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Chronic indolent ulcers and wounds of the skin and subcutaneous tissue

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ABSTRACT

Here we provide literature review on the problem of chronic indolent ulcers and wounds of the skin and subcutaneous tissue, which burden both patients and their families, significantly worsen patients' quality of life, often cause death, and are associated with significant financial costs.

The review notes that the vast majority of chronic ulcers/wounds fall into three main categories: venous ulcers, diabetic ulcers, and decubital ulcers. The smaller fourth group is due to arterial ischemia. The data on the incidence of various categories of chronic ulcers/wounds are provided; modern concepts of their etiopathogenesis are described, including defects of vascularization and oxygen supply to wounds, reduced activity of endothelial progenitor cells, suppression of proliferation and migration of keratinocytes and fibroblasts, dysfunction of HIF1 regulatory cascade, and sharp decrease in the regenerative capacity of the tissue.

This review describes conventional treatments for chronic ulcers/wounds based on wound toilet and conservative approaches, as well as modern approaches, including treatment of chronic ulcers/wounds with negative pressure, methods using physical factors and hydrogels, biological therapy using antibodies to tumor necrosis factor alpha, growth factors, and stem cells. We substantiated the need for discovering new methods of prevention and treatment of these pathologies based on the use of cell and gene technologies.

Keywords: *chronic indolent ulcers/wounds of the skin and subcutaneous tissue, etiology, pathogenesis, therapy.*

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Chronic indolent ulcers and wounds of the skin and subcutaneous tissue represent a pressing issue for global and domestic healthcare. Most often they accompany such pathological processes as diabetes mellitus (DM) and venous insufficiency and develop in bedridden patients (bedsores).

In Russia, more than 2.5 million people suffer from chronic indolent ulcers of the lower extremities. Women and men are affected with the same frequency. In one third of cases ulcers do not heal over a long period of time; in 70% of patients, they repeatedly recur and lead to a significant deterioration of the patients' quality of life [1].

Indolent ulcers represent a heavy burden for both patients and their families; they are accompanied by pain, infection, loss of function and financial costs, and often lead to amputations or sepsis. In the US, ca. 15 billion USD is spent annually on care for patients with indolent chronic ulcers of the lower extremities [2]. Such ulcers heal after 6 months of standard treatment only in 30-75% of patients [3]. Although chronic ulcers/wounds are mostly secondary to such issues as aging of the population, obesity and diabetes, they spread as a "silent epidemic" affecting the quality of life of more than 40 million people worldwide [4].

By their etiological structure, trophic ulcers of the lower extremities may be venous and arterial, they may develop on the background and/or due to diabetic neuro- and angiopathy, hypertension (Martorell syndrome), systemic diseases (diseases of blood, metabolism, connective tissue, vasculitis), congenital malformations of the vascular system (angiodysplasia), radiation exposure, gout and antiphospholipid syndrome [5-8].

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The vast majority of chronic ulcers/wounds fall into three main categories: venous ulcers, diabetic ulcers and decubital ulcers. The smaller fourth group is caused by arterial ischemia.

Over half of all cases of chronic ulcers/wounds of the lower extremities are *venous congestive ulcers*, which complicate the course of chronic venous insufficiency in 15-18% of cases [10,11]. Pain syndrome that accompanies chronic ulcers leads to depression, increased irritability, decreased self-esteem and social activity of patients [12]. The rate of disability among patients with the varicose disease accompanied by progressive ulcers of the shins reaches 10-30%, and according to a number of authors it can be as high as 50%. At the same time, almost 10% of people develop a fatal chronic ulcer during their lifetime [13].

Arterial ulcers/wounds are less common than venous. They occur as a result of arterial insufficiency, usually caused by atherosclerosis, rarely thromboembolism or radiation injury [14]. The narrowing of the artery lumen reduces blood perfusion, leading to ischemia and hypoxia. Occlusion of lower limb arteries is defined as a disease of peripheral vessels with such risk factors as smoking, diabetes, hypertension, hypercholesterolemia [15].

Trophic ulcers are detected in 5-10% of patients with diabetes and are among the most frequent manifestations of this disease [16]. Type 2 DM pandemic is associated with the development of such complications as diabetic foot syndrome. The severity of limb lesions in DM leads to a twofold increase in the mortality of these patients relative to patients who do not develop this DM complication; the patients who underwent amputation have the most unfavorable prognosis [17]. In addition to being a major negative predictor for longevity, amputation is a costly part of healthcare expenses: if the costs of primary healing of an ulcer range from 7 to 17 thousand USD, the costs associated with the amputation of a lower limb amount to 30–60 thousand USD [18,19] . In Russia, the direct costs of amputation amount to about 1000–1200 USD [20.]

The economic burden of diabetes is rapidly increasing worldwide, due to the rising cost of medical services, aging populations and an increase in the incidence of diabetes [21–23].

It is clinically important that 85% of amputations in diabetic patients can be prevented by taking preventive measures that reduce the risk of ulcer formation, as well as by the use of the correct treatment of an ulcer that has already developed [24].

One of the major problems of modern medicine is the prevention and treatment of decubital ulcers that occur in patients in medical and preventive institutions. Decubital ulcers are common in patients with impaired mobility and sensory perception, paralyzed or unconscious, who can neither feel nor respond to the periodic need to change the position of the body. The incidence of decubital ulcers ranges from 2.7 to 29%, reaching 40-60% in patients who sustained spinal injury, 66% in patients with hip fractures and 33% in patients hospitalized into intensive care units [25]. With the development of decubital ulcers, the duration of the patient's stay in the hospital increases, as does the requirement for dressing facilities, instruments and equipment. In some cases, surgical treatment is required. An estimated cost of treatment of decubital ulcers in one patient ranges from 5 to 40 thousand USD in the United States. In the UK, the cost of caring for patients with decubital ulcers is estimated at £ 200 million per year with an annual growth of 11%. In addition to the economic costs associated with the treatment of decubital ulcers, one has to take into account the severe physical and mental sufferings experienced by the patient and his relatives. The onset of decubital ulcers is often accompanied by severe pain, depression, infectious complications (abscess, purulent arthritis, osteomyelitis, sepsis). The development of decubital ulcers is accompanied by consistently high mortality. According to various sources, the mortality in patients admitted to nursing homes with decubital ulcers ranges from 21 to 88% [25].

What is known about the pathogenesis?

Currently, chronic ulcers/wounds and trophic ulcers are considered as a single concept, since their development and formation are usually either symptoms or consequences of one or several underlying diseases [26].

Conditions for the formation of chronic ulcers/wounds include local tissue hypoxia, recurring injuries (for example, neuropathic ulcers of the feet in patients with diabetes), ischemia, chronic persistent local infection, excessive production of proteases in the wound and reduced activity of growth factors [27].

Recently, the researches have started to believe that defects in vascularization and oxygen supply to the wound, a decrease in the activity of endothelial progenitor cells, suppression of the proliferation and migration of keratinocytes and fibroblasts, and, as a result, a sharp decrease in the regenerative capacity of the tissue form the basis for pathogenesis of chronic ulcers. An important role belongs to dysfunction of the regulatory cascade of hypoxia induced factor-1 (HIF-1 is a heterodimer consisting of two subunits - HIF-1α and HIF-1β), which is the main regulator of oxygen homeostasis and mediates adaptive cellular responses to hypoxia, regulating expression of genes involved in angiogenesis, metabolic changes, proliferation, migration, and cell survival [28].

Chronic ulcers/wounds are believed to be characterized by lengthening of the inflammatory phase, cell aging and reduction of their ability to proliferate, shortage of receptors for growth factors, absence of bleeding that can trigger a cascade of normal healing processes, and high levels of proteases [29].

It has been shown that chronic ulcers/wounds often have increased content of growth factors, but their bioavailability decreased, and proinflammatory cytokines, such as IL-1α, IL-1β, IL-6 and TNF-α, disturb the balance between proteases and their inhibitors, potentiating

the inflammation. This imbalance increases the degradation of the extracellular matrix, disrupts cell migration and reduces fibroblast proliferation and collagen synthesis. Thus, multifactorial stimuli create and enhance a hostile microenvironment in which the delicate balance between proinflammatory cytokines, chemokines, proteases and their inhibitors that exist in acute wounds is disturbed [30, 31].

Symbiosis of pathogenic and saprophytic microorganisms, which leads to increased production of proteases and growth factors, destruction of the extracellular matrix, and increased tissue hypoxia plays an important role in the stagnation of the inflammatory process [26]. It has been noted that bacteria that colonize chronic wounds often form polymicrobial biofilms, while within acute wounds the incidence of such formations is minimal [32]. It has been suggested that the biofilm "controls" the inflammatory response of the host, potentiating the production of nutrients in the form of inflammatory exudate [33].

What is known about the treatment?

A number of methods for treating chronic indolent ulcers have been developed to date, but research and developments in this field are still ongoing.

Traditional methods of treating chronic ulcers/wounds are based on wound toilet and conservative approaches, including the use of compression and drug therapy with platelet disaggregants, phlebotonizing drugs, peripheral vasodilators, drugs with metabolic action, immunotropic and antibacterial agents. Surgical treatment of wounds (or debridement) is carried out if there is a large volume of necrotic tissues and fibrin. However, the healing time for ulcers with such treatment tactics remains quite long, and the application of the described methodologies often does not lead to complete healing of chronic ulcers/wounds and either provides only temporary relief or ends with amputation.

One of the modern methodologies is the therapy of chronic wounds/ulcers with negative pressure (vacuum-assisted closure therapy, negative-pressure wound therapy), which consists of controlled application of pressure below the atmospheric one in the local wound environment using a sealed wound dressing connected to a vacuum pump [34,35]. However, the doctors in the Russian Federation has not yet gained sufficient experience in the practical application of this technique.

The feasibility of using physical factors in the complex therapy of chronic ulcers has been demonstrated, in particular for low-intensity laser radiation, platelet mass and autologous platelet-rich plasma, combined methods of treatment using hyaluronic acid and zinc laser phoresis, ultrasound, photodynamic therapy, hyperbaric oxygenation [26,36– 42].

Various hydrogels are proposed for the treatment of chronic indolent ulcers, including those based on polyethylene glycol (starpeg) and heparin derivatives of glycosaminoglycan (GAG) for maximum sequestration of chemokines from the wound; gelatin-based hydrogels as a "sprayed" dressing material that can deliver cellular ineterleukin (IL-8 and MIP-3A) directly to the wound; gels containing nitric oxide (NO) [45] and growth factors (aFGF and bFGF); hydrogels that inhibit the activity of matrix metalloproteinases and myeloperoxidase, oxidative stress and bacterial contamination [43–47]. However, these are mainly experimental works on laboratory animals.

Modern methods for treatment of chronic ulcers, which have not yet received widespread use in the Russian Federation, include methods associated with the use of biological preparations, in particular infliximab, which is an antibody to the tumor necrosis factor alpha, as well as stem cells [48-51].

Despite the high cost of the therapy, the effectiveness and economic viability of using the epidermal growth factor drug in diabetic foot syndrome have been demonstrated [52-53]. However, such drugs are currently not available for sale in the Russian Federation.

The first and only FDA approved growth factor is the platelet growth factor PDGF (or becaplermin), which has been used since 1997 under the trade name Regranex for wound/ulcer healing, particularly for diabetic foot ulcers [54]. Other growth factors have been used for the treatment of various acute and chronic wounds with varying degree of success [55]. Relatively recently, an angiotensin receptor agonist, called aclarastide, has been used to treat diabetic foot ulcers; however, upon transition to phase III of clinical trials, the study was discontinued after its ineffectiveness had been established [56]. The use of other growth factors, such as bFGF and VEGF, produced ambiguous clinical results, despite promising results from *in vitro* studies in animals [57-63].

The etiology of chronic ulcers/wounds is diverse and the cellular and molecular mechanisms of their development and healing are complex and poorly understood, which prevents researchers from finding a single therapeutic approach to their treatment. A wide range of comorbidities makes it difficult to define therapeutic goals and conduct clinical trials.

Despite the developed treatment methods, there are a relatively small number of effective procedures for treatment of chronic ulcers/wounds due to insufficient data on biological mechanisms of action for the existing treatments.

The advancement of research in this area is further hindered by insufficient funding, a limitation on the use of preclinical animal models and the difficulty of assessing the final result in clinical trials (complete closure of chronic wounds) [64].

The foregoing determines the need to search for and implement into healthcare practice new approaches and methods for the treatment, diagnosis and prevention of chronic indolent ulcerative and wound skin defects, which would primarily be based on the use of advanced cellular and gene technologies.

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