Translated by E.V. Trushina

Review
https://doi.org/10.23934/2223-9022-2024-13-4-676-683

A New Look at the Processes of Edema Formation of the Recipient Wound Bed and the Possibility of Its Assessment Using Modern Instrumental Diagnostic Methods in Experiment and Clinical Practice

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ABSTRACT The complete closure of extensive wound defects is a serious problem of modern surgery. In a significant part of clinical cases, practicing surgeons have difficulties in the surgical treatment for extensive soft tissue wounds, especially those that have existed for a long time and have no tendency to heal. Split-skin grafting is the operation of choice when closing chronic wounds, as it has a number of advantages over other options for skin plastic surgery. At the same time, the percentage of split-skin graft engraftment depends on the state of the recipient bed in most cases, the degree of which is determined by such mutually influencing processes as inosculation, angio- and vasculogenesis (angiogenesis regulator), occurring simultaneously in the graft itself and the receiving wound bed. The review presents studies by domestic and foreign authors concerning new possibilities of instrumental assessment of the condition of the recipient wound bed, namely the degree of its edema. The results of scientific papers describing the relationship between the degree of swelling of the wound and the result of its plastic closure are shown. The features of modern methods of optical bioimaging are revealed when they are used in determining the amount of fluid in soft tissue wounds both in experiment and clinical practice.

Keywords: split-skin grafting, chronic wound, recipient bed, swelling of the wound bed, amount of fluid in the tissue, instrumental diagnostics
For citation Pavlenko IV, Baleev MS, Gostev VN. A New Look at the Processes of Edema Formation of the Recipient Wound Bed and the Possibility of Its Assessment Using Modern Instrumental Diagnostic Methods in Experiment and Clinical Practice. *Russian Sklifosovsky Journal of Emergency Medical Care.* 2024;13(4):676–683. https://doi.org/10.23934/2223-9022-2024-13-4-676-683 (in Russ.)
Conflict of interest Authors declare lack of the conflicts of interests
Acknowledgments, sponsorship The study had no sponsorship

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DRS — diffuse reflectance spectroscopy
MRI — magnetic resonance imaging
NIR spectroscopy — near-infrared spectroscopy
OAS — optoacoustic spectroscopy
OCT — optical coherence tomography
PET — positron emission tomography
RCT — randomized controlled trial
RS — Raman spectroscopy
THS — terahertz spectroscopy

INTRODUCTION

Extensive wound defects of the skin are one of the most common problems that surgical specialists encounter in their daily practice. The main causes of extensive wound formation are thermal and mechanical damage to the skin, necrotizing soft tissue infections, surgical interventions associated with the removal of tumors together with the area of the affected skin [1]. Some extensive wound defects tend to heal slowly, forming a separate nosological group referred to in the literature as chronic soft tissue wounds [2].

Most researchers note that successful treatment of chronic wound defects is one of the leading problems in modern surgery of wounds of the body's integumentary system [3]. It is known from world practice that countries suffer significant economic costs when providing specialized medical care to patients with chronic wounds: over £5 billion is spent annually on treating chronic wounds in the UK [4], while in the US this figure is approaching US$25 billion per year [5]. The following fact is noteworthy: in the foreseeable future, the problem of treating chronic wounds will only become more acute due to the growing number of people suffering from diabetes, atherosclerosis, and the general trend towards aging of the planet's population [6].

The **aim** of our review is to search in domestic and foreign literature for new scientific approaches to the processes of edema formation in wound defect tissues, as well as objective non-invasive methods of instrumental diagnostics of the level of edema of the recipient wound bed.

FEATURES OF VASCULARIZATION OF A FREE SKIN GRAFT IN THE EARLY POSTOPERATIVE PERIOD

Split-skin grafting is the "gold standard" in the treatment of extensive skin defects. This skin grafting technique allows for highly effective and minimally invasive reconstruction of integumentary tissues. The key link in the successful closure of a wound defect and the complete split graft engraftment is its adequate vascularization [7].

Insufficient vascularization of the skin graft creates favorable conditions for increased proliferation of microorganisms inhabiting the surface of the wound defect, development of an infectious process in the site of surgical intervention, as well as graft necrosis as a result of its hypoxia. Therefore, to achieve a satisfactory result of free skin grafting, restoration of blood flow between the graft and the wound bed is a priority.

The literature describes different views on the processes of blood flow restoration in the transplanted free graft. At the end of the 19th century, there was a theory that the viability of a free graft during the first 48–72 hours after transplantation was maintained by simple diffusion of nutrients from the recipient bed followed by "direct connection" of the graft microvessels to the wound microvessels [8]. This process was called "inosculation". Inosculation is characterized by a close interaction between the pre-formed microvascular network of the graft and the microcirculatory bed of the wound granulation tissue. Later, researchers proposed dividing the inosculation process into two components: external and internal ones [9].

The processes of internal inosculation occur in the skin graft and consist of regression of the transplanted skin area's own microvessels with their subsequent replacement by ingrowing microvessels of the recipient bed. External inosculation is characterized by the "proliferation" of graft microvessels and their reconnection to the microcirculation of the wound bed. Inosculation ensures reperfusion of the transplanted skin graft for several days, thus maintaining its viability, and is a "forced measure" due to the impossibility of rapid transplant tissue revascularization depending primarily on the capabilities of angiogenesis, the physiological rate of which averages 5 μm/h [10], which is insufficient to prevent hypoxic death of the graft's cells [11]. It was later proven that transplant revascularization is ensured not only by the processes of angiogenesis, that is, the formation of a new microvascular network as a result of the migration and proliferation of endothelial cells from previously formed microvessels, but also vasculogenesis – the formation and development of blood vessels de novo from mesodermal precursor cells [12].

Thus, in the existing scientific paradigm, a concept was developed according to which the viability of the skin graft depends on such dynamic processes as inosculation, angiogenesis and vasculogenesis. Modern researchers have established that most of the microcirculatory bed of the transplant regresses and is replaced by ingrowing microvessels from the wound bed. After internal inosculation for 48–72 hours, the graft is re-saturated with oxygen, which triggers angiogenic transformation of the preserved central microvessels in the transplanted skin area.

SWELLING OF THE RECIPIENT WOUND BED TISSUE AS ONE OF THE REASONS FOR UNSATISFACTORY RESULTS OF FREE SKIN GRAFTING

Despite the fact that free skin grafting is a technically simple procedure, the percentage of transplant engraftment is often far from ideal. The outcome of this plastic intervention largely depends on the condition of the recipient wound bed. Microangiopathy of the vessels in granulation tissue of the recipient bed, accompanied by edema of the latter, creates conditions for impaired revascularization after transplantation [13].

Considering the significant number of elements that form the pathophysiological basis of the problem of slowing down, and then a decrease in the regenerative potential of damaged integumentary tissues (uncontrolled infectious process in the wound, insufficient blood flow through the arterial bed, venous outflow disorders, damage to the lymphatic system, etc.), leading to the emergence of such a typical pathological process as hypoxia of the wound bed tissues, there are a large number of approaches to its solution.

One of these approaches, aimed at forming new scientific knowledge about the hypoxic state of tissues, is implemented by studying the mechanisms of excessive accumulation of interstitial fluid in the wound bed and periwound tissues. It is known that local edema leads to an increase in the distance between capillaries, a decrease in the number of functioning capillaries, which creates additional difficulties for the diffusion of oxygen to the end consumers - cells [14].

As early as the 5th century BC, the "father of medicine" Hippocrates suggested that treatment of long-term non-healing wound defects of the lower extremities should be carried out in parallel with complex treatment of edema in the specified anatomical areas [15]. This thesis has been repeatedly confirmed in many studies [16]. However, a reliable connection between the impact of edema fluid in the tissues of the wound bed, as well as its quantity, on the processes of free graft engraftment has not been established to date.

In modern vascular surgery and phlebology, there is such a concept as "chronic edema of the soft tissues of the lower extremities", that is, a local increase in the amount of interstitial fluid in the skin and subcutaneous fat, which is associated with chronic disease of the arteries/veins of the lower extremities, and exists for more than 3 months [17]. The causes of this condition may be lymphedema, venous insufficiency, obliterating diseases of the arteries of the lower extremities, cancer, heart failure, trophic disorders of soft tissues of various origins, and obesity.

A large research conducted by a group of scientists from France, Denmark, Great Britain, Ireland and Australia found that almost 40% of patients receiving medical care in inpatient settings of European medical institutions have chronic edema of the lower extremities. Moreover, the authors proved that the presence of chronic edema at the level of the shins often leads to the subsequent development of purulent-inflammatory complications in patients, such as phlegmon of various cellular spaces [18].

In her study, Gniadecka M. showed that patients with signs of heart failure and lymphedema in the presence of chronic edema rarely develop gross changes in the structure of the skin of the lower extremities, which, as a rule, do not lead to skin defect formation [19]. However, this fact was not confirmed in patients with fibrous lipodermatosclerosis [20].

MECHANISMS OF WOUND BED EDEMA FORMATION IN PATIENTS WITH VASCULAR DISEASES OF THE LOWER EXTREMITIES. TRADITIONAL METHODS OF EDEMA ASSESSMENT IN THIS GROUP OF PATIENTS

There are basic mechanisms for soft tissue edema formation in the lower extremities and proven scientific facts that reveal the relationship between the presence of recipient bed edema and the outcome of free graft engraftment.

Soft tissue edema formation in the lower extremities in obliterating diseases of the arteries occurs according to the following pathophysiological scenario. The accumulation of metabolic products as a result of ischemic tissue damage leads to a partial release of the liquid portion of the blood beyond the vascular cavity, and the slow blood flow in the arterioles and arterial parts of the capillaries additionally damages the capillary walls, which aggravates the release of plasma into the interstitium, increasing the volume of intercellular fluid and additionally compressing the elements of the microcirculatory chain [21]. The worsening of symptoms of edema syndrome in patients of this profile is aggravated by their forced position in bed, when, due to impaired arterial flow, patients often put their legs below the level of the bed. In a fundamental study by a research group from the Regensburg University Hospital (Germany) led by Schreml S., a connection was established between swelling of the integumentary tissues observed in obliterating diseases of the peripheral arteries and the risk of developing wound defects [22].

Researchers noted that after reconstructive interventions on the arteries of the lower extremities, postoperative edema was formed in the soft tissues [23]. The incidence of such edemas varies from 40 to 100% of clinical cases [24]. In this case, the degree of edema is usually determined by measuring the circumference of the lower extremities. The median increase in the volume of the operated limb is on average 20–26% compared to the contralateral one. The mechanisms of formation of such edemas have certain patterns. Classical works formulated the main pathophysiological factors that lead to edema formation after angioplastic interventions on the arteries of the lower extremities: hyperemia in response to surgical trauma [25], limb immobilization, increased microvascular permeability [26], inflammation associated with reperfusion [27], and impaired lymphatic and venous circulation. It is known that wound defects at the level of the lower extremities, which are often found in patients requiring surgical interventions on peripheral arteries, are difficult to treat due to the presence of edema syndrome.

The mechanisms of formation of integumentary tissue edema in diabetes mellitus are associated with the development of systemic damage to several organs and their systems. The causes of skin edema in this cohort of patients are complications of uncontrolled hyperglycemia such as diabetic nephropathy, lower extremity arterial disease, chronic heart failure, diabetic neuropathy, and diabetic microangiopathy [28]. Apelqvist J. et al. in a clinical trial involving 314 patients with diabetic foot syndrome at different stages of soft and bone tissue damage indicated a connection between the development of the chronic wound defect, the presence of edema, and the possibility of its plastic closure. According to the authors, 38% of patients in the study group with long-healing foot wounds had swelling of the lower extremities, and 58% of patients with severe swelling after unsuccessful attempts at plastic wound closure required amputation of the foot and shin at different levels [29].

Convincing data were obtained in a work by the authors' collective of the Center for Lower Extremity Ambulatory Research at the Rosalind Franklin University of Medicine and Science (USA). The scientists led by Wu S.C. suggested the possibility of using compression hosiery to relieve lower limb edema before and after plastic closure of chronic wounds caused by diabetes mellitus without negative consequences for the microcirculation system between the graft and wound defect, as well as blood circulation in the lower extremities in general. To confirm their hypothesis, the researchers conducted a randomized controlled trial (RCT) involving 80 diabetic patients with wound defects of the shin and foot, as well as edema of the lower extremities. The RCT results showed that the use of compression hosiery statistically significantly reduces the level of edema in patients of the study group, improving the results of plastic surgery [30].

The materials of a large-scale cross-sectional study performed by an international group of scientists from the Wound Healing Center (Denmark), Department of Dermatology and Cutaneous Surgery, University of Miami (USA), the Vascular Medicine Department of Montpellier University Hospital Center (France), and Nottingham University Hospitals (UK) are worthy of attention [31]. The research involved 7077 patients with chronic lower limb edema from 40 medical organizations in 9 European countries. The aim of the work was to study the prevalence of long-term non-healing wound defects and risk factors for their occurrence in patients with chronic lower limb edema. The research found that chronic soft tissue wounds were present in 12.7% of patients (n=899) with chronic edema. Of these, chronic wounds in 627 patients had mixed etiology with a predominance of arterial insufficiency signs in the anamnesis, 103 patients had wounds due to chronic venous insufficiency and lymphedema, 100 patients had bedsores, 69 patients had wounds due to diabetes, as well as after traumatic injuries and surgical interventions. Based on the results of their work, the researchers formulated the following conclusions:

— the greatest contribution to the formation of a wound defect in patients with chronic edema is made by chronic diseases of the arteries of the lower extremities;

— risk factors for wound formation are male gender, age over 85 years, underweight, limited mobility, and diabetes mellitus;

— compression therapy reliably reduces the risk of wound defects, including in patients with impaired arterial blood flow.

Edema formation in venous insufficiency occurs as follows. Changes in blood flow, namely its retrograde nature in varicose veins of the lower extremities, are accompanied by a decrease in the shear force near the endothelial wall and tangential tension of the venous wall [32], which leads to damage to endothelial cells, adhesion of leukocytes and platelets, infiltration of the venous wall by macrophages, release of proinflammatory cytokines and matrix metalloproteinases [33] contributing to the degradation of the intercellular matrix of the venous wall and the leakage of fluid from part of the blood into the interstitial space with edema formation, which subsequently becomes chronic [34].

The above mechanisms of soft tissue edema and the skin defect zone formation, the following “vicious circle” ultimately create. After the formation of a chronic edema area, processes begin in the latter that lead to a disruption of the oxygen utilization mechanism, the formation of local decompensated tissue hypoxia with subsequent development of ulceration of the integumentary tissues and a chronic wound [35]. Colonization of the surface of a long-standing soft tissue defect by multiresistant strains of microorganisms contributes to the maintenance of the inflammatory process with excessive production of interstitial fluid [20].

Traditionally, in clinical practice, edema is assessed by visual examination of the patient by a physician using a four-level or, more often, a two-level classification [36]. There are reports on quantitative assessment of lower limb edema using volumetry (by immersing the limb in a water tank and then measuring the amount of displaced water). Other described methods for assessing edema include limb circumference measurement [37], skin tonometry, as well as magnetic resonance imaging (MRI) [38], X-ray computed tomography [39], positron emission tomography (PET), and ultrasound examination [40]. Methods for measuring limb circumference and volume of displaced water are the most commonly used, however, they are of little use for quantitative assessment of fluid in a specific area of integumentary tissue [41]. Methods such as CT, MRI, PET are more reliable, but expensive.

ДОСТОИНСТВА И НЕДОСТАТКИ СОВРЕМЕННЫХ МЕТОДОВ НЕИНВАЗИВНОЙ ДИАГНОСТИКИ ОТЕКА ТКАНЕЙ РЕЦИПИЕНТНОГО РАНЕВОГО ЛОЖА

Noninvasive quantitative assessment of water content in the body's integumentary tissues is one of the current and advanced tasks in surgery of extensive wound defects. However, existing conventional methods such as MRI, multispiral computed tomography, ultrasound used in clinical practice, have a number of limitations [42].

Among modern bioimaging techniques, most researchers prefer optical methods for measuring water content in biological tissues. The authors highlight the following advantages of these methods for identifying water in tissues: the possibility to contrast a substance of a certain chemical class, high sensitivity in determining the content of the substances under study, and ease of operation of the equipment used [43]. Among the optical methods of bioimaging most frequently used in experimental practice for studying the degree of hydration of integumentary tissues are the following: optical coherence tomography (OCT), near-infrared spectroscopy (NIR), optoacoustic spectroscopy (OAS), diffuse reflectance spectroscopy (DRS), Raman spectroscopy (RS) and terahertz spectroscopy (THS). The general limitations for the listed optical bioimaging methods are as follows:

— the probing depth of the examined area of biological tissue, which, as a rule, does not exceed 0.5 mm, which may be insufficient for examining the condition of the recipient wound bed;

— the lack of universal mathematical algorithms for calculating the obtained data (amount of water), especially in the area of soft tissue wounds [44].

Gurjarpadhye A.A. et al. demonstrated the possibility of using an OCT device to assess the amount of water in pigskin in an experiment [45]. The researchers used the OCT device with an offset light source to assess changes in the thickness of pigskin and its refractive index ex vivo. In order to improve the transmission of the light signal and assess the change in water content in the skin, the authors compressed it using a special device. During the experiment, the following parameters were changed: skin deformation - 58.5%, the refractive index increased from 1.39 to 1.50, the volume fraction of water decreased from 0.66 to 0.20. However, the authors themselves note that the method they described for assessing water in the skin is purely experimental in nature and requires serious revision to be able to use it in clinical practice.

Georgios N. Stamatas demonstrated the effectiveness of NIR spectroscopy in a clinical research to construct a "water concentration map" in the studied area of human skin after modeling edema using histamine. Based on the results of the research, the authors concluded that NIR spectroscopy is a valuable non-invasive tool for studying the pathogenesis of edema in the skin, which can be used to monitor the quantitative water content of the skin in vivo, as well as to observe the effectiveness of anti-edema therapy.

A significant drawback of this method of measuring water content is the low penetrating power of near-infrared light in biological tissue, limited to 3–10 μm [46]. This condition seriously limits the possibility of a comprehensive assessment of the amount of edema fluid in the recipient bed.

Domestic researchers from the Center for Photonics and Quantum Materials at the Skolkovo Institute of Science and Technology conducted a series of experimental and clinical studies to determine the possibility of using OAS to diagnose the degree of skin hydration. The optoacoustic method for studying biological tissues is based on the detection of ultrasound signals generated by the absorbing medium (skin) after exposure to pulsed light. In their work, the authors determined the optimal wavelengths for quantitative assessment of water content in different layers of the skin. The results of the research showed that the OAS method could become a valuable quantitative tool for accurate monitoring of skin water content and find wide application in the treatment of soft tissue wound defects [47].

Yakimov B.P. et al. used the DRS method in their study to assess the water content in human skin. Measurements were taken 4 times in a group of 10 volunteers aged 19 to 25 years during a 90-minute cardio workout (before the start of physical activity, during the activity, 45 minutes after the start, and after the workout). The participants were not prohibited from drinking fluid during cardio training. Based on the results of the study, the authors concluded that possible areas of application of the DRS method in practical medicine may be as follows: assessment of the condition of patients with heart failure, monitoring of patients during infusions, and assessment of skin condition after cosmetic interventions [48]. However, no studies were found on the use of this method in clinical practice in patients with wound defects.

Another method for determining the concentration of water in the skin is RS, the essence of which is to determine the vibrational modes of molecules of a certain type, including water molecules. Choe C. et al. found that the results of using the developed method for calculating the mass fraction of water in human skin are comparable with other optical methods for studying the skin, and the RS method is applicable in medical research [49].

Of particular clinical interest is the THS method, which consists of detecting substances using electromagnetic fields that are in the frequency range from several hundred gigahertz to several terahertz. A group of researchers from the Department of Bioengineering at the University of California (USA) led by Bajwa N. conducted a study aimed at comparing the results obtained using THS and MRI for the quantitative determination of soft tissue edema in a model of superficial and deep burn wounds in rats. Based on the results of the study, the authors obtained a positive correlation between the THS and MRI data in both types of wounds. The results of THS and MRI also revealed biphasic trends consistent with the pathogenesis of burn edema [50].

CONCLUSION

Water, being the main component of the human body, participates in numerous biochemical and biophysical processes occurring in the skin. As studies by domestic and foreign scientists have shown, the result of plastic surgery of skin defects directly depends on the amount of fluid in the recipient wound bed, that is, the degree of swelling of the vulnar tissues.

The studies presented in the paper emphasize the need to research new possibilities of instrumental methods for assessing the degree of tissue edema of the wound bed and paravulnar tissues using the achievements of optical bioimaging. These studies can lead to obtaining new fundamental knowledge, the totality of which can be considered as a separate direction in wound repair surgery. The knowledge obtained can be used both for developing new methods of high-quality plastic closure of wound defects, and techniques for assessing the condition of the recipient bed, the application of which will be possible in everyday clinical practice.

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Received on 10/01/2024
Review completed on 18/07/2024
Accepted on 17/09/2024