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Modern Methods of Treatment of Trophic Ulcers in Patients with Diabetes Mellitus (Literature Review)

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Abstract Diabetes mellitus (DM) is a pathology affecting millions of people around the world, and its global prevalence has increased rapidly over the past thirty years. It is expected that this trend will continue to grow from the current 5.1% to 7.7% in 2030. Depending on the pathogenesis, diabetic foot ulcers are divided into neuropathic, ischemic or neurochemical. Neuropathic foot ulcers often occur on the plantar surface of the foot in areas with high pressure, for example, in the projection of the heads of the metatarsal bones of the foot. They account for more than 50% of diabetic foot ulcers, and they are often painless. Standard therapy for diabetic foot ulcers includes monitoring and maintaining blood glucose levels, primary wound treatment, unloading of the affected area, dressing, antibacterial therapy. Wound infection is a predictor of long-term wound healing and amputation of the lower extremities. Timely detection of infection and adequate antibacterial therapy of diabetic foot will reduce these risks. And, conversely, unjustified antibiotic treatment is associated with a number of side effects, including resistance to antibacterial drugs. Over the past decades, a large number of fundamental and clinical studies have been conducted, during which new methods of treating diabetic foot ulcers have been developed, including growth factors, bioengineered skin substitutes, stem cells, which has reduced the healing time of wounds. Despite this, there is still a significant gap between the current and desired results of treatment of diabetic foot ulcers, so there is a need to conduct further research to determine the effectiveness of standard interventions and develop practical recommendations for their use based on evidence.

Keywords Trophic ulcer, Diabetes mellitus, Diabetic foot ulcer, Diabetic foot, Ulcer treatment

1. Introduction

Diabetes mellitus (DM) is a pathology affecting millions of people around the world, and its global prevalence has increased rapidly over the past thirty years. It is expected that this trend will continue to grow from the current 5.1% to 7.7% in 2030 [1].

One of the most common complications of diabetes is the appearance of diabetic foot ulcers (DFU). According to the International Diabetes Federation, the risk of developing foot ulcers in a person with diabetes is about 25%. The prevalence of this pathology among the population of a particular country varies from 4 to 10%. The risk of amputation in people with diabetes is 10-30 times higher compared to the general population, and every year one million people with diabetes undergo lower limb amputation. Most limb amputations (85%) are preceded by ulceration of the foot, and mortality after amputation is 15-40% after 1 year and 39-80% after 5 years [2].

With proper treatment in patients with diabetes mellitus, in most cases (60-80%) ulcers have positive healing dynamics, from 10% to 15% of these ulcers remain active, and from 5% to 24% lead to limb amputation after about 6-18 months [3].

40% of patients with DFU after treatment for one year have a relapse of this disease, almost 60% have a relapse within three to five years [3].

2. Mechanisms of Development of Diabetic Foot Ulcers

Depending on the pathogenesis, DFU is divided into neuropathic, ischemic or neurochemical. Neuropathic foot ulcers often occur on the plantar surface of the foot in areas with high pressure, for example, in the projection of the heads of the metatarsal bones of the foot. They account for more than 50% of diabetic foot ulcers, and they are often painless. Ischemic or neurochemical ulcers are more common at the tips of the toes or the lateral border of the foot [4].

DFU have a complex pathogenesis of development. The main factors are diabetic neuropathy and peripheral artery disease (PAD), while trauma is a trigger mechanism in the occurrence of DFU [5].

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Diabetic neuropathy. An increase in blood glucose level initiates oxidative stress on nerve cells, leads to neuropathy, as a result of which nerve fibers of the sensitive, motor and autonomous type are affected. Violation of the integrity of the motor neurons of the foot muscles can lead to an imbalance of flexors and extensors, anatomical deformities, ulceration of the skin. Damage to the autonomic nerves disrupts the functions of the sweat glands, the skin of the foot becomes less moist, which leads to cracks in the epidermis and destruction of the skin. Due to a decrease in peripheral sensitivity, patients may not notice the existing foot ulcers [5].

An excessive amount of blood glucose leads to changes in the peripheral arteries of the foot. Dysfunction of endothelial cells is the most important sign of microcirculation disorders, as it leads to a decrease in vasodilators, in particular the synthesis of nitric oxide. The level of thromboxane A2 in plasma increases with subsequent persistent vasoconstriction and hypercoagulation of plasma, which leads to an increased risk of ischemia and ulceration. In the endothelium, there are changes in the proliferation of endothelial cells, thickening of the basement membrane, increased blood viscosity, changes in microvascular tone, proliferation of smooth muscle cells, a decrease in antioxidant capacity and a decrease in local angiogenesis [6].

Vascular diseases. Peripheral vascular diseases are more common in diabetic patients than in people without diabetes. In 1990, a Framingham study showed that women with diabetes were 1.5 times more likely to have no pulse on their legs than women without diabetes. Subsequently, a study of diabetic foot showed that from 18% to 39% of patients with DFU had signs of arterial disease. Although ischemia caused by arterial disease is the main cause of vascular diseases mediating ulceration, more recent data indicate that both venous insufficiency and microvascular changes are important factors [5].

Arterial ischemia. Diabetes is a known risk factor for the development of PAD, so it is not surprising that ischemia affects the development of DFU. Ischemia leading to DFU is most often caused by atherosclerotic occlusion of the tibial arteries. In addition, the arterial vascular network of diabetic patients does not sufficiently provide collateral blood circulation around the distal deep artery of the thigh or knees, which leads to a decrease in the supply of oxygen, nutrients and antibiotics to the distal parts of the lower extremities. Patients with diabetes mellitus are less likely to experience pain from lameness secondary to their neuropathy, which can lead to the progression of ischemia [6].

Venous insufficiency. Diabetes is usually associated with chronic venous insufficiency, but whether insufficiency causes ulceration of the foot is definitively unknown. Studies have shown that in patients with diabetes, changes in venous hemodynamics are observed, which can contribute to the occurrence of edema, which leads to a reduction in the time of filling of veins, loss of arteriovenous response and increased venous pressure, which indicates that edema in diabetes occurs due to increased blood pressure, which is transmitted to the venous system. In addition, medial thickening of small veins has been reported in patients with diabetes mellitus, which suggests that the existing microvascular venous changes may also contribute to this process. Thus, venous hemodynamics and microvascular changes are associated with edema, which contributes to the formation of DFU [7].

Microvascular changes. Diabetes also causes changes in the microcirculatory system, which disrupt the work of arteries, veins and capillaries and affect wound healing. Structural microvascular changes that occur in diabetes include thickening of the capillary basement membrane, a decrease in the size of the capillary lumen and degeneration of pericytes, which worsens the expansion and narrowing of blood vessels. Some of these effects may be due to increased endothelin 1 levels and the expression of ADAMS-15 in diabetic patients. Such factors are expressed on the endothelium and probably contribute to the deterioration of arterial venous connections and stimulation of endothelial cells and inflammation. In addition, in patients with DFU, these microvascular changes can disrupt normal transport through the capillary wall and contribute to local destruction of blood vessels and inflammation, which leads to the development of DFU and worsens wound healing [6].

3. Main Principles of Treatment of Diabetic Foot Ulcers

Standard therapy includes monitoring and maintaining blood glucose levels, primary wound treatment (debridement), unloading of the affected area, dressing, antibacterial therapy. In the absence of a proper effect, adjuvant treatment methods are resorted to [8].

Monitoring and maintaining blood glucose levels is recommended to optimize blood glucose levels to improve wound healing. The Cochrane Review (IWGDF Update 2019), assessing the impact of blood glucose targets in type 2 diabetes mellitus, showed that adequate glycemic control reduced the risk of lower limb amputation by 35% [9].

Primary wound treatment Wound treatment plays an important role in the fight against wound infection, since devitalized tissues are a place of accumulation of bacteria, act as a physical barrier to antibiotics and limit the immune response aimed at fighting infection. There are basic types of wound treatment: surgical, autolytic, enzymatic, mechanical and biological necrotomy [10].

Surgical treatment of the wound involves the removal of all necrotic and devitalized tissue in an «acute way», which contributes to the formation of granulations and reepithelization. It is fast and effective and allows to remove large volumes of hyperkeratosis and dead tissues [11].

Autolytic treatment. This method involves the use of bandages that provide a moist environment in the wound so that the host's defense mechanisms (neutrophils,

macrophages) purify the devitalized tissue with the help of the body's own enzymes [10].

Wound treatment with hydrogels. Hydrogels are specialized dressings made of insoluble polymers that bind a relatively large volume of water. The mechanism of action of hydrogel dressings is to facilitate wound healing by autolytic treatment. Autolytic treatment uses the body's own enzymes and moisture to rehydrate, soften and partially digest devitalized tissues. This requires a moist, well-vascularized wound to create optimal conditions for proteolytic enzymes that destroy necrotic tissue. Autolysis is highly selective, proceeds without damage to the surrounding skin [12].

Enzymatic treatment is carried out with the help of various enzymatic agents capable of removing necrotic and flaky material without damaging healthy tissues [13].

Collagenolytic enzymes (collagenases). Collagenases specifically break down collagen, which is the main component of the skin. Their role is especially important during the restoration of damaged skin during wound healing. In healthy tissue, macrophages and fibroblasts secrete collagenase at the site of tissue damage and promote wound healing by removing necrotic tissue. In chronic wounds, as it is observed in DFU, the secretion and activity of endogenous collagenases are disrupted, which leads to insufficient removal of necrotic tissue. The process by which collagenase removes tissue is an enzymatic treatment. Bacterial collagenase has a unique ability to destroy human collagen. The available data suggest that the mechanism of action of clostridial collagenase is to stimulate the migration of keratinocytes. In addition, peptide fragments stimulate the proliferation and migration of keratinocytes and fibroblasts, thereby contributing to wound healing. Ointment with clostridial collagenase (CCO) is the most common agent used for enzymatic treatment, contains collagenases of the metallopeptidase family and is derived from Clostridium histolyticum. However, the ointment has not been widely used in the treatment of DFU, which may be due to the long time required for effective sanitation [12].

Enzymatic processing is expensive and requires skills to apply it. It is indicated specifically for neurochemical and ischemic ulcers, since surgical treatment can be extremely painful [11].

Biological necrotomy. This type of treatment has been developed in recent years using sterile larvae of meat flies of the species Lucilia sericata. Larval wound treatment reduces bacterial load, destroys extracellular matrix, promotes fibroblast migration and improves skin perfusion, stimulates the development of granulation tissue. Larval therapy is suitable for the treatment of infected ulcers, ulcers with abundant exudate and dry gangrenous areas [14].

Mechanical processing. Hydro surgery is a form of mechanical treatment that uses a stream of sterile saline solution under high pressure directed into a wound defect [14].

There is not enough evidence to support the advantage of using a particular method. Surgical treatment of wounds remains the preferred method of DFU rehabilitation [15].

4. Unloading of the Affected Area in Diabetic Foot Ulcers

Unloading of the affected area is a prerequisite for the healing of plantar ulcers. There are various unloading methods. The most effective method of unloading, which is the gold standard, is the individual unloading bandage Total-Contact Cast (TCC). It is made of gypsum or fast-hardening fiberglass cast materials, has a relatively low cost. It is indicated for effective discharge of ulcers located on the front or middle part of the foot. TCC is contraindicated in ulcers located on the back of the foot. Severe foot ischemia, deep abscess, osteomyelitis and skin diseases are also absolute contraindications to the use of TCC. Blindness, ataxia, obesity and recurrent edema, usually in patients with end-stage renal failure, are relative contraindications to the use of TCC. In infected ulcers or ulcers with severe exudation that require frequent dressing changes, TCC should not be used (unless a hole is made under the area of the ulcer for examination and regular dressing changes). Problems associated with the use of TCC are not uncommon, include skin abrasions, usually on the shin or toes, and are associated with poorly selected TCC [16].

There are special removable devices Removable Cast Walkers (RCW) designed for people with diabetic feet. They have lightweight, durable semi-rigid side walls that help support the limb while providing full skin protection. The sole has a swinging type, which allows you to effectively unload the front part of the foot while standing and walking. The base of the foot is wide, and there is enough space in it for dressing material. The advantages of RCW are that their use does not require special training, they are easily removed for wound treatment and dressing. In addition, they can be used by patients with severe diseases of the peripheral arteries of the lower extremities and/or with purulent diseases of the feet [17].

Low shoes. Currently available unloading half-boots are not suitable for healing ulcers. There are half-boots for unloading either the front of the foot or the back of the foot. They relieve pressure on the affected area of the foot to a lesser extent than cast shoes, and they are rarely used. They are difficult to walk in, they often cause pain in the opposite limb, and patients with unstable posture cannot use them. Low shoes are indicated for patients who cannot tolerate other unloading devices [16].

Therapeutic shoes. Therapeutic shoes and insoles are alternative methods of treating wounds located on the forefoot, especially custom-made ones. They can reduce the pressure at the site of ulceration by 40-50%. They are indicated for patients who do not tolerate other unloading devices [17].

Other unloading methods. The constant use of crutches can help in relieving wounds located in the front or middle part of the foot. Using a wheelchair is a very effective method of unloading, especially if there are large wounds or wounds on the heel, and other methods of unloading are not

shown. In many patients with active or recurrent ulcers, ulcers completely healed after mandatory prolonged bed rest for other medical reasons (for example, after surgery for a hip fracture) [18].

5. Local Bandages

DFU are diverse, so there is no universal dressing that would be suitable for all types of wounds. The main purpose of the dressing is to create a moist environment conducive to granulation, autolytic processes, and angiogenesis. It should also be suitable for removing excessive amounts of wound exudate. There are different types of dressings, each of which has its advantages and disadvantages [19].

Gauze. Advantages: low cost, affordable, suitable for gangrenous wounds. Disadvantages: adheres to the wound bed and can cause bleeding when removed; does not create a moist environment; has limited absorption capacity; provides weak protection from bacterial contamination; fibers can be incorporated into wound tissue [19].

Films. Advantages: semi-permeable, (it is possible to inspect the wound), durable, form a bacterial barrier, require replacement every 4-5 days. Disadvantages: they are used only for flat or superficial wounds; some patients may be allergic to glue in the bandage [20].

Sponges. Advantages: suitable for ulcers with low or high volume of exudate, provide thermal insulation. Disadvantages: the absorbency of various materials may vary during use; insufficient evidence base confirming their effectiveness [19].

Hydrogels. Advantages: effective, versatile and easy to use; selectively act on the problem area without damaging the surrounding healthy tissue; promote autolysis and wound healing; reduce the risk of infection; well remove mucus and necrotic tissue from wounds. Disadvantages: they are not suitable for neurochemical ulcers, in which a minimum amount of exudate is released [20].

Hydrocolloids. Advantages: they are safe, have a selective effect; are well suited for necrotic lesions with a moderate exudate content; can be used with shoes; adhesive surface prevents slipping; do not require daily change of dressing; inexpensive. Disadvantages: may contribute to the development of anaerobic infection [21].

Alginates. Advantages: they are good absorbents of exudates; can be used for infected ulcers; some have hemostatic properties. Disadvantages: they are not suitable for neurochemical ulcers, in which a minimal amount of exudate is released; they can injure the wound bed; they can dry out and form a plug in the wound bed; careful removal using a large amount of physiological solution is required [21].

Dressings with antimicrobial properties (Sorbact). Advantages: they bind wound bacteria quickly and effectively; support the natural healing process of wounds; do not cause the development of bacterial resistance; are indicated for infected or heavily contaminated ulcers with a loose base. Disadvantages: high cost, insufficient evidence base [21].

Dressings with honey. Advantages: have anti-inflammatory and bactericidal properties; reduce the formation of reactive oxygen species; enzymatic treatment; have regenerative properties; are indicated for all types of ulcers, except gangrenous. Disadvantages: bandages are suitable only for superficial ulcers, insufficient evidence base [22].

Bandages with activated carbon. Advantages: bactericidal activity; reduce unpleasant odor; are indicated for infected and heavily contaminated ulcers. Disadvantages: high cost; with a large volume of exudate, secondary dressing may be required; with ulcers with a small amount of exudate, it is recommended to apply a paraffin bandage on the wound surface to prevent dryness [19].

Microfiber. Advantages: high absorption capacity; used in a humid environment; absorb and retain microorganisms. Disadvantages: expensive; few publications confirming the effectiveness [20].

Dressing with sucrose octa sulfate. Advantages: effective in the treatment of neurochemical ulcers. Disadvantages: high cost; no proven efficacy in neuropathy; ineffective in the treatment of infected ulcers; suitable for ulcers only with low and moderate exudation [20].

Indications for the use of bandages depending on the condition of the wound:

healthy granulosa tissue - film, hydrocolloid, sponge in the presence of exudate;

loose base, exudate - alginate, sponge, microfiber, sorbet; 3) loose base, necrosis - hydrogels; loose base, pronounced infectious process - alginates, Sorbet, dressings with activated carbon, honey or silver; dry gangrene - dressing with alcohol solution or povidone-iodine; neurochemical ulcers - dressing with octa sulfate sucrose.

A wide range of types of bandages are available, and some of them are currently being studied. There is currently insufficient data to recommend any particular type of dressing [23].

6. Antibacterial Therapy for Diabetic Foot Ulcers

Wound infection is a predictor of long-term wound healing and amputation of the lower extremities. Timely detection of infection and adequate antibacterial therapy of diabetic foot will reduce these risks. And, conversely, unjustified antibiotic treatment is associated with a number of side effects, including resistance to antibacterial drugs [24].

It is recommended to start antibacterial therapy in the presence of signs of an inflammatory process (pain, erythema, local fever, edema) and / or with the appearance of pus. Before starting the course of antibacterial therapy, it is necessary to conduct a microbiological examination of the wound to determine the sensitivity of pathogens to

drugs. Antibacterial therapy should be aimed at aerobic gram-positive cocci in mild and moderate infections. Severe infections should be treated with broad-spectrum antibiotics. It is recommended to carry out a 1-2-week course of antibiotics for mild infections and 2-3 weeks for moderate and severe infections. After eliminating the clinical signs of the infectious process, antibiotics should be discontinued [25].

Mild infection of diabetic foot: flucloxacillin or allergy to penicillin, clarithromycin, erythromycin or doxycycline.

Moderate or severe infection of diabetic foot: flucloxacillin with gentamicin and/or metronidazole; co-amoxiclav with or without gentamicin; co-trimoxazole (with penicillin allergy) with gentamicin and/or metronidazole; ceftriaxone with metronidazole [25].

In the presence of Pseudomonas aeruginosa according to the results of microbiological examination: piperacillin with tazobactam; clindamycin with ciprofloxacin and / or gentamicin. If MRSA is suspected: vancomycin, teicoplanin, linezolid [24].

Revascularization interventions in patients with DFU with hemodynamically significant stenoses and/or occlusion of the arteries of the lower extremities, balloon angioplasty with or without stenting should be performed [26].

Adjuvant methods of treatment. In the absence of an effect on the background of standard therapy, it is necessary to use additional methods of treatment. The most common adjuvant methods of treatment include: bioengineered skin substitutes, energy therapy, negative pressure therapy, hyperbaric oxygen therapy, growth factors, stem cell therapy [27].

Bioengineered skin substitutes currently, many skin substitutes have been developed. They are divided into matrices containing allogeneic cells, matrices with autologous cells and matrices without cells. Matrices containing cells consist of fibroblasts, keratinocytes and other living cells. Cell-free matrices do not contain cells, but serve as an extracellular matrix framework to support fibroblast migration and re-vascularization [28].

Matrices containing allogeneic cells. This group includes Apligraf and Dermagraft. An apligraph is an allogeneic two-layer cultured equivalent of skin obtained from the foreskin of newborns. Mechanism of action: acts as an epidermal layer containing keratinocytes and a dermal layer containing fibroblasts. It differs from human skin in that there are no blood vessels, hair follicles, sweat glands in it. Dermagraft is a cryopreserved skin substitute obtained from fibroblasts of the skin of the foreskin of newborns, which are cultured in vitro into a bioabsorbable mesh. Fibroblast cells remain metabolically active after implantation, secrete human skin collagen growth factors, matrix proteins and cytokines that form a skin substitute [29].

Matrices containing autologous cells. This group includes Hyalograft 3D, Laserskin and Tran Cell. They are developed from cells taken from skin biopsies from the patients themselves. Tran Cell is a medical grade polymer containing 20% carboxylic acid, which allows keratinocytes to attach and multiply [29].

Acellular dermal matrix (ADM) has been used for several years for wound healing, tissue repair. The extracellular matrix plays an important role in wound healing, as it provides structural support for the regeneration of damaged tissue. The donor skin, which is decellularized, retains biologically active substances and acts as a framework for repopulation of host cells. It is believed that it promotes wound healing by promoting vascularization and providing a barrier to bacteria, and a moist wound environment, which increases cell regeneration. Graft Jacket is an allograft made from human donor skin, which serves as a framework for cellular and vascular growth in wounds [30].

According to the Cochrane Review, bioengineered skin substitutes used to treat DFU have shown positive results in wound healing compared only with standard treatment. The existing evidence base is insufficient to determine which of the bioengineered skin substitutes is the best [31].

7. Energy Therapy

Electrical stimulation. Electrical stimulation accelerates angiogenesis, collagen synthesis and keratinocyte migration [32].

Shock wave therapy. Extracorporeal shock wave therapy (ESWT) is believed to stimulate wound healing, promote angiogenesis, accelerate immune response and fibroblast proliferation [32].

Electromagnetic therapy stimulates and activates physiological healing due to factors that reduce oxidative stress and inflammation, as well as enhance the proliferation of cells responsible for tissue repair [33].

Laser therapy helps to reduce inflammation, stimulate angiogenesis and the development of extracellular matrix components, has an antibacterial effect [34].

Phototherapy causes photochemical reactions that lead to a rapid increase in metabolic activity and cell growth, vasodilation and angiogenesis [34].

Negative Pressure Therapy (NPT)

NPT is a new method of treating diabetic foot ulcers. This method of treatment uses a sub atmospheric pressure created by a pump that is connected to an elastic foam shell with open cells covered with an adhesive film to maintain a closed environment, also connected to a container for collecting wound secretions and exudate. The optimal sub atmospheric pressure for wound healing is approximately 125 mmHg [35].

Experimental data indicate that NPT improves blood flow, reduces tissue edema and removes exudate, pro-inflammatory cytokines and bacteria from the wound area. These physiological changes contribute to the development of a moist wound environment and can increase the rate of cell division and granulation tissue formation [36].

This therapy is contraindicated in patients with an active bleeding ulcer. Caution should also be exercised in patients receiving anticoagulant therapy, as there is a risk of bleeding. Currently, NPT is indicated for complex wounds of diabetic

foot [35].

8. Hyperbaric Oxygen Therapy (HBOT)

There is strong evidence that fibroblasts, endothelial cells and keratinocytes multiply at a higher rate in an oxygen-rich environment. Moreover, white blood cells kill bacteria most effectively when they are supplied with oxygen. Oxygen in high concentrations can accelerate wound healing in diabetes. Treatment with hyperbaric oxygen therapy consists in the periodic administration of 100% oxygen. It is delivered to the chamber, where the absolute pressure rises to 2-3 atm. This lasts from one to two hours. The full course usually includes 30-40 such sessions. This method can usually be implemented in multi-bed chambers, where the patient breathes 100% oxygen through a face mask [37].

9. Growth Factors

One of the additional directions in the treatment of DFU is the use of growth factors. Currently, platelet growth factor (PDGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) have been studied to a greater extent [38].

Platelet Growth Factor (PDGF) stimulates wound healing and promotes the formation of granulation tissue. In case of tissue damage, the release of PDGF stimulates the movement of macrophages and fibroblasts to the site of damage. This is also important in the formation of granulation tissue. It is believed that its action stimulates fibroblasts around the wound to multiply and migrate to the wound area. Fibroblasts are involved in the formation of the extracellular matrix, which activates the cells forming granulation tissue and, consequently, wound healing [39].

The basic fibroblast growth factor (bFGF) was originally discovered in 1974 as a substance in the pituitary gland extract of cattle with the ability to stimulate growth, and the complete amino acid sequence of bFGF was determined in 1980. bFGF promotes cell division and plays an important role in chemotaxis and angiogenesis [38].

Vascular Endothelial Growth Factor (VEGF) is one of a group of signaling proteins that stimulate vasculogenesis and angiogenesis. VEGF acts on endothelial cells, monocytes, T cells in the foci of inflammation, stimulating angiogenesis. As a result of VEGF action, there is an increased migration of proinflammatory cells and cytokines to the injury sites, which promotes granulation and wound healing [39].

Epidermal growth Factor (EGF) activates mesenchymal and epithelial cells, stimulates angiogenesis and restoration of the epidermis after injury. It acts autocrine and paracrine on the corresponding receptors [40].

In 2015, a Cochrane review of 28 randomized control trials of 11 different experimental growth factors was conducted. The meta-analysis noted insufficient evidence to recommend or refute the use of growth factors in the treatment of DFU. PDGF is the only recombinant cytokine growth factor approved for the treatment of DFU as a topical therapy [40].

Stem cell therapy Stem cell-based therapy has become a promising area for the treatment of DFU. Stem cells synthesize and secrete cytokines that promote cell recruitment, immunomodulation, extracellular matrix remodeling, angiogenesis and neurodegeneration, which promotes wound healing [41].

Some preliminary studies show that locally applied autologous cultured bone marrow cells can heal chronic human wounds that are not amenable to other treatments, including growth factors and bioengineered skin substitutes [42,43].

Thus, over the past decades, a large number of fundamental and clinical studies have been conducted, during which new methods of treating DFU have been developed, including growth factors, bioengineered skin substitutes, stem cells, which has reduced the healing time of wounds. Despite this, there is still a significant gap between the current and desired results of DFU treatment, so there is a need to conduct further studies to determine the effectiveness of standard interventions and develop practical recommendations for their use based on evidence. It is also necessary to continue developing new methods of treatment, which would reduce the number of lower limb amputations resulting from (more than 80% of cases) long-term non-healing DFU, improve the quality of life of patients, and thereby reduce mortality.

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