A REVIEW OF TREATMENT OPTIONS FOR CHRONIC DIABETIC WOUNDS

Przegląd leczenia przewlekłych ran cukrzycowych

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Abstract

Chronic diabetic wounds are one of the main complications of untreated or poorly controlled diabetes. The most common type of chronic diabetic wound is a diabetic foot ulcer. Healing such wounds is extremely difficult and requires diligence on the part of both the physician and the patient. Therefore, it is important to gain a thorough understanding of the available methods for treating diabetic foot ulcers. A literature review was conducted using the PubMed and Google Scholar databases, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following search terms and their combinations in English were used: "chronic diabetic wound", "treatment", "diabetic foot ulcers", "wound healing", "advanced wound care", and the Boolean operator "and". Articles published between 2020 and 2025 were included. Treatment methods were divided into wound bed preparation, oxygen-based therapies, mechanical and biological therapies, tissue engineering approaches, and wound dressings. All therapies were described based on the available information. Chronic diabetic wounds are a serious clinical problem affecting an increasing number of patients. The approach to treatment should be multidisciplinary and individualised to the patient's needs. There are many methods available for treating diabetic foot ulcers. However, not all of them have been sufficiently studied to allow their safe and reliable use in patients.

Streszczenie

Przewlekłe rany cukrzycowe są jednym z głównych powikłań nieleczonej lub niewłaściwie kontrolowanej cukrzycy. Najczęstszym rodzajem przewlekłej rany cukrzycowej jest owrzodzenie stopy cukrzycowej. Gojenie takich ran jest niezwykle trudne i wymaga staranności zarówno ze strony lekarza, jak i pacjenta. Dlatego ważne jest, aby dokładnie poznać dostępne metody leczenia owrzodzenia stopy cukrzycowej. Przegląd literatury przeprowadzono z wykorzystaniem baz PubMed i Google Scholar, zgodnie z wytycznymi Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Podczas przeglądania wyżej wymienionych baz danych użyto następujących haseł i ich kombinacji w języku angielskim: „chronic diabetic wound", „treatment", „diabetic foot ulcers", „wound healing", „advanced wound care" oraz operatora „AND". Uwzględniono artykuły opublikowane w latach 2020–2025. Metody leczenia podzielono na przygotowanie łożyska rany, terapie tlenowe, terapie mechaniczne i biologiczne, a także metody inżynierii tkankowej i opatrunki na rany. Wszystkie terapie opisano na podstawie dostępnych informacji. Przewlekłe rany cukrzycowe stanowią poważny problem kliniczny, dotykający coraz większej liczby pacjentów. Podejście do leczenia powinno być wielodyscyplinarne i zindywidualizowane, dostosowane do potrzeb pacjenta. Istnieje wiele metod leczenia owrzodzenie stopy cukrzycowej. Jednak nie wszystkie z nich zostały wystarczająco przebadane, aby można je było bezpiecznie i niezawodnie stosować u pacjentów.

Keywords: chronic diabetic wound; treatment of chronic wound; diabetic foot ulcer; DFU healing; wound healing

Słowa kluczowe: przewlekła rana cukrzycowa; leczenie przewlekłej rany; owrzodzenie stopy cukrzycowej; gojenie się OSC; gojenie się ran

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Introduction

Diabetes mellitus (DM) is one of the ten leading causes of mortality worldwide and a major contributor to the global demand for medical care. It is estimated that nearly 500 million people worldwide have diabetes [1], with diabetic foot ulcers (DFUs) being one of its major complications [2]. According to statistics, chronic, non-healing wounds develop in approximately one in three to one in five patients with DM, with a recurrence rate of 40% within one year and 65% within five years [1].

Physiological wound healing is defined as a natural process that occurs in response to structural tissue damage, including damage to the skin. This process involves complex and complementary interactions between various cell types, mediated through networks of soluble factors, including cytokines, growth factors, metabolites, and chemokines. Wound healing progresses through four overlapping and sequential phases: haemostasis, inflammation, proliferation, and remodelling (scar maturation). However, in patients with diabetes, wounds exhibit impaired healing, prolonged inflammation, and reduced rates of epithelialisation [3]. Impaired wound healing has an exceptionally complex pathophysiology and is associated with chronic hyperglycaemia, which contributes to numerous systemic complications. This results in a range of local pathological manifestations within the wound microenvironment, including barrier dysfunction and infection, impaired angiogenesis and microvascular complications, atherosclerosis, a suboptimal chronic inflammatory response, and neuropathy [1, 3]. Oxidative stress induced by hypoxia further impairs wound healing, as the partial pressure of oxygen within the wound is often below the critical threshold required for complete tissue repair. All these factors contribute to impaired wound closure, and when combined with inadequate foot care, ultimately lead to the development of diabetic foot syndrome, with ulcers most commonly occurring in areas subject to recurrent trauma and pressure [1]. In many patients with type 2 diabetes, ulcers develop on the lower limbs, representing the most severe form of diabetic wounds (DWs) [3].

The prognosis for patients with DFUs is significantly poor. Approximately 33% of diabetic ulcers fail to heal completely and progress to chronic wounds. Among patients whose ulcers initially heal, 65% experience recurrence within three years, highlighting the chronic and recurrent nature of this condition. Furthermore, around 20% of moderate to severe DFUs result in amputation, and individuals with diabetes are up to 25 times more likely to undergo limb loss than non-diabetic individuals. Moreover, the presence of DFU in diabetic patients is associated with reduced quality of life, decreased physical function, an increased risk of depression and anxiety, and is an independent risk factor for mortality [3].

This study aims to review the available treatment methods for diabetic foot syndrome and to emphasise that, given the prevalence of this condition, the choice of therapy should be individualised for each patient. Treatment decisions should be based on comorbidities, overall health status, and specific patient needs.

Material and methods

The literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two databases, PubMed and Google Scholar, were used for the literature search. The review process began in October 2024 and continued until May 2025. The databases were searched by four independent investigators. None of the investigators was involved in any of the included studies.

The following search terms and their combinations in English were used when searching the aforementioned databases: “chronic diabetic wound”, “treatment”, “diabetic foot ulcers”, “wound healing”, “advanced wound care”, and the operator “AND”. The inclusion criteria were: period of 2020–2025, type of publication (original research, review, systematic review/meta-analysis), subject matter (treatment of chronic diabetic wounds), and English language. The exclusion criteria were: type of publication (case report, editorial, abstract, poster), inappropriate publication period, and language other than English. A total of 668 papers were identified in PubMed and 836 in Google Scholar. Duplicates and irrelevant papers were excluded. A total of 49 papers fulfilled the inclusion criteria. These comprised 24 original studies, 18 review articles, and 7 systematic reviews/meta-analyses. Data were collected on chronic diabetic wounds, established treatments, and future prospects. A flowchart presenting the article search and selection process according to PRISMA guidelines is presented in Figure 1.

Treatment modalities

Wound bed preparation

Debridement

Surgical

- Sharp debridement

Sharp debridement involves the precise excision of devitalised tissue using scalpels, scissors, or curettes. This technique allows for the rapid removal of necrotic mate-

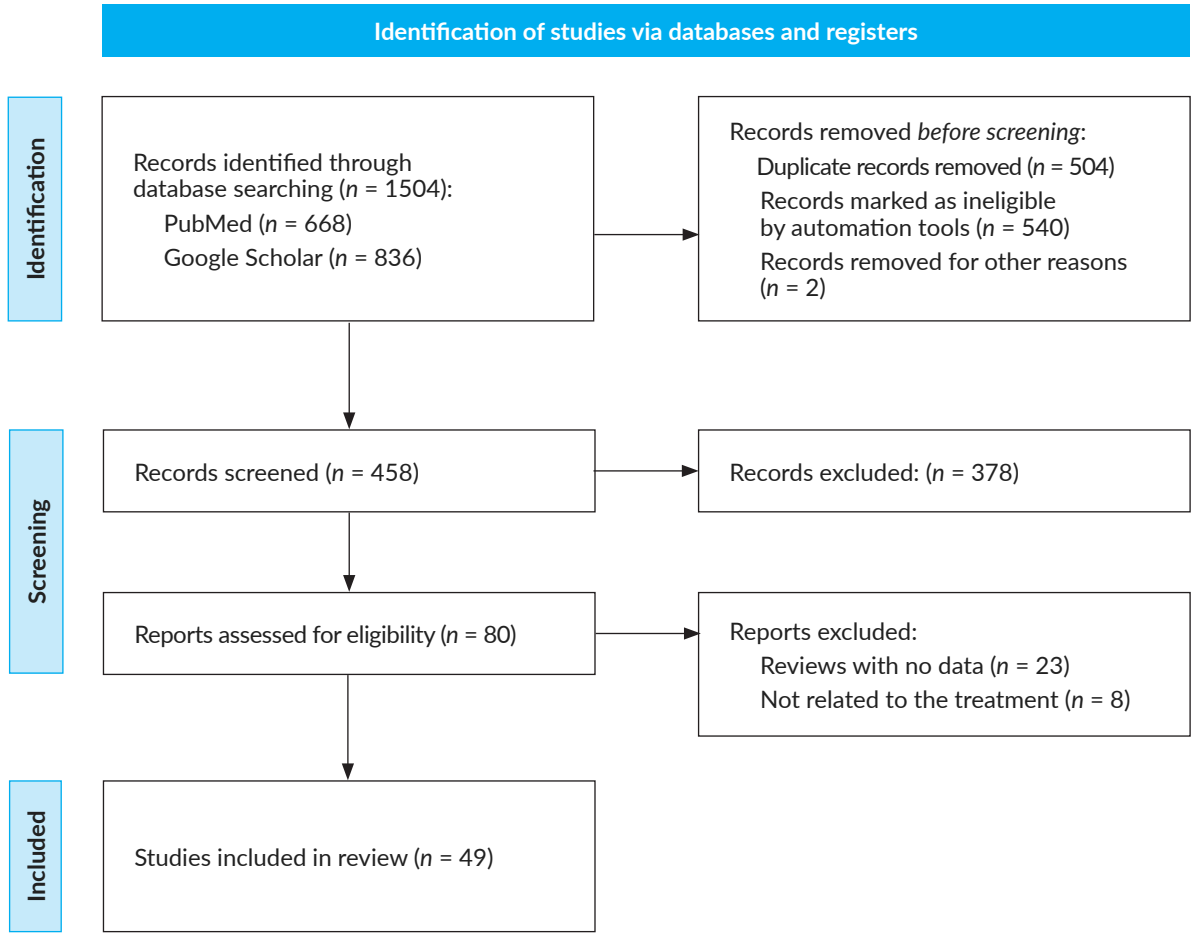

Figure 1. Flowchart of the search and selection of articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

rial, thereby decreasing the bacterial burden and facilitating assessment of the underlying structures. According to Armstrong et al. [4], sharp debridement is considered a first-line therapy in DFU management, emphasising its role in achieving a clean wound bed conducive to healing.

• Surgical debridement in the operating room

For more extensive or deeper wounds, surgical debridement may be performed in an operating room under anaesthesia. This approach is particularly beneficial for patients with significant tissue involvement or those requiring more aggressive intervention. Bandyk highlights that inpatient care, including surgical debridement of infected tissue, is recommended when invasive foot infections develop, particularly when tissue beneath the fascia is involved [5].

The choice of debridement technique is influenced by factors such as the extent of necrosis, presence of infection, patient comorbidities, and overall treatment goals. Boulton et al. emphasise the importance of a multidisciplinary approach, incorporating surgical debridement alongside other interventions, such as off-loading and infection control, to optimise patient outcomes [4].

Autolytic

Autolytic debridement utilises the body's endogenous enzymes and moisture to liquefy and separate necrotic tissue from viable tissue. This process is facilitated by maintaining a moist wound environment, typically achieved through the application of occlusive or semi-occlusive dressings. These dressings retain wound exudate, which contains proteolytic enzymes that break down devitalised tissue, thereby promoting natural tissue regeneration.

One of the primary benefits of autolytic debridement is its selectivity, as it targets only necrotic tissue while preserving healthy tissue, thereby minimising patient discomfort and reducing the risk of bleeding. Additionally, this method is non-invasive and can be easily performed in various settings, including outpatient clinics and home care, thereby enhancing patient compliance. The moist environment created by the dressings not only aids in debridement but also supports cell proliferation and angiogenesis, which are essential components of the healing process.

Despite its advantages, autolytic debridement is generally slower than other debridement methods, such as surgical or enzymatic debridement. It may not be suitable for wounds with extensive necrosis or heavy infection, where more rapid removal of devitalised tissue is necessary. Moreover, maintaining an optimal moist environment requires careful monitoring to prevent maceration of the surrounding skin and to manage exudate levels appropriately [6].

Cleansing solutions

• Superoxidised solutions

Superoxidised solutions, generated through the electrolysis of saline, produce reactive oxygen species with potent antimicrobial properties. A randomised controlled study assessed the efficacy of a neutral-pH superoxidised solution in patients with severe DFUs. The findings indicated significant infection control, a reduction in wound odour, and improvement in the condition of the periwound skin, suggesting its effectiveness as a wound-cleansing agent in DFU management [7].

• Hypochlorous acid (HOCl) solutions

HOCl is recognised for its antimicrobial and anti-inflammatory properties. In a study involving diabetic rats, topical application of HOCl was associated with decreased activity of matrix metalloproteinase-9 (MMP-9), an enzyme linked to delayed wound healing. This reduction in MMP-9 activity correlated with improved histological outcomes, indicating that HOCl may facilitate the healing process in DWs.

The investigation focused on the immersion of debrided DFU tissue in electrochemically generated pH-neutral HOCl. The results demonstrated a significant reduction in microbial bioburden, particularly against *Staphylococcus aureus*, the most prevalent species recovered. This suggests that HOCl can effectively decrease the microbial load in DFUs, potentially reducing the risk of infection [8].

Oxygen-based therapies

Hyperbaric oxygen therapy (HBOT)

HBOT may represent a valuable option for chronic wounds that are unresponsive to standard treatment, as it accelerates healing and modulates oxidative stress and inflammation. During therapy, antioxidant activity increases, while pro-inflammatory markers and MMP-9 levels decline. HBOT also enhances the expression of growth factors such as TGF-β, PDGF, and HIF-1α, which return to normal levels after wound closure, with signalling pathways including NF-κB and MAPKs playing a role in these processes.

Emerging evidence highlights the involvement of adipose tissue in wound repair. Dermal and perivascular adipocytes contribute to healing by releasing fatty acids that support macrophage recruitment, angiogenesis, and vascular remodelling. Although large clinical trials are limited, recent studies indicate that HBOT is effective in patients with advanced diabetic foot ulcers, improving metabolic and inflammatory parameters. Experimental diabetic models further confirm that HBOT accelerates wound closure and reduces MMP-9 expression. Despite these benefits, further research is required to clarify the role of endothelial-derived exosomes in HBOT-mediated diabetic wound healing [9].

Topical oxygen therapy (TOT)

TOT is defined as the topical application of oxygen to a wound, either through continuous diffusion or a pressurised system. There are three types of TOT delivery systems. The first provides continuous delivery of oxygen (CDO), and the second maintains constant low pressure within a contained chamber, and the third uses a cyclically pressurised and humidified contained chamber (TWO2). Until recently, TOT was considered an unproven method of DFU healing, unsupported by clinical evidence. However, a multicentre, open-label, randomised clinical trial conducted by Serena et al. reported the efficacy of TOT in DFU treatment. The study included 145 patients with chronic DFUs. Patients were randomly assigned to a standard-of-care (SOC) group without TOT or an SOC group with TOT. After 12 weeks, 18/64 (28.1%) patients in the SOC group without TOT achieved primary healing, compared with 36/81 (44.4%) patients in the SOC group with TOT (p = 0.044). Subsequently, there was a significant reduction in wound diameter between the SOC group without TOT vs. the SOC group with TOT, with reductions of 40% and 70%, respectively (p = 0.005). Based on these findings, conclusions were drawn about the efficacy of TOT in DFUs [10].

Mechanical therapies

Negative pressure wound therapy (NPWT)

Negative pressure wound therapy facilitates the healing process by applying subatmospheric pressure directly to the wound bed. The system is composed of a foam dressing, a semi-occlusive dressing, and a device for exudate removal. The effectiveness of VAC therapy is attributed to four primary mechanisms: macrodeformation (where applied negative pressure compresses the foam and contributes to wound size reduction), microdeformation (which stimulates cell proliferation, angiogenesis, and the formation of granulation tissue), removal of excess wound fluid (as continuous suction decreases interstitial oedema) and stabilisation of the wound environment (allowing dressing changes to be performed at intervals of approximately 2–3 days).

Vacuum-assisted closure (VAC)

Research by Blume et al. [11] found that complete wound closure was achieved in 43.2% of diabetic foot ulcers treated with VAC, whereas full re-epithelialisation occurred in only 28.9% of cases managed with advanced moist wound therapy. The authors also reported a lower incidence of secondary amputations in the NPWT group (4.1%) than in patients receiving standard wound care (10.2%). Moreover, treatment duration was reduced with the application of VAC therapy. Similarly, Armstrong et al. demonstrated that negative pressure wound therapy led to complete healing in 56% of diabetic foot ulcers, compared with 39% in patients treated with conventional moist wound care methods [12].

Biological therapies

Growth factors

DFUs present significant challenges due to impaired healing processes associated with diabetes. This is corroborated by studies indicating that DFUs are a common complication in patients with diabetes, often lead-

ing to prolonged healing times and an increased risk of infection.

Recent therapeutic approaches have focused on the application of growth factors, such as nerve growth factor (NGF) and becaplermin – a recombinant human platelet-derived growth factor (PDGF-BB) – to enhance wound healing. Research has demonstrated that the topical application of growth factors such as PDGF-BB can accelerate wound healing in patients with DFUs [13].

Nerve growth factor (NGF)

DW, particularly DFUs, pose significant clinical challenges due to delayed healing caused by impaired vascularisation, chronic inflammation, and neuropathy. Standard treatments often fail to restore tissue integrity, necessitating novel therapeutic strategies. One promising approach involves the use of NGF, a neurotrophic factor known for its regenerative properties.

NGF plays a crucial role in skin repair by promoting cellular proliferation and angiogenesis, and modulating the inflammatory response. It interacts with specific receptors, primarily tropomyosin receptor kinase A (TrkA) and the p75 neurotrophin receptor (p75NTR), triggering intracellular signalling pathways essential for wound healing [14].

- Cell proliferation and migration. NGF enhances keratinocyte and fibroblast activity, accelerating the re-epithelialisation process. Studies have demonstrated that NGF-stimulated fibroblasts produce extracellular matrix components that contribute to tissue remodelling and structural integrity.
- Enhancement of angiogenesis. Blood vessel formation is crucial for oxygen and nutrient supply to the wound site. NGF has been shown to upregulate vascular endothelial growth factor (VEGF), leading to improved angiogenesis and enhanced tissue regeneration.
- Inflammation regulation. Chronic inflammation is a major barrier to effective DW healing. NGF modulates the immune response by reducing excessive inflammatory cytokine production while stimulating anti-inflammatory pathways. This effect helps create an environment conducive to wound closure.

Experimental and Clinical Applications of NGF: Recent studies highlight the potential of NGF in DW management [14]:

- Topical NGF application: Clinical trials have shown that NGF-based formulations significantly improve healing rates in DFUs by promoting granulation tissue formation and reducing healing time.
- NGF-loaded hydrogels: Biomaterial research has led to the development of NGF-embedded hydrogels that provide sustained release, enhancing nerve regeneration and reducing inflammation.
- Combination therapies: NGF combined with antioxidant compounds, such as carnosine, has demonstrated enhanced healing outcomes by addressing oxidative stress and neurodegeneration in DW.

Becaplermin (PDGF)

Chronic DWs, particularly DFUs, present a significant challenge in clinical management due to impaired healing processes associated with diabetes. Growth factor therapy has emerged as a promising approach, with becaplermin (recombinant human platelet-derived growth factor-BB, rhPDGF-BB) being the only FDA-approved growth factor treatment specifically designed to enhance wound healing in patients with diabetes. This section explores the mechanism of action, clinical efficacy, and potential risks associated with becaplermin therapy.

Becaplermin, a recombinant form of PDGF-BB, plays a critical role in wound healing by stimulating fibroblast proliferation, collagen synthesis, and angiogenesis. PDGF-BB binds to its receptors on fibroblasts and other mesenchymal cells, promoting cell migration and extracellular matrix production, which are essential for granulation tissue formation and re-epithelialisation. Studies have demonstrated that PDGF-BB also enhances the recruitment of macrophages and neutrophils, facilitating a pro-healing inflammatory response [15].

Clinical trials have evaluated the effectiveness of becaplermin in accelerating DFU healing. A meta-analysis of randomised controlled trials reported that topical application of becaplermin gel significantly increased the rate of complete ulcer closure compared with standard wound care alone. One study demonstrated that becaplermin-treated wounds achieved complete closure approximately 32% faster than those in the control group, reducing the risk of amputation. Furthermore, a long-term observational study suggested that the use of becaplermin in combination with good wound care practices leads to improved limb salvage rates [16].

Despite its efficacy, the use of becaplermin requires careful consideration of potential risks. A retrospective analysis found a slightly increased risk of malignancy among patients who used multiple tubes of becaplermin, prompting a black box warning from the FDA. Although no direct causality relationship has been established, clinicians are advised to avoid using becaplermin in patients with known malignancies or those at high risk of malignancy. Additionally, some studies have reported local adverse reactions, such as erythema, pruritus, and mild pain at the application site [15].

Stem cell therapies

Stem cells obtained from various sources can be used for wound repair and regeneration. These include endothelial progenitor cells (EPCs), bone marrow-derived mesenchymal stem cells (BM-MSCs), adipose tissue stem cells (ASCs), dermal stem cells (DSCs), and induced pluripotent stem cells (iPS). Stem cell transplantation is a promising therapeutic option for treating hard-to-heal wounds, as transplanted cells can differentiate and provide growth factors, leading to improved angiogenesis, lower treatment costs, and an improved quality of life for patients. Recent studies have focused on the mechanism, applications, and clinical trials. Key areas of research include MSCs, exosomes, and biomaterials [17].

MSCs have a multidirectional effect in DFU therapy, contributing to improved blood supply, epidermal regeneration, cell recruitment to the wound, modulation

of the immune response, and reduction of inflammation. However, the efficacy of MSC therapy in DFUs may be limited by hyperglycaemia and chronic inflammation, which can negatively affect the survival and function of MSCs. Therefore, controlling glucose levels and inflammation is an important aspect of DFU therapy with MSCs [18]. MSCs can be obtained from tissues such as bone marrow and umbilical cord, with umbilical cord mesenchymal stem cells (UCMSCs) being obtainable without invasive surgery and having a higher proliferation capacity than bone marrow-derived cells [18].

Apoptotic extracellular vesicles (ApoEVs) of mesenchymal stem cells (MSCs) are extracellular vesicles produced by apoptotic MSCs that can induce tissue regeneration. The mechanism of action of ApoEVs involves inhibition of macrophage pyroptosis at the wound site. A study by Wang et al. showed that ApoEVs-UCMSCs significantly improved wound healing in mice with DM2, as demonstrated by a reduction in wound area and an increased healing rate. Animal studies have confirmed the ability of MSCs to improve blood flow and neovascularisation under ischaemic conditions and to reduce the surface area of chronic lower extremity wounds. Song et al. also tested hydrogel products containing exosomes derived from adipocytes. The hydrogel structure provides a controlled release of exosomes, contributing to a long-lasting therapeutic effect [18]. The mechanisms of action of MSCs are presented in Figure 2.

Platelet-derived therapies

The International Working Group on the Diabetic Foot (IWGDF) recommends against the use of autologous platelet therapy (including platelets from a blood bank) as an adjunctive therapy to standard care, except for autologous leukocyte-platelet and fibrin patches. This recommendation is based on the high risk of bias and methodological issues identified in studies of platelet gel and PRP, which currently preclude the implementation of these therapies in routine clinical practice [19].

Platelet-rich plasma (PRP)

PRP is a therapeutic method that involves collecting a blood sample by venepuncture and then extracting platelet-enriched plasma, which is subsequently injected intradermally or subcutaneously into the patient. Applied PRP enhances the release of growth factors, cytokines, chemokines and extracellular vesicles (EVs) from platelets, which can subsequently be stimulated using various methods of activation. Unlike the now widespread use of autologous PRP, PRP-derived exosomes obtained from donor mixtures from a pool of healthy individuals with precisely defined biological characteristics may be more effective in treating wounds, particularly those that are difficult to heal, such as diabetic ulcers.

A study investigating the effects of human platelet-rich plasma (hPRP) on canine mesenchymal stem cells (cMSCs) showed that hPRP stimulated the proliferation and migration of cMSCs and increased the levels of phosphorylated ERK, AKT/PKB, and FAK proteins in cMSCs, suggesting that factors released from hPRP activate various cell survival- and migration-related signalling pathways. The study also highlighted that aquaporins (AQP1 and AQP5) play a key role in hPRP-induced cMSC migration. These findings suggest the potential use of hPRPs in regenerative stem cell therapies, including wound healing [20].

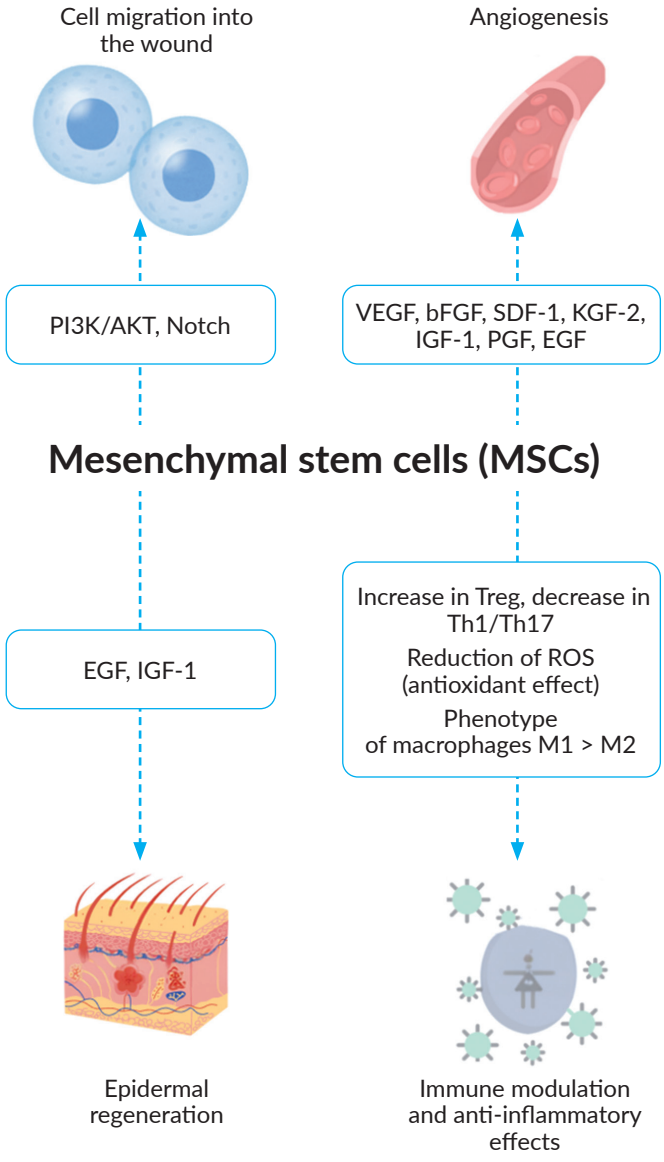

Figure 2. Mechanisms of action of MSCs [18]

Abdel Hafez et al. provided evidence for the beneficial effects of PRP in the treatment of diabetic cardiomyopathy in rats. Treatment with PRP preparations improved biochemical parameters associated with diabetes and cardiac damage, reduced oxidative stress in cardiac tissue, increased cardiomyocyte proliferation, and decreased fibroblast proliferation, potentially reducing fibrosis [21].

Platelet gel

Activated platelet gel (APG) is a preparation made from isolated platelets obtained from blood drawn from a patient or donor. The resulting platelet concentrate is then activated, leading to the release of growth factors and other substances from the platelets that are important for healing and tissue regeneration. Various factors can

be used for activation, such as calcium chloride or thrombin. The activated platelet concentrate is then converted into a gel that can be readily applied to the wound.

Platini et al. showed that APG is an effective and safe adjunctive treatment for DFUs in the elderly, accelerating healing (with a 1.38-fold higher healing rate than conventional treatment), reducing hospitalisation time (by an average of 16.97 days) and potentially reducing the risk of infection and amputation compared with traditional treatments. However, some results were characterised by heterogeneity and a lack of statistical significance for certain parameters, requiring careful interpretation [22].

Olszewska et al. presented an in vitro study of human keratinocytes to assess the effects of PRP and RAPID biodynamic haematogel (RBH) on cell growth. The results showed that both PRP and RBH stimulated the growth of human keratinocytes compared with a negative control (medium without additives), with RBH showing a stronger effect. RBH is an autologous platelet-rich and leukocyte product developed by Biotherapy Services. It is manufactured using a point-of-care (POC) system, allowing clinicians to produce RAPID gel at the bedside. As an autologous product, it minimises safety concerns [23].

Autologous platelet products

- Platelet-rich fibrin (PRF)

PRF is an autologous platelet concentrate consisting of a fibrin matrix rich in platelets and leukocytes. Unlike PRP, PRF is produced without the use of anticoagulants or activating factors of bovine origin (such as thrombin), making it an all-natural, autologous biocomposite. PRF is gaining an advantage over recombinant growth factors in the treatment of musculoskeletal injuries [24].

- Human platelet lysate (hPL)

hPL is a biological compound produced by the disintegration (lysis) of human platelets and the release of their contents.

Unlike PRP or APG, in which platelets are preserved intact and activated, hPL is produced by deliberately disrupting the platelets, as the lysis process releases their entire contents, including growth factors stored in platelet α-granules. Low concentrations of autologous hPL (5% and 10%) are most effective in stimulating the migration of human keratinocytes while having a less inhibitory effect on cell proliferation. Higher concentrations (e.g. 20%) may have a cytotoxic effect [25]. Alhawari et al. showed that treatment efficacy, as measured by wound area reduction, was significantly higher in the hPL group than in the placebo group treated with platelet-poor plasma (PPP). In the hPL group, 9 of 10 patients (90%) achieved complete healing within 12 weeks or sooner [26]. A summary of platelet-derived products used in DW therapy is presented in Table 1.

Tissue engineering approaches

Hydrogels

Stem-cell-loaded hydrogels

DWs are particularly challenging to treat because of the persistent inflammatory state that disrupts normal healing. Various stem cell populations, including embryonic stem cells, induced pluripotent stem cells, and MSCs, have been explored for their regenerative potential. Among these, MSCs support wound repair by reducing oxidative stress and enhancing angiogenesis. However, their therapeutic effectiveness may be limited when administered via direct injection, as this approach can impair cell viability and function.

Hydrogels have therefore gained attention as advanced wound dressings because of their biocompatibility, ability to maintain a moist environment, and structural resemblance to the native extracellular matrix. Their three-dimensional architecture provides a protective niche for stem cells under the hostile inflammatory and oxidative conditions characteristic of diabetic wounds, while also minimising the adverse effects associated with direct cell delivery. Several strategies for hydrogel-based stem cell

Table 1. Summary of platelet-derived products in DW therapy

Product	Characteristics	Mechanism of action	Application	Research and effectiveness
Activated platelet gel (APG)	Gel derived from activated platelets	Releases growth factors to promote healing	Treatment of wounds including diabetic ulcers	Reduces the length of hospitalisation, accelerates wound healing, and may reduce the risk of infection and amputation (Platini et al.) [22].
Platelet-rich plasma (PRP)	Platelet-rich plasma obtained from the patient's blood and administered by injection	Stimulates the secretion of cytokines, chemokines, and growth factors	Tissue regeneration, wound healing, cell therapy	Improves wound healing and muscle regeneration; donor-derived PRP may be more effective in treating hard-to-heal wounds (Abdel Hafez et al.) [21].
Platelet-rich fibrin (PRF)	Natural autologous concentrate of platelets and leukocytes without anticoagulants	Forms a fibrin matrix to promote healing and regeneration	Treatment of musculoskeletal injuries, tissue regeneration	May outperform recombinant growth factors in treating musculoskeletal injuries (Narayanaswamy et al.) [24].
Human platelet lysate (hPL)	Product obtained by the lysis of platelets, resulting in the release of their contents	Stimulates skin cell migration and proliferation	Wound therapy, tissue regeneration	Low concentrations (5–10%) stimulate keratinocyte migration, high concentrations may be cytotoxic (Alhawari et al.) [26].

application have been developed, including preformed hydrogel patches, injectable in situ–gelling systems, and hydrogel microspheres. Of these, microsphere-based hydrogels offer a greater surface area, improved distribution, and enhanced functional versatility, enabling efficient cell delivery to the wound site. Consequently, stem cell–loaded hydrogel microspheres are considered a promising approach for future clinical use.

Although combined hydrogel–MSC therapies show substantial promise in DW management, the high plasticity of MSCs presents clinical challenges. While their multilineage differentiation capacity underpins their regenerative potential, it also raises concerns about possible tumour formation, which must be carefully addressed [27].

Desferrioxamine-laden silk nanofiber hydrogels

Impaired angiogenesis and persistent inflammation are key factors contributing to the development and poor healing of DFUs. Desferrioxamine (DFO), known for its pro-angiogenic properties, has been applied clinically in DFU management, although it typically requires repeated injections. To enhance therapeutic efficacy, sustained-release, biocompatible delivery systems for DFO have been proposed. In vitro studies demonstrated that silk nanofibre-based hydrogels incorporating DFO influence endothelial cell migration and gene expression, while also modulating macrophage inflammatory responses. These findings were further validated in diabetic wound models in vivo, where DFO-loaded hydrogels reduced abnormal vascularisation and chronic inflammation, leading to faster wound closure and enhanced collagen formation [28].

Diabetic wounds are difficult to repair, primarily due to insufficient blood vessel formation within the injured tissue. Increasing evidence indicates that DFO enhances the activity of hypoxia-inducible factor-1α (HIF-1α), which in turn stimulates the production of pro-angiogenic growth factors and supports neovascularisation. Based on this mechanism, a synergistic interaction between BG and DFO has been proposed to further enhance VEGF expression. Studies have shown that sodium alginate hydrogels incorporating both BG and DFO are more effective in promoting diabetic wound closure than formulations containing either component alone. This improved outcome is attributed to the cooperative upregulation of HIF-1α and VEGF, leading to enhanced vascularisation of the wound site [29].

Matrices

Acellular dermal matrix (ADM)

ADM is a biomaterial obtained by removing cells from human skin while preserving its extracellular structure, allowing its use as a scaffold in tissue engineering.

A study published in the *Journal of Surgical Research* in 2022 evaluated the effect of a morphologically transformed decellularised dermal matrix (ADM) on chronic DWs in rats. The results showed that the application of ADM significantly accelerated the wound healing process, increasing the rate of tissue regeneration compared with the control group. Furthermore, an improvement in the quality of newly formed skin tissue was observed, indicating the potential of ADM in the treatment of chronic wounds in diabetic patients [30].

Gormley et al. 2022 evaluated the efficacy of foetal bovine acellular dermal matrix (FBADM) in the treatment of severe DFUs in patients with chronic limb ischaemia. The use of FBADM in the treatment of these wounds contributed to a significant acceleration of the healing process, compared with traditional dressings, which may reduce the risk of amputation. In addition, FBADM showed a positive effect on the reconstruction of the dermal layer, promoting faster wound closure [31].

Bilayer reconstituted matrix

Decellularised, purified, reconstituted bilayer matrix (DPRBM) is a biomaterial derived from animal tissues from which cells, lipids, and antigens have been removed, leaving a protein structure similar to that of the human dermis. It consists of two layers: an upper, compact layer that acts as a barrier and a lower, porous layer that promotes cell migration and proliferation. Thanks to these properties, DPRBM promotes natural wound healing processes by providing an appropriate environment for tissue regeneration [32].

Stromal vascular fraction (SVF) gel

SVF gel is an autologous preparation obtained from adipose tissue that contains concentrated stem cells and natural extracellular matrix. It is used in wound therapy to promote healing and tissue regeneration. A study published in the *Journal of Surgical Research* in 2018 evaluated the therapeutic effects of ECM/SVF gel on wound healing and the mechanisms underlying this process. The gel was shown to promote wound healing by accelerating re-epithelialisation, reducing fibrosis and adhesions, and stimulating cilia formation, suggesting its potential in wound healing [33].

Skin substitutes

An article by Vecin and Kirsner published in 2023 discussed the efficacy of various skin substitutes in the treatment of chronic DW. Biological products, such as Apligraf and Dermagraft, promote regeneration by providing living cells that stimulate angiogenesis. Integra and Matriderm, as acellular matrices, create a temporary scaffold for new tissue formation. Studies indicate that, in certain cases, the best results are obtained with substitutes containing growth factors and stem cells, which significantly accelerate healing and reduce complications [34].

Wound dressings

Sucrose octasulphate (TLC-NOSF) dressings are specialised materials used in the treatment of chronic wounds, such as diabetic and venous ulcers. They work by modulating the wound microenvironment, thereby promoting the healing process and improving patients' quality of life. An article published in the journal *Hautarzt* in 2020 presented evidence for the efficacy of sucrose octasulphate dressings (TLC-SOS) in the treatment of chronic wounds,

including DFUs. The EXPLORER study, involving 240 patients with neurovascular DFUs, found that the use of TLC-SOS dressings significantly accelerated wound healing compared with neutral dressings. Furthermore, an analysis of data from eight observational studies involving a total of 10,220 patients with chronic wounds of various origins showed that TLC-SOS dressings effectively promote the healing process, which may lead to faster tissue regeneration and a reduced risk of complications associated with chronic diabetic ulcers [35].

Discussion

The efficacy of various wound-cleansing solutions compared with normal saline has been the subject of systematic reviews. One such review indicated that solutions like Dakin's solutions and chloramines, as well as hypertonic saline, may enhance ulcer healing compared with normal saline or standard treatment. However, the studies reviewed were of low quality with a high risk of bias, underscoring the need for more rigorous research to draw definitive conclusions [9].

Despite its promising therapeutic benefits, NGF-based treatments face challenges related to stability, effective delivery, and potential side effects. Future research should focus on optimising controlled-release systems, such as nanocarriers or bioengineered scaffolds, to maximise NGF efficacy in wound healing [14].

Although becaplermin remains the most widely used PDGF-based therapy, ongoing research is exploring alternative growth factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), for their potential synergistic effects in wound healing. Combining PDGF with other regenerative approaches, such as stem cell therapy or biomaterial scaffolds, may further optimise outcomes for patients with chronic DWs [15].

Becaplermin represents a significant advancement in the treatment of chronic DWs by leveraging the regenerative properties of PDGF-BB. While clinical evidence supports its efficacy in promoting wound closure, its use should be carefully tailored to individual patient risk profiles. Future research should focus on optimising combination therapies that harness the full potential of growth factors while mitigating potential adverse effects.

Due to IWGDF's position on autologous platelet therapy, researchers are taking steps to improve the quality of research, apply reporting standards, incorporate relevant clinical and economic considerations, and use more innovative research methodologies to generate more reliable and useful evidence on the efficacy and effectiveness of various DFU therapies in the future [19]. Studies of the cost-effectiveness of such therapies are also lacking, but those available indicate that they may not be cost-effective compared with standard therapies [20].

Conclusions

Chronic diabetic wounds are a serious clinical problem affecting an increasing number of patients. The approach to treatment should be multidisciplinary and individualised to the needs of each patient. There are many methods for treating DFUs; however not all of them have been sufficiently studied to support their safe and reliable use in patients.

Author contributions

Dominika Żyła – conceptualisation, original draft preparation, visualisation, investigation, methodology, writing, review, and editing; Katarzyna Zych – visualisation, writing, review, and editing; Jakub Jagiełło – methodology, writing, review, and editing; Milena Krawczyk – writing, review, and editing; Adam Jakubas – writing, review, and editing. All authors have read and agreed to the published version of the manuscript.

References

1. Burgess JL, Wyant WA, Abdo Abujamra B, et al. Diabetic wound-healing science. Medicina (Kaunas), 2021; 57(10): 1072. doi: 10.3390/medicina57101072
2. Oyebode OA, Jere SW, Houreld NN. Current therapeutic modalities for the management of chronic diabetic wounds of the foot. J Diabetes Res, 2023; 2023: 1359537. doi: 10.1155/2023/1359537
3. Holl J, Kowalewski C, Zimek Z, et al. Chronic diabetic wounds and their treatment with skin substitutes. Cells, 2021; 10(3): 655. doi: 10.3390/cells10030655
4. Armstrong DG, Tan TW, Boulton AJM, Bus SA. Diabetic foot ulcers: a review. JAMA, 2023; 330(1): 62–75. doi: 10.1001/jama.2023.10578
5. Bandyk DF. The diabetic foot: Pathophysiology, evaluation, and treatment. Semin Vasc Surg, 2018; 31(2–4): 43–48. doi: 10.1053/j.semvascsurg.2019.02.001
6. Boulton AJM, Armstrong DG, Kirsner RS, et al. Diagnosis and management of diabetic foot complications. Arlington (VA): American Diabetes Association; 2018.
7. Martínez-De Jesús FR, Ramos-De la Medina A, Remes-Troche JM, et al. Efficacy and safety of neutral pH superoxidised solution in severe diabetic foot infections. Int Wound J, 2007; 4(4): 353–362. doi: 10.1111/j.1742-481X.2007.00363.x
8. Grealy L, Wilson P, Gillen C, et al. Immersion of debrided diabetic foot ulcer tissue in electrochemically generated pH neutral hypochlorous acid significantly reduces the microbial bioburden: whole-genome sequencing of Staphylococcus aureus, the most prevalent species recovered. J Hosp Infect, 2023; 138: 42–51. doi: 10.1016/j.jhin.2023.06.006
9. Capó X, Monserrat-Mesquida M, Quetglas-Llabrés M, et al. Hyperbaric oxygen therapy reduces oxidative stress and inflammation, and increases growth factors favouring the healing process of diabetic wounds. Int J Mol Sci, 2023; 24(8): 7040. doi: 10.3390/ijms24087040
10. Serena TE, Bullock NM, Cole W, et al. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. J Wound Care, 2021; 30(Sup5): S7–S14. doi: 10.12968/jowc.2021.30.Sup5.S7
11. Blume PA, Walters J, Payne W, et al. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care, 2008; 31(4): 631–636. doi: 10.2337/dc07-2196
12. Normandin S, Safran T, Winocour S, et al. Negative pressure wound therapy: mechanism of action and clinical applications. Semin Plast Surg, 2021; 35(3): 164–170. doi: 10.1055/s-0041-1731792.

13. Sridharan K, Sivaramakrishnan G. Growth factors for diabetic foot ulcers: mixed treatment comparison analysis of randomized clinical trials. Br J Clin Pharmacol, 2018; 84(3): 434–444. doi: 10.1111/bcp.13470
14. Ji X, Zhou J, Zhou Z, et al. Recovering skin-nerve interaction by nanoscale metal-organic framework for diabetic ulcers healing. Bioact Mater, 2024; 42: 112–123. doi: 10.1016/j.bioactmat.2024.08.024
15. Chen M, Chang C, Levian B, et al. Why are there so few FDA-approved therapeutics for wound healing? Int J Mol Sci, 2023; 24(20): 15109. doi: 10.3390/ijms242015109
16. Loveland JD, McMillen RL, Cala MA. A multicenter, retrospective, case series of patients with charcot neuroarthropathy deformities undergoing arthrodesis utilizing recombinant human platelet-derived growth factor with beta-tricalcium phosphate. J Foot Ankle Surg, 2021; 60(1): 74–79. doi: 10.1053/j.jfas.2020.08.030
17. Ma K, Luo C, Du M, et al. Advances in stem cells treatment of diabetic wounds: A bibliometric analysis via CiteSpace. Skin Res Technol, 2024; 30(4): e13665. doi: 10.1111/srt.13665
18. Song Y, You Y, Xu X, et al. Adipose-derived mesenchymal stem cell-derived exosomes biopotentiated extracellular matrix hydrogels accelerate diabetic wound healing and skin regeneration. Adv Sci (Weinh). 2023; 10(30): e2304023. doi: 10.1002/advs.202304023
19. Chen P, Vilorio NC, Dhatariya K, et al. Guidelines on interventions to enhance healing of foot ulcers in people with diabetes (IWGDF 2023 update). Diabetes Metab Res Rev, 2024; 40(3): e3644. doi: 10.1002/dmrr.3644
20. Parascandolo A, Di Tolla MF, Liguoro D, et al. Human platelet-rich plasma regulates canine mesenchymal stem cell migration through aquaporins. Stem Cells Int, 2023; 2023: 8344259. doi: 10.1155/2023/8344259
21. Abdel Hafez SMN, Zenhom NM, Abdel-Hamid HA. Effects of platelet rich plasma on experimentally induced diabetic heart injury. Int Immunopharmacol, 2021; 96: 107814. doi: 10.1016/j.intimp.2021.107814. Erratum in: Int Immunopharmacol. 2024; 133: 112089. doi: 10.1016/j.intimp.2024.112089
22. Platini H, Adammayanti KA, Maulana S, et al. The potential of autologous platelet-rich plasma gel for diabetic foot ulcer care among older adults: a systematic review and meta-analysis. Ther Clin Risk Manag, 2024; 20: 21–37. doi: 10.2147/TCRM.S433033
23. Olszewska A, Duan J, Javorovic J, et al. Manufacture and initial characterisation of RAPID™ biodynamic haematogel, an autologous platelet and leukocyte-rich plasma gel for diabetic foot ulcers. Gels, 2024; 10(9): 572. doi: 10.3390/gels10090572
24. Narayanaswamy R, Patro BP, Jeyaraman N, et al. Evolution and clinical advances of platelet-rich fibrin in musculoskeletal regeneration. Bioengineering (Basel), 2023; 10(1): 58. doi: 10.3390/bioengineering10010058
25. Jafar H, Hasan M, Al-Hattab D, et al. Platelet lysate promotes the healing of long-standing diabetic foot ulcers: A report of two cases and *in vitro* study. Heliyon, 2020; 6(5): e03929. doi: 10.1016/j.heliyon.2020.e03929
26. Alhawari H, Jafar H, Al Soudi M, et al. Perilesional injections of human platelet lysate versus platelet poor plasma for the treatment of diabetic foot ulcers: A double-blinded prospective clinical trial. Int Wound J, 2023; 20(8): 3116–3122. doi: 10.1111/iwj.14186
27. Huang JN, Cao H, Liang KY, et al. Combination therapy of hydrogel and stem cells for diabetic wound healing. World J Diabetes, 2022; 13(11): 949–961. doi: 10.4239/wjd.v13.i11.949
28. Ding Z, Zhang Y, Guo P, et al. Injectable desferrioxamine-laden silk nanofiber hydrogels for accelerating diabetic wound healing. ACS Biomater Sci Eng, 2021; 7(3): 1147–1158. doi: 10.1021/acsbiomaterials.0c01502
29. Kong L, Wu Z, Zhao H, et al. Bioactive injectable hydrogels containing desferrioxamine and bioglass for diabetic wound healing. ACS Appl Mater Interfaces. 2018; 10(36): 30103–30114. doi: 10.1021/acsami.8b09191
30. Kim MJ, Lee WB, Park BY. Effect of morphologically transformed acellular dermal matrix on chronic diabetic wounds: an experimental study in a calvarial bone exposure diabetic rat model. J Surg Res, 2022; 272: 153–165. doi: 10.1016/j.jss.2021.11.009
31. Gormley S, Hart O, French S, et al. The use of fetal bovine acellular dermal matrix in severe diabetic foot ulceration and threatened limbs with tissue loss the use of FBADM as an adjunct for complex wounds. Vascular, 2024; 32(3): 619–625. doi: 10.1177/17085381221141115
32. Armstrong DG, Orgill DP, Galiano RD, et al. Use of a purified reconstituted bilayer matrix in the management of chronic diabetic foot ulcers improves patient outcomes vs standard of care: Results of a prospective randomised controlled multi-centre clinical trial. Int Wound J, 2022; 19(5):1197–1209. doi: 10.1111/iwj.13715
33. Sun M, He Y, Zhou T, et al. Adipose extracellular matrix/stromal vascular fraction gel secretes angiogenic factors and enhances skin wound healing in a murine model. Biomed Res Int, 2017; 2017: 3105780. doi: 10.1155/2017/3105780
34. Vecin NM, Kirsner RS. Skin substitutes as treatment for chronic wounds: current and future directions. Front Med (Lausanne), 2023; 10: 1154567. doi: 10.3389/fmed.2023.1154567
35. Dissemond J, Augustin M, Dietlein M, et al. Sucrose Octasulfat – Evidenz in der Behandlung chronischer Wunden [Sucrose octasulfate-evidence in the treatment of chronic wounds]. Hautarzt. 2020; 71(10): 791–801. German. doi: 10.1007/s00105-020-04637-9