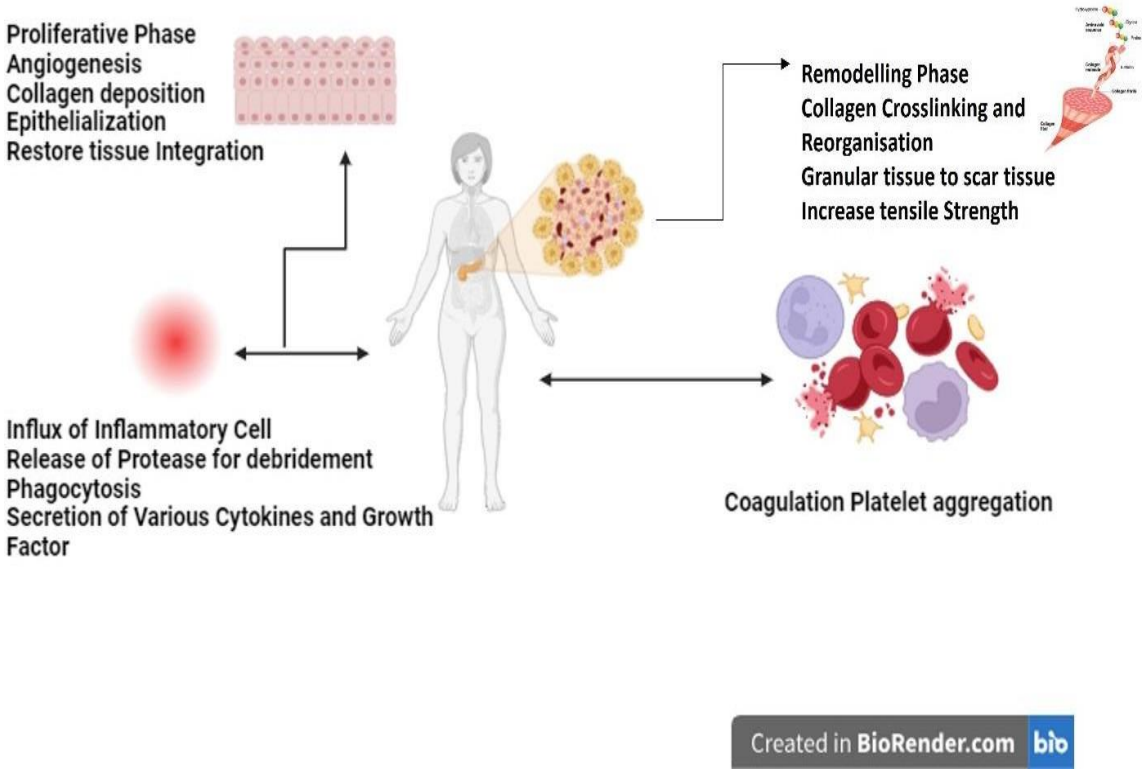

Fig.1. Normal wound healing is disturbed

Diabetic Effects on The Process of Healing

Three steps make up the complex wound's healing process**.** Inflammation, proliferation, and contraction. That often occur together, and remodeling. Blood clots and immune cell infiltration are hallmarks of the inflammatory phase. Strong angiogenesis and epithelialization are hallmarks of the proliferative phase [5]. Scarring, wound maturation, and remodeling occur towards the conclusion of the proliferation phase [6]. Diabetes obstructs almost all of these recovery mechanisms.

Diabetic wound inflammation

Diabetes wounds exhibit a longer inflammatory stage of wound healing in diabetes wounds as opposed to nondiabetic wounds. This proinflammatory condition might hinder the healing process

and perhaps lead to the development of chronic wounds [7]. The first group of macrophages (M1) during the wound healing process is normally phagocytic and proinflammatory. In diabetic wounds, macrophages release too many cytokines that cause inflammation [9]. However, M2 macrophages, which are anti-inflammatory, promote angiogenesis, and make extracellular matrix (ECM), eventually replace them. Also, diabetic wounds are more likely to have inflammatory macrophages than anti-inflammatory ones [8]. To add insult to injury, neutrophils release inflammatory mediators, free radicals that amplify oxidative stress, and cytotoxic enzymes. In diabetic wounds, oxidative stress causes pathological repair to take longer and causes more tissue damage to occur [10]. Overproduction of neutrophil extracellular traps (NETs) occurs when neutrophils seek out and ensnare microbes. Diabetic wounds perpetuate an inflammatory state that impedes wound healing by upregulating NET production. Microribonucleic acid (miRNA) is another molecular alteration that leads to increased inflammation in wounds caused by diabetes. In skin that hadn't been hurt, levels of miRNA that helps with healing were similar in people with and without diabetes. However, expression of this miRNA changed after the wound, suggesting that miRNA may play a part in inflammation that isn't working properly. Epigenetics and transcription factor Diabetes wounds are characterised by pathogenic inflammation, which is made worse by dysregulation. Chronic inflammation is a major factor in the poor healing of diabetic wounds, according to a large body of research on both human and animal models. Long-term inflammation slows down the healing process, increasing the risk of chronic wounds. In models of diabetic mice, it promoted wound healing by decreasing inflammation and increasing levels of several healing-promoting growth factors. [14]. Additionally, hypertrophic and keloid scars, which are considered pathological scars, are associated with it [11–13]. It is crucial to decrease inflammation throughout the healing process in those with diabetes to lessen the chance of scarring. Proper wound healing requires the restoration of blood flow, which mostly occurs during the proliferation phase [15]. Base levels of angiogenic factors including vascular endothelial growth factor (VEGF) and antiangiogenic factors such pigment epithelium-derived factor and angiogenesis-1, maintain the quiescent vasculature in healthy skin. When blood oxygen After an injury, the body reacts by producing more angiogenic factors and less antiangiogenic ones when levels fall too low. One of the primary causes of wounds not healing as effectively as they could is inadequate angiogenesis, which can take many different forms. Later in the remodelling stage of wound healing, vascular maturation and pruning in diabetic wounds require vascular maturation factors such as platelet-derived growth factor (PDGF). Initially, diabetic wounds may lack sufficient proangiogenic factors due to the reduced ability of macrophages to produce them. Moreover, the downregulation of factors involved in capillary maturation coincides with an increase in factors involved in antiangiogenic processes. Matrix metalloproteinases and microRNAs (miRNAs), which are known to inhibit angiogenesis, are additional factors [16]. Damage to vascular maturation factors hinders the progression of wound healing, this causes it to slow down. The purpose of this is to stabilize the just formed capillary bed. Due to a lack of maturation factors, wounds take longer to heal and are more likely to become chronic or reoccur [5]. The risk of infections increases due to impaired leukocyte migration into the wound caused by changes in diabetes vasculature and insufficient oxygen delivery [17].

Diabetic Wound Scarring

Maturation, remodeling, and scar formation are normal aspects of the healing process of wounds. At this stage, wound contracture and the disintegration of extra collagen result in scarring. Collagen and extracellular matrix (ECM), the components of scars, are secreted by fibroblasts. A number of characteristics distinguish newly formed cutaneous scars from the original tissue, such as the density of collagen fibers and the absence of hair follicles or sebaceous glands [18].

Research has shown that diabetic wounds mend with scars that differ structurally and have reduced collagen production compared to healthy wounds. These alterations result in a scar has less contractile strength and more collagen, resulting in a scar that can't heal properly because of its lower tensile strength [19]. A plausible Fibroblasts are senescent cells that are unable to divide, which may be the cause of diabetic wounds not healing enough. In cases when diabetic wound contraction is insufficient, granulation and reepithelialization accelerate the healing process. The scar matrix from diabetes cannot endure forces that are both shear and tensile [20].

Diabetes and Wound Healing After Surgery Healing Complications

A number of wound problems, such as infections, dehiscence, and scarring, are more common in individualswith diabetes, as mentioned before. Diabetes patients experience Across most surgical subspecialties, there is a higher incidence of infection at the surgical site, even when compared directly to postoperative glucose elevation. It appears that diabetes increases the risk of infection via more pathways than hyperglycemia [21]. In addition, obesity and other prevalent comorbidities greatly raise the risk of infections at both the superficial and deep incisional surgery sites [22]. Diabetes patients undergoing abdominal panniculectomies are at greater risk for complications such as wound dehiscence, infections, readmission, sepsis, and lengthier hospital stays after the procedure. Diabetics are at a higher risk of infection after abdominal wall repairs when using the traditional mesh reinforcing approach [23]. Ischemia, dehiscence, nipple-areolar complex cesses, and accelerated flap necrosis are complications of diabetes that prolong the healing process after breast reconstruction [24]. Diabetes has been linked to several issues, including surgery site infections in cosmetic breast surgery [25]. Patients with diabetes are undergoing implant placement procedures.The incidence of complications with mastopexy is greater [26]. In a different study that looked at breast, body, and face cosmetic treatments, diabetes was linked to a higher chance of illness. From the same study, it was found that wound problems happened more often with body procedures than with face or breast operations. But it's still not clear why diabetic wounds look different in different places [27]. People with diabetes who have hand surgery are more likely to have problems with their wounds healing, such as infections, stiffness after surgery, and wounds that heal slowly [28]. This has been shown by both the carpal tunnel openings and the trigger finger, however the latter is less obvious [29–31]. Infections and hospital stays were more common among those with diabetes longer after having a face fracture fixed [32].

Health and diabetes-related injuries

A person's nutritional state greatly influences how well their injuries go away [33In type 2 diabetics, a patient's nutritional state is a powerful independent predictor of surgical wound healing and infection risk. Poorly treated wounds are more likely to be severe according to the subjective global evaluation of nutritional status. One common technique for determining the severity of diabetic ulcers is Wagner grading. [34]. During the anabolic stage of wound healing, we must enhance our diet. Anabolic hormones speed up wound healing to a catabolic state by raising insulin resistance and lowering diabetes levels [35]. Protein loss, hyperglycaemia, a negative nitrogen balance, increased energy consumption during rest, and a higher risk of malnutrition are metabolic abnormalities in diabetes. Less lean body mass is seen in diabetic individuals with wounds, fatter breakdown, and ongoing protein loss due to microalbuminuria than diabetic patients who have no wounds. These procedures make it clear that, in comparison to normal wound healing, nutrition is

considerably more important for diabetic wound repair. In order to enhance the nutritional condition of diabetes patients, it is necessary to assess the extent of decrease of lean body mass, identify any macro- and micronutrient deficiencies, and then implement a diet that addresses these requirements. Whey protein supplementation aids cutaneous wound healing by bringing cytokine levels back to normal, as shown in wounds that are not caused by diabetes [36]. Diabetes patients have poor wound healing because their skin is compromised from the beginning. decreased thickness of the dermis layer and disarray Collagen is one of two traits of diabetic skin that is unharmed. The harmful chemicals known as advanced glycation end products (AGEs) induce oxidative stress, age, and skin stiffness, and they build up considerably more quickly in diabetic skin [37]. Considering all these changes to the skin, patients with diabetes face a reduced likelihood of fully recovering from wounds. In diabetic mouse models, wounds exacerbated the deleterious effects of dietary AGEs, leading to chronic inflammation and a postponed recovery [38]. Patients with diabetes must limit their food intake of extra AGEs while their wounds are healing, as they naturally produce more AGEs. Individuals with diabetes who have injuries have to cut less on meat and fatty foods and change their cooking methods to avoid frying, grilling, and roasting in order to lower their AGE intake [39].

Mechanical understanding

In addition to the many consequences, such as psychological mental anguish and despair, a wound that refuses to heal might be due to the sluggish healing process associated with diabetes. Consequences include infections including septicemia, gangrene, osteomyelitis, cellulitis, and functional impairments such trouble walking. It is well-known that diabetics have impaired wound healing, but the specific etiology and the illness's pathogenesis is uncertain. Recovery can only occur through the coordinated activity of biochemical mediators that are activated by inflammatory cells and different pathways. Studies have linked the failure of diabetic wound healing to changes in cellular and metabolic components and activity. Numerous cell types are involved in wound healing. These comprise endothelium cells, B cells, T cells, fibroblasts, monocytes, macrophages, keratinocytes, and more. These cells create and control a variety of growth factors and cytokines. Monocytes, which subsequently mature into macrophages, release pro-inflammatory cytokines such as IL-1β2, TNF-α3, IL-64, IGF-16, and TGF-β7. Both those with diabetes and those without it may relate to this. This critical stage involves the production of neutrophils, T cells, B cells, keratinocytes, fibroblasts, IL-10, mast cells, and endothelial cells. These cells also aid in the production of TGF-β, IGF-1, and VEFG [40]. Macrophages aid in the process of healing. Macrophage polarization and regulation are impacted by epigenetic modifications resulting from oxidative stress and hyperglycemia. Delays in wound healing may be caused by dysregulated macrophage polarization [41-42]. Research has shown that a complicated chemical process slows down wound healing in people with diabetes. Studies reveal that diabetes in animal models inhibits the synthesis of growth factors, keratinocyte and fibroblast migration and proliferation, neutrophil and macrophage activity, and other wound healing processes and other healing-associated factors.

Other things that make it harder for diabetics to heal are narrow blood vessels, metabolic problems, low oxygen levels brought about by alterations in the red blood cell membrane, hemoglobin glycation, and malfunctioning bodily systems [45]. Hypoxia occurs when blood vessel constriction reduces the amount of oxygen that can reach wounds. Nutritional and oxygen deficiencies brought on by glycation of hemoglobin provide a second obstacle to repair. As a stress reaction to cellular hypoxia or glucose scarcity, UPR8 causes unfolded proteins to accumulate within the endoplasmic reticulum. This UPR, linked to the production of inflammatory mediators, is activated in the moments after skin or tissue injury. DWs had a longer duration of UPR activation and produced more pro-inflammatory chemokines than normal wounds [46].

Local ischemia, caused by diabetic microvascular complications, considerably inhibits wound healing. Among these issues and engaged in several physiological functions are miRNAs9, a family of noncoding RNAs with a length ranging from nineteen to twenty-four nucleotides. Scientists have connected changes in miRNA levels to a variety of diseases and impaired wound healing [47]. While wounds are healing, one microRNA called MiR-210 stops the proliferation of keratinocytes by targeting E2f3 when oxygen levels are low [48]. By focusing on globin transcription factor 2 and VEGFR210, MiR-200b decreases angiogenesis [49]. Angiogenesis, re-epithelialization, fibroblast migration, keratinocyte migration, inflammation, and epithelization are all influenced by various microRNAs (miRNAs) in diabetic wounds [50-51]. Additionally, there are physiological factors to consider, such as elevated serum matrix metalloproteinase-9 levels [52], issues with Some of the factors that have been linked to these changes include reduced epidermal nerves inadequate barrier function, AGE11-mediated PDGF modification, alterations in skin neuropeptide expression, decreased inflammatory response, collagen accumulation, and variations in the ratio of various types of collagen [53], and an imbalance between the buildup and re-modelling of ECM components by matrix metalloproteinase [54-55].

Chemical signaling, oxidative stress, and free radicals are all involved

The figure illustrates the significant evidence that has emerged over the past few decades, assisting with a range of procedures. By means of the Maillard reaction and three routes—the polyol, hexosamine, and diacylglycerol pathways—in addition to the nitric oxide Glomerular Advanced Glycation End Products (AGEs) are created when PKC pathways are inhibited and hyperfiltration occurs, which results in neuropathy. Oxidative stress as well as mitochondria's excess synthesis of reactive oxygen species speed up these processes [56]. Diabetes complications and impaired wound healing are both exacerbated by increased oxidative stress. The transcription factor NRF212 regulates cell motility, apoptosis, proliferation, differentiation, and adaptive response to oxidative stress [57]. NRF2 activity in response to high hyperglycaemia and oxidative stress facilitates damage control and repair. Long et al. used both indirect and direct methods to show that turning on NRF2 reduced the amount of oxidative stress caused by diabetes and controlled the expression of genes related to cell migration, proliferation, and TGF-β [58]. Metabolic issues and B-cell dysregulation are linked to the expression of the stress-inducible gene ATF-313 in diabetes [59]. Healing may take longer than expected because of the erratic pro-inflammatory response, which causes oxidative stress by activating ATF-3 and iNOS. The healing process is hindered due to defective cellular differentiation and remodelling, as shown by Badr et al. who found that Increases in caspase-3, -8, and -9 activity and free radical levels and ATF-3 and iNOS expression is abnormally up-regulated [60].The body heals with the aid of HβD 1, 2, 3, and several proinflammatory cytokines, such as MIP1α14, MIP-215, and KC16, which destroy germs and cause an accumulation of leukocytokines. Metamorphosed Neutrophils, monocytes, macrophages, and dendritic cells comprise leukocytes. Research has demonstrated that both its soluble and membrane-bound forms of CX3CL117 promote the recruitment of fibroblasts and macrophages [34–36]. Unfortunately, according to Badr et al, when MIP1, MIP-2, and CX3CL1 levels are off, STAT318 levels are off too, and AKT/PKB and NF-B levels go down activation. The levels of HβD 1, 2, and 3 were also reduced. When combined, these variables make diabetic wound healing more difficult [61]. Diabetic peripheral neuropathy slows healing of wounds This is accomplished by blocking the autonomic nervous system's ability to function. sensory, and motor nerve systems. Unfortunately, nerve dysfunction and ischaemia are caused by protein kinase being activated too much and abnormal glycation of proteins in nerve cells. This happens because of high blood sugar and oxidative stress [62]. The development of diabetic wounds is greatly accelerated in patients with

sensory neuropathy, which is defined by a diminished or absent awareness of pain. Diabetics' wounds bleed more readily because they are painless. In diabetics, altering the Akt/mTOR pathway impairs wound healing. Diabetes-induced rat model, according to new research by Huang et al [63]. AKT and IR/IRS/PI3K and IR/SHC/ERK are two instances of insulin signalling pathways that facilitate wound healing, according to Lima et al. It improves diabetic wound healing, promotes angiogenesis, increases tissue synthesis of VEFG and SDF1a, and phosphorylates Enos by activating these pathways [64]. Research has shown that matricellular proteins are crucial in wound healing because they link ECM proteins to receptors on cell surfaces and interact with these proteins. Contributing to the matricellular protein Al-420 is involved in processes such as migration of keratinocytes, angiogenesis, and reepithelialization. AL-4 may activate the SRC, ERK, and AKT when it attaches to integrin β1 signalling cascades as well as begin activating JAK1/STAT3. By turning on STAT3, damaged tissue may experience angiogenesis, an increase in NO production from keratinocytes, and an upregulation of iNOS21 expression. While AL-4 expression is normally modest in healthy skin, it becomes dramatically elevated in injured skin. However, reduced AL-4 expression in diabetes patients also affects angiogenesis and re-epithelialization, slowing down the healing process [65].

How the Immune System Works

An important part of the healing process is the appropriate regulation of the innate immune system. TLRs22 After activation is complete, only innate immune responses and inflammation may begin. The downregulation of TLRs-2 in wounded tissue compromises the immune system and inflammatory response in diabetics. The recruitment of many inflammatory cells is delayed by the reduced chemotactic effect [66–69]. Diabetes makes a person more vulnerable to infections by impairing the immune system and delaying the healing of wounds. The development of biofilms by bacteria that come into touch with the wound site is one factor contributing to diabetic wounds. The microbes in these biofilms slow down the healing process to defend themselves against the immune system and antibiotic therapies. It is the leading cause of diabetic lesions that result in lower limb amputations [70]. Inflammation is one of the many functions of immune system cells. Monocytes, T lymphocytes, B lymphocytes, and mast cells are some of these cells. Dysregulation of these cells may result in impaired host immunity in diabetics. Because diabetes raises levels of pro-inflammatory cytokines including TNF-α and IL-6, it also promotes insulin resistance, hyperinflammation, and an interruption of the inflammatory cascade. An increase in effector T cells may be the reason of the elevated TNF-α level. In patients with diabetic wounds, the range of TCR-V2 increased and the frequency of naïve T-cells decreased (Maura et al.). Ultimately, we have an excess of effector T cells [71]. Increased AGE levels can affect immunity by triggering the production of many cytokines, including TNF-α and IL-6. Slower healing, hyperactive immunological responses, and death may result from AGEs interfering with cell function. In the end, this may prevent the production of collagen [72]. Mast cells release the angiogenic factors VEFG, TGF-1, and FGF [48]. Numerous studies have shown the involvement of mast cells, macrophages, endothelial cells, and fibroblasts during the healing process of wounds. It encourages matrix remodelling, upsetting the delicate balance of pro- and anti-angiogenic elements in the wound [73-81].

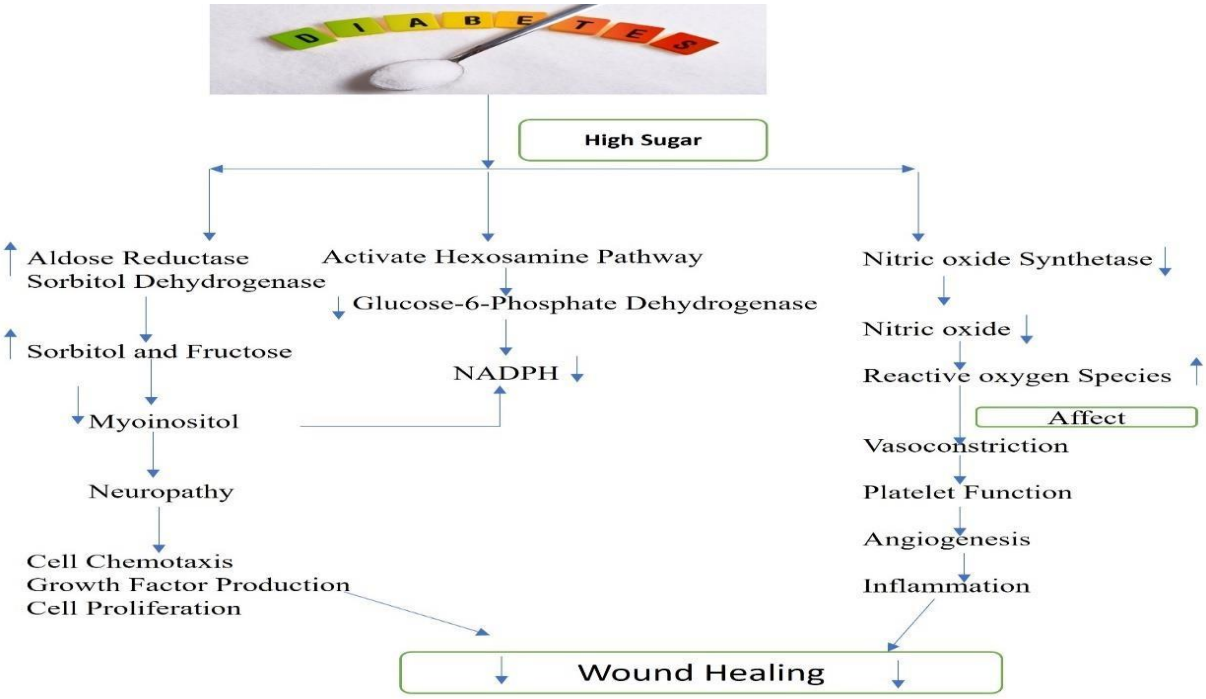

Fig. 2. The main mechanisms that cause diabetic wounds to heal more slowly [134]

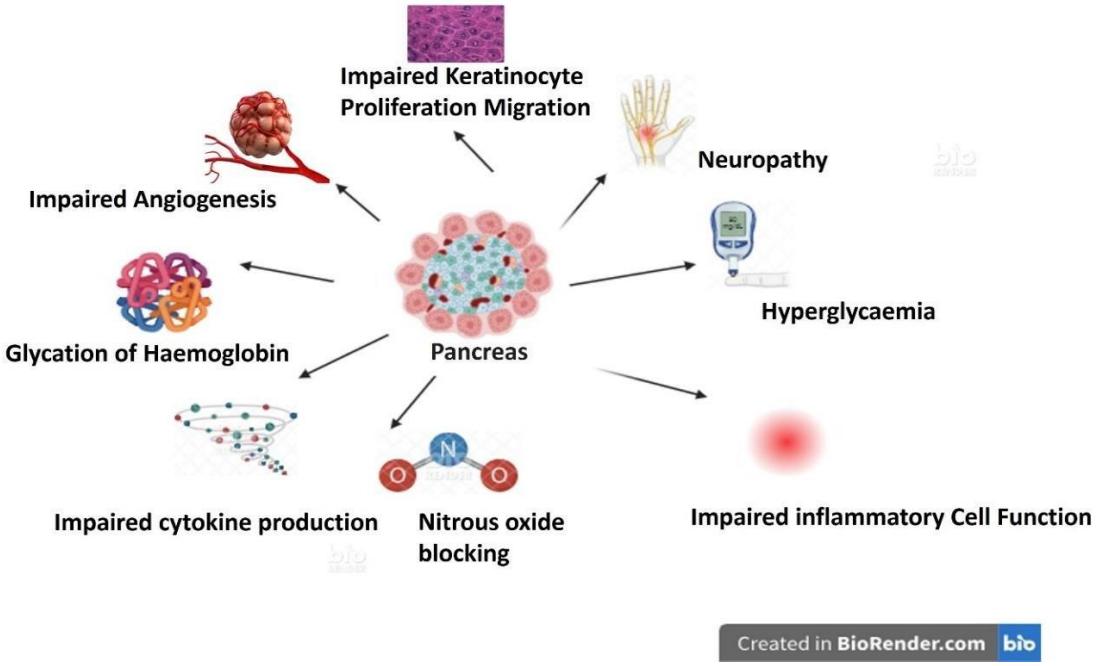

Fig. 3. Causes of Diabetic Wounds

Table 1 Diabetic wound care was the focus of therapeutic effort

Element components that promote growth	Delivery Method and Path	Molecular Destination	Final Product and Process	Target tissue and animal Model	References
PDGF/TGF-α	Gel	PDGF and TGF-α	Improving fibroblast and keratinocyte activity to aid in healing	A genetically altered mouse with diabetes	[82]
Essential fibroblast growth factor	Nanofibers/ Particularly	Fibroblast	Improvements in migration, ECM repair and remodeling, fibroblasts attachment, blood vessel development, and proliferation	Diabetic rats	[83]
Factor that develops on human skin	Cream	EGF	Speeds up the recovery process	Diabetic foot ulcers	[84]
Formulated from a recombinant EGF	Microspheres	EGF	Enhanced Increasing proliferating cell nuclear antigen promotes skin healing and fibroblast proliferation	sores caused by diabetes	[85]
PDGF	Gel	PDGF	Enhanced reendothelialization on, cell proliferation, and angiogenesis	Rats with diabetes	[86]
Fundamental Fibroblast Progression Factor	Sponge gelatine	———	Facilitate recovery	ulcers on the skin	[87]
Platelets	Gel	PGDF, TGF-α, VEGF	Reduce pain, improve re-epithelialization, and granulation tissue development	Wounds that persist on the skin	[88]
Recombinant PDGF	Gel	PDGF	Improves ERK phosphorylation and c-fos protein expression are elevated during healing; thus, capillary density, granulation tissue thickness, epithelialisation, and	Diabetic rats	[89]

Fusion protein	Collagen	VEGF	Boosts blood vessel development and keeps VEFG activity high	Diabetic rat model	[90]
Acidic fibroblasts generated from human cells	The collagen sponge made of chitosan	FGF	Improves the skin's blood vessel formation, collagen production, and cell turnover	Diabetic rats	[91]
Formulated from a recombinant EGF	Nanofibers made of poly-ethylene glycol and poly-epsilon-caprolactone	EGF	Enhances keratinocyte expression and proliferation	Diabetic ulcers	[92]
The relationship between arginine and EGF	Hyaluronic acid sponge	EGF	Reducing wound size with enhanced epithelization		[93,94]
A growth factor for keratinocytes	Nanoparticles	KGF	Better re-epithelialization and granulation tissue production leads to faster healing.	Chronic wounds	[95]
Plasmid bFGF	Electrospun fibres made of poly (ethylene imide).	FGF	Better maturation, reepithelialization, and collagen production leads to faster recovery.	diabetic skin injury	[96]
EGF	Conjugated Dextrin Topically	———	Quicker healing of wounds, the development of new skin, more both angiogenesis and granulation tissue	Diabetic (Db/db) Mouse	[97]
Two-fold growth factor	Nanoparticles	PDGF-BB and VEGF	Enhanced granulation tissue development, re-epithelialization, and angiogenesis, all of which accelerated the healing process.	———	[98]
In PDGF	Hydrogel	———	Reduced reactive oxygen species and increased collagen biosynthesis	wound healing	[99]
PDGF-BB	Hydrogel	———	Greater granulation tissue development and angiogenesis accelerate healing.	Geneticall y diabetic mice	[100]

FGF	Chitosan movie/specifically	In FGF	Increased ECM production shortened healing time and decreased area of wound.	Genetically diabetic mice	[101]
Human epidermal growth factor recombinant	Foam	———	Enhanced healing by re-epithelialization, collagen deposition, and increased contraction rate	Diabetic wounds	[102]
VEGF	Nanoparticle	VEGF Receptor -2	Improvements in keratinocyte migration and proliferation as well as an increase in VEGFR2 mRNA levels	Wounds in people with and without diabetes	[103,104]
			Synthetic drugs		
Azelnidipine	Resolution	eNOS	Enhanced histologic processes and accelerated healing with stimulation of NO production	Stroke rat models Diabetes and Skin Wounds in Rats	[105]
AL–CS–PGA hydrogel	Hydrogel	Collagen	Promotes faster recovery via increased epithelialization and collagen regeneration	Rats with diabetes	[106]
Atorvastatin gel	Hydrogel is a	———	Speedier recovery with epithelization and closure within a week	Diabetic rats	[107]
Erythropoietin	Cream	VEGF	Shorter duration to wound closure, higher levels of hydroxyproline and VEGF, and denser microvascular tissue	Rats with diabetes	[108]
Pentoxifylline	Cream	MMPs and TIMP-1	Increases healing by increasing and decreasing MMP expression	Rats with diabetes	[109]
			TIMP-1 expression		

GW501516	Polymer Microparticle/	Peroxisome proliferator-activated receptor	Accelerated wound healing by decreasing the oxidative wound micro-environment	Diabetic wound	[118]
Deferoxamine	Intra-peritoneally	HIF-1α, SDF-1α, VEGF	By up-regulating HIF-1α, endothelial tube formation and cell proliferation are increased, which promotes neovascularisatio n and repair.	Rats with diabetes	[110]
	Topically	———	Neovascularizatio n and healing increased when TNF-α, MMP-9, and IL-1β protein levels and mRNA expression were decreased.	Rats with diabetes	[111]
Substance P	I.V.	Endothelial cell adhesion molecules or IL-8	Maximizes the number of macrophages and early white blood cells that encourage skin wound healing and restoration.	Diabetic murine wounds	[112]
Propranolol	Oral Solution	IL-8, MMP-9, VEGF, and TGF-β	Enhances increasing blood vessel density, collagen deposition, cell proliferation, mast cell count, and nitric oxide level while lowering MMP-9 and inflammatory cell levels	Diabetic rats	[113-115]
Metformin (Glucophage)	PLGA/nanofibril lar collagen membrane	MMP-9	Improved wound healing via reduced MMP-9 expression and enhanced re-epithelialization and collagen I production	Diabetic wound	[116]
New kind of nano-insulin	Silver nanoparticles	TNF-α, IL-10, and IL-	Promoting quicker wound	Diabetic rats	[117]

MK0626	Dipeptidyl peptidase-4 inhibitor/ Oral	HIF-1α / SDF-1	Endogenous progenitor cell recruitment, healing, and angiogenesis were all markedly enhanced.	Diabetic mice	[119]
Phosphosphingosine	Conducive Poly (caprolactone) /gelatin	Epithelial-to-mesenchymal transition and endothelial mesenchymal	Release fibrous structure to improve wound healing in diabetics	Diabetic mice	[120]
Adenosine	ointment	PPARδ, or AMP-activated protein kinase	Diminish the AGE receptors and PPARά reduce the number of AGE receptors and PPARά.	Diabetic mice	[121]
Venom from bees	injections subcutaneously	Ang-1, Tie-2, and Nrf2 signalling	Ang-1, Nrf2, and Tie-2 downstream signaling levels are restored, and wound healing is improved by increasing BD-2 and collagen expression.	Mice with diabetes	[122]
Curcumin in	Composite graft linked to porous PLGA microparticles and a Cryptomodule	——	enhanced and quicker healing of wounds due to the skin's capacity to renew with higher tensile strength Other approaches	Diabetic rats	[123]

Growth factors are participating in delayed healing of wounds

For the many stages of wound healing to begin and continue, growth factors are essential. (Fig. 4). Numerous abnormalities, such as diminished growth factor receptor expression or accelerated growth factor degradation, exacerbate wound healing in diabetics. Platelets release PDGF, a crucial serum mitogen. It promotes cell proliferation, matrix production, and the development of connective tissue. During the late inflammatory phase, macrophages, a crucial cell type in the wound region, persistently produce PDGF. The specific properties of PDGF draw in macrophages and inflammatory cells. Collagen, proteoglycans, and glycosaminoglycans are all partially synthesised with its help.

It promotes fibroblast migration and proliferation, angiogenesis, and the development of a temporary extracellular matrix, and protein synthesis in tissue granulation during the course of wound healing. Diabetes-related wounds have reduced production of PDGF and its receptors, which implies that PDGF contributes to the healing process. Many PDGF clinical investigations have shown faster recoveries. BFGF28 affects a wide range of biological functions. These include mesodermal cell proliferation, endothelial cell proliferation, cell migration, fibroblast growth and multiplication, and extracellular matrix metabolism. Granulation tissue grows more rapidly and intensely, which aids in the healing process. One of the skin's most powerful angiogenic cytokines, VEFG, may have a significant effect on the

two rate-limiting phases of wound healing, angiogenesis and vasculogenesis. The primary elements of this process are capillary endothelial cells migrating and proliferating and proteases breaking down the extracellular matrix. of capillaries that already existed. When VEFG is applied to diabetic wounds, capillary density rises, improving metabolism and circulation. When blood flow is restored to wounded tissues, wound healing is expedited. This paves the way for the transport of oxygen and nutrients, which the reparative cells need to grow and operate. It is a critical regulator of wound revascularisation and permeability and an essential component of granulation tissue formation. Inflammation is the outcome of VEFG receptor-1 activation, while VEFG receptor-2 activation, Angiogenesis is induced by the two receptors that control the actions of VEFG. Low levels of VEFG in local wounds are associated with diabetes, which slows the healing process. The primary reason wounds do not heal, according to researchers, is because of abnormal VEFG receptor patterns, which include lower VEFG mRNA levels, greater VEGFR-1 levels, and lower VEGFR- 2 levels. Cell migration, motility, angiogenesis, proliferation, and mesenchymal regeneration are all boosted by EGF, which is produced when platelets bind to EGF receptors. The two peptides that make up IGF are IGF-1 and IGF-2. IGF-1 promotes keratinocyte and fibroblast proliferation, cell granulation, and re-epithelialization, among other functions, during wound healing. IGF-1 expression declines in diabetics may lead to anomalies in cell granulation. The pH of the wound environment regulates its affinities. People and animals with diabetes both experienced delays in healing because of lower levels of TGF-β and IGF-1 at the site of wounds [128, 129].

Transforming growth factor β

Growth factors alter in order to facilitate wound healing. Growth factors, neutrophils, macrophages, lymphocytes, keratinocytes, and fibroblasts are among the inflammatory cells that are drawn to and activated by tumour growth factors. These agents reduce ECM breakdown while increasing angiogenesis, vascularization, and ECM synthesis. TGF-β has been shown to decrease in wound healing environments in the presence of diabetes. Several investigations have demonstrated that the MMP-producing genes' promoter regions include an inhibitory element that reduces the gene's expression and is dependent on TGF-β1. Reduced TGF-β levels result in excessive growth factor breakdown, whereas increased MMP expression causes an excess of growth factor breakdown. Factors impacting transcription Smad-2, Smad-3, and Smad-4 activate and deactivate genes that target TGF-e and generate MMP. TGF-1 stimulates Smad-2 and Smad- 3 to increase collagen synthesis. Lower TGF-1 levels prolong the healing process of DWs from the inflammatory phase into the proliferation phase by attracting more activated inflammatory cells. Previously, it was believed that high levels of TGF-3 were the primary reason of low TGF- 1 levels in diabetics. In the conclusion, there was a decrease in collagen synthesis and an increase in macrophage activity. Increased macrophage activity in diabetics lengthens the inflammatory phase and raises reactive oxygen species. The lack of or abnormal expression of these growth factors causes diabetic wounds to heal slowly and unsatisfactorily [130-131].

Myeloprotegerins' function in delayed wound healing

During Angiogenesis, extracellular matrix the matrix metalloproteinase family of enzymes is essential for wound debridement, remodeling, and the initial stages of epithelialisation. The importance of wound healing has led to a recent surge in research on collagens, proteoglycans, and elastin. According to research, abnormalities in growth factor production are the main reasons why diabetics' wounds don't heal properly, cytokines, and other molecular components. The healing process is less successful as a result of these imbalances and aberrant gene expression in all relevant cells. Therefore, chronic nonhealing wounds usually appear during the inflammatory stage and cannot develop at the same time. The discovery of several molecular variables and targets has revolutionised the management of diabetic wounds. We may categorise these management techniques according to the molecular targets that either

directly or indirectly regulate their function. There are direct connections between stem cells, autologous fibroblasts or keratinocytes, and many growth factors (PDGF, EGF, VEFG, FGF, KGF, and TGF-α). The preceding sections have already covered the significance and intent of these goals. Growth factors, collagen synthesis/degradation, matrix metalloproteinase (MMP), pro- and anti-inflammatory cytokines, and nitric oxide levels are some of these goals. is an enzyme that plays a specific part in wound healing is unknown; however, it may help keratinocytes migrate away from the basement membrane and aid macrophages and neutrophils in destroying the matrix as they clear injured or necrotic tissue. Chronic wound fluid has metalloprotease (MMP) levels that are around sixty times more than acute wound fluid levels; these increased levels are indicative of diabetic wounds, according to the research. Because of this increase in protease activity, the body's normal capacity to repair itself is impaired and tissue disintegration is accelerated. Several possible reasons might be at play here. One is that MMPs are directly impacted by elevated glucose levels, which alter their expression and level. One more is that TIMP expression is downregulated when levels of profibrotic and inflammatory cytokines are consistently high. Last but not least, MMPs are indirectly impacted with the creation of sophisticated glycation products. Thus, they eliminate matrix proteins, growth factors, and receptors—all of which are essential for wound healing [132- 133].

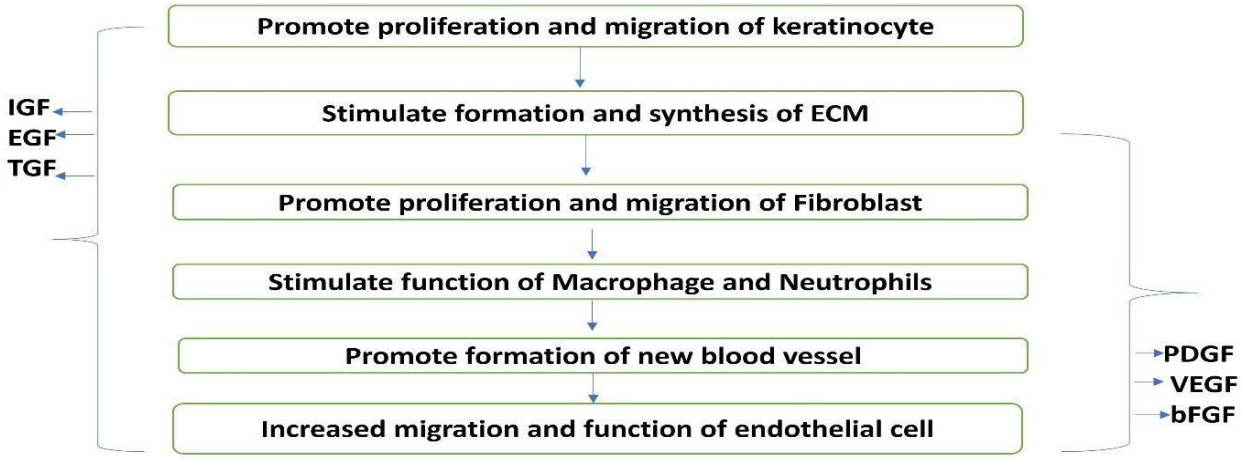

Fig. 4. Important growth factors' effects on various cells and the wound-healing process

Molecular objectives

The growing molecular comprehension of how diabetes affects inadequate the importance of wound healing has led to a sharp rise in study in recent years. According to research, abnormalities in the production of growth factors, cytokines, and other molecular components are the main reasons why diabetics' wounds don't heal properly. These imbalances and abnormal gene expression in all key cells make the repair process less successful. Consequently, chronic nonhealing wounds typically manifest during the inflammatory phase and are unable to develop concurrently. The discovery of several molecular variables and targets has revolutionised the management of diabetic wounds. We may categorise these management techniques according to the molecular targets that either directly or indirectly regulate their function. PDGF, TGF-α, EGF, VEFG, FGF, and KGF are among the growth factors that have direct interactions with autologous fibroblasts, keratinocytes, and stem cells. The significance and intent behind these goals have previously been discussed in the sections above. Growth factors, nitric oxide levels, matrix metalloproteinase (MMP), pro- and anti-inflammatory cytokines, and collagen synthesis/degradation are some of these objectives. Key factors linked to angiogenesis are among the molecular targets that many medications may directly affect. Diabetes wound therapy highlights are shown in Table 1, which categorises these methods according to the therapeutic substances utilised, which include medications, growth factors, alternative treatments, and stem cells. In addition, Table 1 shows the molecular targets that are

involved in therapeutic treatments via forms, systems, or drugs, either directly or indirectly [134].

Experimental studies

Numerous clinical experiments were conducted in an attempt to find a cure to There is a worldwide health crisis. Tardive et al; (2014) found that the treatment group's amputation risk was 0.029 times higher than the control groups in a photodynamic treatment clinical investigation. Park et al. (2018) conducted a phase III multicentre, double-blind, randomised, placebo-controlled experiment to evaluate the safety and effectiveness of a novel growth factor therapy spray containing recombinant human epidermal growth factor (rhEGF) for the treatment of diabetic wounds. Patients who received rhEGF had a considerably higher chance of finishing the healing process than those in the placebo group (73.2% vs. 50.6%, respectively; $p = 0.001$).Furthermore, the rhEGF-treated group showed a faster rate of repair regardless of HbA1c levels ($p = 0.029$). Compared to the placebo group, those on rhEGF saw a shorter median duration for a 50% decrease in ulcer size and a shorter time for full ulcer healing. Asadi et al. (2017) conducted a single-blind, placebo-controlled, low-intensity cathodal direct current research. The findings of the study suggest that electric stimulation may speed up the healing of ischaemic ulcers by causing the wounded region to produce healing factors like VEGF and HIF-1α. Soleimani et al. (2017) conducted a double-blind, randomised, placebo-controlled trial to examine the benefits of flaxseed oil, an omega-3 fatty acid. Plasma TAC, serum hs-CRP, insulin metabolic indicators, ulcer size, and GSH levels improved in diabetic wound patients after taking omega-3 fatty acid supplements for 12 weeks [134]. Table 2 summarises the findings of a number of recent clinical investigations intended to speed up the healing process for diabetic wounds.

Table-2 List of diabetic wound clinical trial studies

S.No.	Study design	Drugs/ Methods	Result	References
1.	Phase III Randomization-Based Clinical Trials Phase III Clinical Trials Based on Randomization	Topical gel	Boosts the pace of re- epithelialization in shallow wounds	[135]
2.	Controlled, randomized experiment	Honey dressing	The treated group exhibited significantly higher levels of healing area and microbiological clearance as compared to the control group.	[136]
3.	Controlled, randomized experiment	Jelly	The placebo group showed no improvement in healing time, area, or rate. Compared to the control group, the treated group's healing time was much shorter. The percentage of ulcers that healed showed no significant difference among the groups.	[137]

4.	randomized clinical trials	Honey-infused Manuka dressing	The use of dragon's blood cream significantly expedites the healing process. notable decrease in both the size of the sore and the typical healing period for an ulcer.	[138]
5.	Randomized, Double-blind	Dragon's blood cream	The treated group's wound area was much less than the control groups.	[139]
6.	Randomized controlled single-blind	Wave treatment	Significant reduction in the average the length of time it takes an ulcer to heal and the extent of the lesion .	[140]
7.	Single-arm clinical trial	Gel	In comparison to the control group, the treated group had a markedly reduced wound area.	[141]
8.	Controlled, randomized experiment	Patch system	Within 20 weeks, 34% of ulcers in the group treated with the Leuco Patch had healed, compared to 22% in the group that received	[142]

Approaches to treatment in the future

Numerous wounds related to diabetes can be caused by Peripheral neuropathy, peripheral vascular Foot issues and illness are risk factors. Notwithstanding technical developments like the application of skin cells that have been bioengineered and conventional care, the percentage of wound recuperation in insulin has reportedly stayed under 50%. Significant improvements in the evaluation of diabetic wounds have been made possible by novel treatments such as inflammatory mediator inhibitors, cytokine stimulators, extracellular matrix, matrix metalloproteinase inhibitors, epidermis substitutes, genetic and vasculature stimulators, and therapy with stem cells. Researchers are now investigating many prospective therapies for diabetic wounds. The modalities include stem cell therapy, platelet-rich plasma, substance P, sphingosine 1-phosphate, shockwave treatment, laser therapy, and therapies derived from natural products. Tables 1 and 2 show that these methods are essential for developing a safer, more effective treatment for diabetic wounds. Research on many of these methods is still ongoing, with only human clinical trials testing them thus far.

Conclusion and future perspectives

S. Patel, et al (2019) studied that the Peripheral neuropathy, peripheral artery disease, and foot diseases are among the many risk factors that might lead to diabetic wounds. Wound healing rates for diabetics have reportedly stayed around 50% despite advances in technology like bioengineered skin cells and the widespread use of standard care. Novel nonconventional therapeutic approaches are rapidly emerging in the field of diabetic wound research. Multiple investigations have discovered a variety of variables that lead to poor wound healing. Often seen in diabetics. New therapy techniques and products have significantly improved wound healing management in diabetes. Researchers have explored and tested growth factor, dual growth factor, anti-inflammatory, cytokine, matrix metalloproteinase (MMP), angiogenesis, extracellular matrix (ECM), stem cell, and natural product-based approaches, yielding mixed results. Understanding the fundamental approach and inventing newer carriers is crucial. When it comes to managing impaired wounds, combination treatments have the potential to be a significant topic for future study. The result is that diabetic wounds heal more quickly. Diabetic wound healing medicines that target specific phases need further investigation. It may be beneficial to better assess the degree of recovery.

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All authors participated equally.

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