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Long-Term Non-Healing Wounds: a new vision of an old problem

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ABSTRACT

Long-term non-healing wounds most often develop in patients with a burdened morbid background in the form of diabetes mellitus complicated by angio- and/or neuropathy, decompensated form of venous insufficiency, in bedridden patients for a long period. Long-term non-healing wounds are a health problem that has devastating consequences for patients and leads to serious costs for health systems and society. Unresolved problems in the treatment of long-term non-healing soft tissue wounds still account for the negative impact on the economy in any country in the world, regardless of its level of development.

Keywords: *long-term non-healing wounds, unresolved problems, health care system costs*

In the literature, there is statistical information according to which more than a billion people around the world suffer from long-term non-healing soft tissue wounds. This colossal number of patients requiring long-term and close attention of medical personnel, with periodic shifts of outpatient and inpatient treatment, naturally causes huge financial costs. For example, in a study by a group of specialists from the United States led by S.R. Nussbaum [1], it was revealed that almost 15% of Medicare owners (8.2 million) had at least one type of long-term non-healing wound. Surgical infection was the most common category (4.0%), followed by diabetic infections (3.4%). Total Medicare cost estimates for all types of wounds ranged from $28.1 billion to $96.8 billion, including the cost of treating the infection, with the most expensive costs being for surgical wounds ($11.7, $13.1 and $38.3 billion), followed by diabetic foot ulcers ($6.2, $6.9 and $18.7 billion). The highest point-of-care costs were for hospital outpatients ($9.9-$35.8 billion), followed by hospital inpatients ($5.0-$24.3 billion).

To identify the extent of this health problem, we analysed the systematic literature published over the past ten years in the most popular databases. The results showed that health-related quality of life was lowest for physical pathologies and, based on average scores, scores were lowest in the physical role area for both patients with long-term non-healing wounds and patients with wound-related amputations. According to M. Olsson et al. [17].

The cost burden was mainly related to amputations in patients with concomitant type 2 diabetes mellitus, where the cost of hospitalisation ranged from $12,851 to $16,267 for this patient population. Patients with long-term non-healing wounds have a poor quality of life-re-

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lated to overall health, and the costs associated with wounds are significant. This dictates the need to develop and implement treatment strategies for long-term non-healing wounds aimed at improving health-related quality of life and effectively reducing costs for this group of patients.

M. Rodrigues et al. [18] have estimated that in developed countries, the costs associated with the treatment of long-term non-healing wounds account for up to 3% of total healthcare costs. In the United States, for example, the total cost of long-term non-healing wounds is estimated to be around US$ 50 billion per year. The situation is likely to be exacerbated by low healing rates.

C.E. Fife et al. [7] In their scientific article, they reported that publicly available rates of soft tissue wound healing are significantly overestimated. In particular, data from randomised controlled trials give an average recovery rate of 40%, while the reported rate is usually above 90%.

The classification of soft tissue wounds into acute and chronic is based on the pathogenesis of their development, possible complications and processes associated with their regeneration. Acute soft tissue wounds undergo a series of molecular processes that eventually lead to the restoration of structural integrity. At the same time, wounds that do not heal for a long time cannot start rapid regeneration and are characterised by pathological processes such as continuous inflammation, constant infections and necrosis. As a rule, there are four overlapping phases in acute wound healing, namely, hemostasis, inflammation, proliferative phase, and remodelling [11].

When an acute wound appears, the very first reaction is hemostasis, which stops bleeding and prevents blood loss. During the inflammatory phase, skin damage activates a complex immune response that destroys pathogens entering the wound and prepares tissues to restore anatomical integrity. The latter occurs in the proliferative phase and includes the formation of granulation tissue, neovascularisation, and re-epithelialization. Finally, the healing of an acute wound is completed by a remodelling phase, during which the granulation tissue is replaced by a scar, and the epidermis is freed of immune cells that either die as a result of apoptosis or move to the dermis [5].

Immune cells and factors are key regulators and participants in the wound-healing process. Neutrophils and basophils are the first to react to soft tissue damage. In addition, in the studies of L. Cañedo-Dorantes et al. [2], other innate and acquired immune cells, such as macrophages, mast cells, Langerhans cells, T cells, and B cells, are involved in the pathogenesis of soft tissue injury.

A group of researchers led by M.M. Azevedo [8], having conducted several experimental experiments, proved that it is the dysregulation of the immune response in the process of wound healing that leads to the occurrence of chronic, that is, long-term non-healing wounds.

In chronic wounds, the inflammatory phase becomes very prolonged, which ultimately leads to poor and delayed healing. Persistent inflammation in such wounds is characterised by several features. In particular, there is an excessive number of pro-inflammatory macrophages, while the number of macrophages with anti-inflammatory phenotypes is small. In addition, macrophages found in long-term non-healing wounds have a limited ability to remove dead neutrophils. This leads to the formation of a highly inflammatory environment with an overabundance of inflammatory mediators, such as tumour necrosis factor-α and interleukin-1β. In turn, wound macrophages in wounds that do not heal for a long time release several matrix metalloproteinases, namely matrix metalloproteinases-2 and matrix metalloproteinases-9, which destroy the extracellular matrix and prevent the onset of the proliferative healing stage [16].

Treatment of wounds that do not heal for a long time remains a challenge, as the persistent inflammation in these wounds is very difficult to control. One of the reasons for this is the formation of bacterial biofilms on the surface and inside wounds that do not heal for a long time. Such biofilms, covering the surface of the wound, often interact with the patient's immune system. In particular, neutrophils and pro-inflammatory macrophages are activated. As a result of the stimulation of cellular immunity, there is an accumulation of inflammatory cytokines, such as tumour necrosis factor-α and interleukin-6, as well as matrix metalloproteinases directly in the wound itself. On the other hand, the unregulated immune environment in patients with a long-term non-healing wound is a favourable condition for maintaining bacterial reproduction, which in turn leads to the emergence of a vicious circle in the form of progressive biofilm growth with stimulation of a continuous inflammatory process.

In clinical practice, the phenomena of difficulty in removing such biological films, designated as "fibrin film", "demarcation surface", "dry wound", etc.

It is known that the elimination of the formation of such biological films by conservative (medication) is considered one of the most difficult tasks in the treatment

of wounds that do not heal for a long time. According to A. Omar et al. [14] Difficulties in the destruction of such wound biofilms by drugs are associated with several factors that form the basis of the pathogenetic mechanism and the pathomorphological picture of the wound itself. Among them, researchers identify such factors as the low permeability of antimicrobial agents through the biofilm of a wound that does not heal for a long time; the presence of several species of microorganisms in symbiotic living conditions, excessively rapid development of resistance of microorganisms, biofilm, long-term non-healing wound to the antibacterial drugs used, and several other problems associated with the state of microcirculation, innervation of body tissues. The rapid development of antibiotic resistance in biofilm bacteria and many other problems.

Based on the studies carried out, several basic strategies have been proposed to improve the regeneration of wounds that do not heal for a long time. Summarising this information from the literature, they can be divided into groups by the strategy of approach to solving this problem.

M.N. Kathawala et al. proposed to classify strategies to improve the regeneration of long-term non-healing wounds into biological agents, biomaterials and cell technologies [9].

Bioactive molecules that stimulate neovascularisation and re-epithelialization have shown positive results in preclinical studies. In addition, they can be combined with biomaterials, which can improve their half-life and promote controlled release. On the other hand, biomaterials can be used on their own to provide physical protection to damaged soft tissues.

Another therapeutic strategy for wound healing is cell technologies using mesenchymal stem cells derived from bone marrow, fat cells, epidermal cells, and others. Numerous studies have shown that cell therapy improves wound healing by enhancing angiogenesis and re-epithelialization.

It is important to note that the above strategies can be used for immunomodulatory purposes in the regeneration of wounds that do not heal for a long time.

As discussed above, the immune system is a key factor in the treatment of wounds, as well as in the formation of wounds that do not heal for a long time. This provides a rationale for the use of immunomodulation to improve the healing of acute and chronic wounds. To date, multiple immunomodulatory strategies have been proposed for the restoration of soft tissue wounds. These include cell strategies, molecular therapies, and biomaterial-based approaches [15].

Meanwhile, an important aspect in the pathogenesis of long-term non-healing wounds is the role of the innate and acquired immune system, which will be discussed below. The physiological process of wound healing includes four stages: hemostasis, inflammation, proliferation, and maturation. The correct and coordinated work ensures a strict staged regenerative process. However, when wounds do not go through this organised process, their healing is delayed, and this eventually leads to chronic or long-lasting wounds. Common signs of non-healing wounds are exudation, reinfection, tissue necrosis, defective re-epithelialization, decreased angiogenesis, and excessive production of reactive oxygen species [12].

In general, chronic wounds can be divided into three main categories: diabetic foot ulcers, vascular ulcers, and pressure ulcers. They are usually observed in elderly people suffering from pathological conditions such as diabetes mellitus, vascular diseases and obesity. Diabetes mellitus affects all four stages of skin damage repair. In general, diabetic ulcers are associated with a high pro-inflammatory profile caused by overexpression of inflammatory cytokines, such as tumour necrosis factor-α, and decreased production of mediators that promote healing, including interleukin-10 and TGF-β. This leads to the polarisation of macrophages towards the M1 phenotype, activation and degranulation of CD8+ T cells, which leads to tissue necrosis.

Chronic wounds are characterised by the long-term presence of populations of myeloid cells, such as macrophages, neutrophils, and monocytes, at a late stage of inflammation. In contrast, the percentage of Langerhans cells, dermal dendritic cells, and eosinophils decreases throughout the process. Mast cells are also involved in the development of wounds that do not heal for a long time. Skin mast cells are degranulated in diabetic ulcers, and inhibiting their activity accelerates wound healing. T cells are involved in maintaining the pro-inflammatory profile of wounds that do not heal for a long time. The ligand for CXCR3, which is found in Th1 cells, is highly expressed in chronic inflammation. In addition, patients with diabetic ulcers have increased levels of inflammatory T cell subtypes such as Th1, Th17, and Th22. Immune cells actively interact with non-blood-forming cells, such as keratinocytes, through the secretion of various signalling molecules. Keratinocytes make a significant contribution to the formation of wounds that do not heal for a long time, but the exact mechanism of their action is not fully understood. Dysregulation of some microRNAs, such as miR-34a/c, miR-203, miR-19a/b, and miR-20a, in keratinocytes af-

fects immune functions and leads to delayed healing of soft tissue wounds [13].

Thus, inhibiting the expression of miR-19a/b and miR-20a slowed wound healing and induced a stronger inflammatory response in mice by activating the NF-ϰB pathway, leading to overexpression of pro-inflammatory cytokines and chemokines in keratinocytes.

The process of formation of a long-term non-healing wound is also regulated epigenetically by microRNAs that control inflammatory responses through modulation of signalling pathways. Wnt/β-catenin, NF-ϰB, PI3K/Akt/mTOR, TGF-β/Smad, and vascular endothelial growth factor growth factor pathways are regulated by microRNAs during the regeneration of long-term non-healing wounds [6].

Immune and structural cells actively express and regulate cytokines, chemokines, and growth factors during the wound-healing process. For example, elevated levels of interferon-γ, vascular endothelial growth factor, and soluble vascular cell adhesion molecule-1 seen in patients with diabetic foot ulcers promote ulcer healing. However, in wounds that do not heal for a long time, the dysregulation of certain factors is disrupted, which is partly responsible for the pathogenesis of the injury. In mice deficient in the interleukin-36 receptor antagonist, delayed wound healing was observed due to overproduction of interleukin-36γ, TGF-β and CXCL1, excessive infiltration of neutrophils and macrophages, and excessive formation of granulation tissue. In addition, the chemokine receptor CCR4 negatively affects long-term non-healing wounds caused by diabetes mellitus. Diabetic mice depleted of CCR4 showed reduced expression of cytokines that promote wound healing, such as interleukin-6, interleukin-12, interleukin-1β, tumour necrosis factor-α, and interleukin-10. In a study by A.P. Sawaya et al. [3], Dysregulation of transcription factors FOXM1 and transcription transducer and activator-3 in patients with diabetic foot ulcers was revealed. FOXM1 and the signalling transducer and transcriptional activator-3 are responsible for the proliferation of macrophages and neutrophils and their recruitment into the microenvironment of the diabetic wound.

Thus, inhibition of transcription factors FOXM1 and transcription-3 signal transducer and activator in patients with diabetic foot stimulates the mechanisms of disease progression due to a defective set of immune cells.

In the scientific works of a group of scientists led by J. Dissemond [4], the presence of another factor that contributes to the delay in wound healing was proven. This factor is known as matrix metalloproteinases. During normal wound healing, cells in the injured area, such as fibroblasts, keratinocytes, and immune cells, are induced by local mediators to secrete matrix metalloproteinases. These mediators include various cytokines and growth factors involved in wound healing, such as TGF-β, vascular endothelial growth factor, epidermal growth factor, interleukins, and interferons.

Matrix metalloproteinases are usually required in small amounts and are responsible for proper epithelialisation and proliferation. However, their dysregulation leads to impaired epithelialisation and is closely related to difficult-to-heal wounds. In general, increased expression of matrix metalloproteinases-9 by activated neutrophils is associated with delayed ulcer healing in patients with diabetes mellitus. In addition, high glucose levels can stimulate the overexpression of matrix metalloproteinases-9 through activation of the ERK/AP1 signalling pathway [10].

Thus, the development of a long-term non-healing wound occurs when the immune system is unable to continue the normal repair process, resulting in a prolonged presence of neutrophils and pro-inflammatory macrophages in the damaged skin, which contributes to inflammation, tissue fibrosis, and poor vascularisation.

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UZOQ VAQT BITMAYDIGAN JAROHATLAR - ESKI MUAMMOGA YANGICHA YONDASSHUV

B.Y. Umarov

Milliy bolalar tibbiyoti markazi

ABSTRAKT

Uzoq muddatli shifo topmaydigan jarohatlar ko'pincha angio- va / yoki neyropatiya bilan asoratlangan qandli diabetda og'ir morbid fon bo'lgan bemorlarda uzoq vaqt davomida yotoq yaralar bemorlarda rivojlanadi. Uzoq muddatli bitmagan jarohatlar bemorlar uchun halokatli oqibatlarga olib keladigan va sog'liqni saqlash tizimlari va jamiyat uchun jiddiy xarajatlarga olib keladigan katta muammosidir. Uzoq muddatli tuzalmaydigan yumshoq to'qima jarohatlarini davolashda hal qilinmagan muammolar dunyoning har qanday mamlakatida, uning rivojlanish darajasidan qat'i nazar, iqtisodiyotga salbiy ta'sir ko'rsatadi.

Kalit so'zlar: uzoq muddatli davolanmagan jarohatlar, hal qilinmagan muammolar, sog'liqni saqlash tizimining xarajatlari

ДЛИТЕЛЬНО НЕЗАЖИВАЮЩИЕ РАНЫ – НОВОЕ ВИДЕНИЕ СТАРОЙ ПРОБЛЕМЫ

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АБСТРАКТ

Длительно незаживающие раны чаще всего развиваются у больных с отягощенным морбидным фоном в виде осложненного ангио- и/или нейропатией сахарного диабета, декомпенсированной формой венозной недостаточности, у прикованных к постели на длительный период тяжелых больных. Длительно незаживающие раны – это проблема со здоровьем, которая имеет разрушительные последствия для пациентов и приводит к серьезным затратам для систем здравоохранения и общества. Нерешенные проблемы в лечении длительно незаживающих ран мягких тканей все еще составляет удельный вес негативного влияния на экономику в любой стране мира независимо от уровня его развития.

Ключевые слова: длительно незаживающие раны, нерешенные проблемы, расходы системы здравоохранения