

# Problems of healing chronic wounds

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**Aim.** The work aimed to analyze and highlight the problems of chronic wound healing and modern methods of stimulation of reparative processes according to literature sources.

An analysis of the scientific literature was carried out, in which views on the problems of wound healing are presented, taking into account the factors affecting the formation and healing of chronic wounds, and modern methods that stimulate reparation processes. Identifying the problems of wound healing will allow a comprehensive approach to the assessment of the wound process, taking into account the factors affecting the healing of injuries.

Modern scientists are actively discussing the problems of wound healing, researching factors influencing the reparative process, including the high prevalence of chronic wounds, diagnosis and treatment of wound infections, age of patients, and state of immunity. In the case of systemic diseases, such as diabetes, cardiovascular pathology, etc., there is a violation of microcirculation, and as a result, there are violations of the phasing of reparative processes at the cellular level. As a result, the alteration process does not end and the process becomes chronic.

In case of a mechanical injury, when adaptation reserves are reduced, primarily of the neurohumoral system, a key role is played by the disruption of regulatory mechanisms at the cellular level. Wound treatment requires surgical treatment, stimulation of angiogenesis, and other reparative processes at the systemic and local levels.

In recent years, various methods of stimulating reparative processes have been used in clinical practice to treat wounds: local administration of recombinant growth factors, use of platelet-rich plasma, biotechnological wound dressings, and artificial skin substitutes. One of the most promising areas of wound treatment is the development of methods for targeted activation of stem cells. However, there are still insufficient data for the practical application of this method. Clinically effective and safe methods are still being developed. Physical methods are promising for improving the healing of chronic wounds. However, the selection of optimal parameters for physical action continues to be an urgent task. Despite the positive results obtained using the methods described above, there is a need for additional experimental studies and randomized controlled trials.

**Conclusions.** Chronic wounds develop as a result of severe systemic diseases, and major mechanical injuries against the background of a decrease in physiological reserves due to emotional and psychological stress, obesity, etc. Choosing the right method of influencing the reparative process, taking into account the leading mechanism of damage repair, becomes very important to ensure the best chance for optimal wound healing.

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## Проблеми загоєння хронічних ран

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**Мета роботи** – за даними фахової літератури проаналізувати та висвітлити проблеми загоєння хронічних ран і сучасні методи стимуляції репаративних процесів.

Здійснили аналіз наукової літератури, в якій викладено погляди на проблеми загоєння ран, враховуючи фактори, що впливають на формування та загоєння хронічних ран, а також сучасні методи, що стимулюють процеси репарації. Визначення проблем порушення процесу загоєння ран дасть змогу здійснити комплексне оцінювання ранового процесу, зважаючи на чинники, що впливають на загоєння пошкоджень.

Нині активно обговорюють проблеми загоєння ран, досліджують фактори впливу на репаративний процес, зокрема високу поширеність хронічних ран, діагностику та лікування ранових інфекцій, вік пацієнтів, стан імунітету. У разі системних захворювань (діабет, серцево-судинна патологія тощо) визначають порушення мікроциркуляції, а отже порушується етапність репаративних процесів на клітинному рівні. В результаті не відбувається завершення процесу альтерації, процес стає хронічним.

У разі механічної травми при зниженні резервів адаптації, насамперед нервово-гуморальної системи, ключову роль відіграють порушення механізмів регуляції на клітинному рівні. Для лікування ран потрібна хірургічна обробка, стимулювання ангиогенезу й інших репаративних процесів на системному та локальному рівнях.

В останні роки для лікування ран у клінічній практиці застосовують різні методи стимуляції репаративних процесів: місцеве введення рекомбінантних факторів росту, застосування тромбоцитарної плазми, біотехнологічних ранових покриттів і штучних замінників шкіри. Один із найперспективніших напрямів лікування ран – розроблення методів спрямованої активації стовбурових клітин. Втім, для практичного застосування цього методу поки що недостатньо даних. Клінічно ефективні та безпечні методи ще на етапі розробки. Перспективними для покращення загоєння хронічних ран є фізичні методи, але визначення оптимальних параметрів фізичної дії залишається актуальним завданням. Незважаючи на позитивні результати, що одержали за допомогою названих методів, необхідні додаткові експериментальні та рандомізовані контрольовані дослідження.

**Висновки.** Хронічні рани виникають внаслідок тяжких системних захворювань, великих механічних ушкоджень на тлі зниження фізіологічних резервів внаслідок емоційно-психологічних стресів, ожиріння тощо. Визначення правильного методу впливу на репаративний процес, враховуючи провідний механізм репарації пошкоджень, стає дуже важливим для забезпечення найкращих шансів для оптимального загоєння рани.

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Wounds include any violation or damage to the anatomical structure and function due to severe damage to organs, such as the skin. Environmental factors significantly impact the body's ability to respond to injury. And even though the skin has innate reparative abilities, as in any biological process, sufficient perturbation of the system leads to aberrations, which in the case of wounds are manifested by excessive scarring on the one hand or incomplete healing on the other [1].

The prevalence of chronic wounds due to various causes is approximately 2.2 per 1000 population [2]. The 5-year mortality rate for diabetic foot ulcers is 30.5 %, which is comparable to cancer-related mortality (31 %) [3]. Wounds are also an economic burden for healthcare systems worldwide [4].

## Aim

The aim is to analyze and highlight the problems of chronic wound healing and modern methods of stimulation of reparative processes according to literature sources.

A review and analysis of scientific literature were conducted based on publications included in Scopus, Web of Science, and PubMed databases. For the analysis, it was decided to include mainly articles published in English. An analysis of the scientific literature was carried out, presenting views on the problems of wound healing, taking into account the factors affecting healing and modern methods that stimulate the reparation process.

**Modern ideas about the problems of healing chronic wounds.** Wound healing requires a complex interaction between the immune, circulatory, nervous, and other systems. When the skin is injured, complex interactions occur involving various types of skin cells, peripheral nerve cells, and immune and vascular cells.

The main cells involved in the wound healing process are platelets, neutrophils, monocytes, macrophages, fibroblasts, keratinocytes, endothelial cells, epithelial cells, and myofibroblasts. Rare subsets of stem cells in the skin have also been found that are unipotent in the intact state but become multipotent after skin injury [5]. The epidermis contains various stem cells such as bulge stem cells, interfollicular stem cells, and sebaceous stem cells. On the other hand, the dermis contains two types of stem cell populations, namely, hair follicle stem cells in the dermal papilla and perivascular stem cells [6].

Skin regeneration cannot be achieved without the influence of a neurogenic factor [7]. Thus, in the skin, there is a dense network of sensory nerve afferents and modulators of nervous origin, which interact with epidermal keratinocytes and dermal fibroblasts in two directions to ensure normal wound healing after injury [8].

Wound healing is regulated by numerous cytokines and growth factors. Growth factors such as platelet-derived growth factor (PDGF), transforming growth factor beta and alpha (TGF- $\beta$ , TGF- $\alpha$ ), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and others are of great importance for the regulation inflammatory reaction, stimulation of angiogenesis, formation of granulation tissue and tissue repair [9,10]. Disruption of healing occurs in case of violation of the complex mechanism of interaction between molecules and cells [11]. Understanding the causes of altered expression of molecular factors leading to altered cellular function will provide insight into potential targets for intervention.

So, the proper functioning of the skin, as a neuro-immune-endocrine organ, depends on its ability to repair damage. The immune system plays a central role in wound healing. The state of cellular and humoral immunity can significantly affect overall health [12]. Dysregulation of the immune response during wound healing leads to severe tissue injury.

Elevated levels of pro-inflammatory cytokines, proteases, reactive oxygen species (ROS), or infections caused by various pathogens are observed, leading to aberrations in immune cell recruitment, changes in proteolytic balance, and increased oxidative stress [13]. Chronic inflammation may be associated with low immune activity, for example, as a result of incomplete phagocytosis, or with the characteristics of the pathogen.

The occurrence of biofilm colonization, which is one of the main problems during the treatment of chronic wound infections, can lead to delayed wound healing [14]. Bacterial biofilms interact with the host immune system by activating neutrophils and pro-inflammatory macrophages, resulting in the accumulation of inflammatory cytokines. On the other hand, the unregulated immune environment of chronic wounds encourages bacteria to proliferate, leading to a vicious cycle of biofilm growth and ongoing inflammation [15]. The lack of objective clinical diagnostic criteria for wound infection often leads to the inappropriate use of antibiotics, which puts patients at risk of developing polyresistance of the microbiome to antibiotics [16].

But in most cases, ongoing chronic inflammation, which causes chronicity of the process, is associated with the impossibility of removing the altering factor [17]. Severe pathologies and concomitant diseases, including cardiovascular diseases, diabetes, and diseases of the lungs, kidneys, and peripheral vessels, can significantly alter or inhibit normal wound healing [3,18]. Treatment of trophic ulcers, for example, is associated primarily with the treatment of the underlying systemic disease. So, diabetes is characterized by hyperglycemia, which is a significant cause of the development of inflammation [19]. Circulatory dysfunction at the micro- and macrovascular level is also a leading factor that slows down or prevents wound healing [19]. It has been demonstrated that the correction of arterial hypertension accompanying contributes to healing injuries [20]. However, the treatment of trophic wounds is not always successful due to the formation of pathological feedback.

Old age is another major factor influencing wound healing. In the United States, for example, 3 % of the population over 65 have open wounds [21]. In the cohort of gerontological patients, there is usually a slow metabolism, a violation of hormonal reactions, and a deficiency of nutrients [22]. As people age, the immune system naturally weakens. It is for this reason older people are more susceptible to infections. Some medications work synergistically with age to increase the incidence of chronic wounds. Treating patients receiving chemotherapy, radiation, steroids, methotrexate, and a variety of other drugs can slow down wound healing [23].

Obesity has a detrimental effect on wound healing [24]. In conditions of excessive body weight, blood flow is disturbed. Poor vascularization leads to poor oxygenation, which can further delay normal wound healing. Another factor contributing to poor wound healing in obesity is an immune imbalance. Chronic diseases caused by obesity can create a vicious cycle of inflammation and damage [25]. Separate factors in the deterioration of the treatment results of a chronic wound are a sedentary lifestyle [26], smoking status [27], and experiencing psychological stress [28], nutrient deficiency [29].

#### **Modern methods of stimulation of reparative processes.**

Diagnosis and treatment of chronic wounds is difficult due to the complexity of wound healing mechanisms and the duration of treatment. Therefore, the development and improvement of innovative methods of skin wound healing are relevant for medicine all over the world.

Factors contributing to the delayed healing of chronic wounds are key components of a comprehensive approach to wound care. Limiting or eliminating aggravating factors will also promote better wound healing. For better wound healing, the treatment of comorbidities is necessary: targeted glycemic control is necessary to accelerate wound healing in diabetes; treatment of venous ulcers requires lifelong compression therapy. Adequate perfusion, or improved perfusion, is key to the potential for wound healing in the treatment of patients with arterial ulcers.

Given that the immune system is the leading one involved in the processes of chronic wound healing, the use of immunomodulation to accelerate the healing of chronic wounds is justified. At the same time, stimulating the immune system when it cannot effectively eliminate the infection can worsen chronic inflamma-

tion [30]. Immune system deficiency can be caused by genetics, chemotherapy, radiation, malnutrition, and the like.

Conventional wound care includes various surgical procedures, non-surgical therapies, and skin wound treatment regimens based on pharmacological agents [31]. Surgical processing remains the gold standard for wound care. Non-surgical wound care includes various types of wound dressings and topical formulations. To improve skin regeneration, biotechnological wound coverings, artificial skin substitutes, and 3D printed acellular scaffolds or bioprinted cellular scaffolds are used [32]. But there is the problem of choosing the appropriate treatment for practitioners, for example, the huge market for wound dressings is diverse, but there are no publicly available quantitative data to support the claims of manufacturers [33]. Also, to accelerate the healing of wounds with various types of wounds, preparations of xenogenic origin [34] and biological preparations of placental origin [35] are used.

A promising direction of wound healing stimulation is the local administration of recombinant growth factors such as EGF, FGF, VEGF, GM-CSF, and others that stimulate migration, proliferation, and differentiation of cells in vivo, which allows external modulation of the healing process [36]. Autologous platelet-rich plasma is also effective for wound healing. Its use enhances re-epithelialization, induces angiogenesis, and promotes wound reduction and collagen deposition. However, there are insufficient data on its use in patients with acute and chronic wounds [37].

The latest developments in the field of advanced wound care technologies include nanotherapy and stem cell therapy [6]. For example, stem cell-derived exosomes have been proposed as a desirable source for regenerative medicine due to their role in promoting anti-inflammatory cell phenotypes, cell migration, and angiogenesis [38]. However, currently, available treatments face many limitations, such as short exposure time, low efficacy, high toxicity, high cost, and high risk of infection [39].

To stimulate reparative processes, physical methods are widely used, such as electrical stimulation [40], photobiomodulation therapy [41], hyperbaric oxygen therapy [42], negative pressure wound therapy [43], the use of magnetic fields [44] and magnetic tools [45], the use of ultrasound [46] and others. However, despite the positive results, the problem is the lack of optimal parameters as a standard treatment. Any long-term complications should also be monitored. Differences in wound characteristics, patient demographics, and technique parameters require additional experimental research and randomized controlled trials.

Identifying the problems of wound healing will allow a comprehensive approach to the evaluation of the wound process, taking into account the factors that affect the healing of injuries, which will reduce the risks of complications and improve the treatment of patients with chronic wounds.

## **Conclusions**

1. Chronic wounds develop as a result of severe systemic diseases, and extensive mechanical damage against the background of a decrease in physiological reserves due to emotional and psychological stress, obesity, etc.

2. In the case of severe systemic diseases, such as diabetes, cardiovascular pathology, etc., as a rule, microcirculation disorder

ders are observed, and as a result, violations of the phasing of reparative processes at the cellular level are occurred. This leads to the fact that the completion of the alteration process does not occur, the pathological positive feedback closes and the process becomes self-sustaining with the formation of a non-healing trophic ulcer.

3. In the case of extensive mechanical injury, with a decrease in adaptation reserves, primarily of the neurohumoral system, the key role is played by violations of regulatory mechanisms at the cellular level, both systemic and local.

4. Treatment of wounds requires surgical debridement, stimulation of angiogenesis, and other reparative processes at the systemic and mainly local levels.

5. Platelet-rich plasma, recombinant growth factors, biotechnological wound dressings, etc. are used to stimulate reparative processes. However, despite a large number of studies, clinically effective and safe techniques are still being developed.

6. Physical methods of influencing the wound, such as vacuum dressings, photobiomodulation therapy, etc., have shown high efficiency and safety. However, the selection of optimal parameters of physical impact continues to be an urgent task.

7. One of the most promising areas of wound treatment is the development of methods for targeted activation of stem cells. Their role in the course of reparative processes is being studied. However, there are not enough data for the practical application of such methods.

**Prospects for further research.** In the future, it is planned to study the mechanisms of reparative processes of injuries, which will allow a scientifically based approach to the choice of methods and ways of treating chronic wounds. It is advisable to conduct a meta-analysis to quantify the importance of each factor affecting wound healing.

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