ISSN NO: 2770-2936
Date of Publication:10-11-2023

# The Role of Collagen in The Mechanisms of Chronic Wound Healing for Diabetic Foot Syndrome

**Abdusalomov Bexzod Alisher o'g'li**
Assistant of Department General Surgery No.2, Tashkent Medical Academy

**Abstract.** The review of the world literature, is devoted to the role of collagen in the process of wound healing. The problems of epidemiology of chronic wounds and ulcers of various genesis, physiology and pathophysiology of wound healing phases are considered. The pathogenetic role of different types of collagen, as well as the mechanisms of collagen, macrophage, fibroblasts, matrix metalloproteinases and other cytokines in healing ulcers are discussed. The prospects of development and use of medical products and preparations based on collagen in the treatment of patients with chronic wounds and ulcers are shown. The results of clinical studies on the effectiveness of collagen with preserved (native) and unsaved (fractionated) structure are presented. The advantages of using native collagen in the treatment of diabetic foot syndrome are demonstrated.
**Keywords:** collagen; chronic wounds; trophic ulcer; diabetic foot syndrome.

**Target.** The increase in the number of patients with chronic wounds, especially those with a complicated course of type 2 diabetes mellitus and the unsatisfactory effectiveness of combination therapy in these patients, has confronted practicing surgeons, endocrinologists and other specialists with the task of finding more advanced and effective methods of treating these patients. Long-term and constant therapy, frequent transition to amputations form an army of disabled people excluded from productive social life, and impose additional costs on budgets at all levels. The pathophysiology of diabetic foot syndrome (DFS) includes many mutually potentiating components (neuropathies, vascular disorders, impaired immunity, infections, etc.) that close in a vicious circle [1–3]. Many works devoted to the treatment of patients with chronic wounds have formed recommended approaches, built on the principles of evidence-based medicine and accepted today by the world community (Table 1).

**Table 1**
**Recommended approaches in the treatment of patients with SDS according to the level of evidence**

| Treatment | Diabetic disease (primary) | Chronic diabetic ulcer |
|---|---|---|
| **Pressure redistribution** | Recommended (1A) | Recommended (1A) |
| **Surgical treatment of the wound** | Recommended (2A) | Recommended (2A) |
| **Antibiotics** | Aerobic treatment gram-positive bacteria (2A) | Broad systemic antibiotics action spectrum (2A) |
| **Dressings using various means** | Recommended (2A) | There is not enough evidence |

Unfortunately, even with the full range of recommended treatment methods with constant monitoring of glycemic levels and pharmacological provision of adequate perfusion, only 24–50% of patients with DFS have an ulcer that heals within 12 weeks [4–7]. The lack of an adequate understanding of the physiology of healing when creating new dressings for the treatment of chronic wounds has not yet allowed us to obtain evidence of the comparative effectiveness of the created dressings of various types in patients with long-term non-healing chronic ulcers. Thus, despite the progress achieved in healthcare, chronic ulcers, especially in diabetes mellitus, remain an extremely pressing medical and social problem, the solution of which requires an in-depth study of the patterns of development that contribute to the activation of protective physiological mechanisms, and the objectification of the most promising treatment methods.

ISSN NO: 2770-2936
Date of Publication:10-11-2023

**Terminology and epidemiology of chronic wounds**. A wound is considered to be chronic (syn.: long-term non-healing wound, trophic ulcer) after 6 weeks of its existence in the absence of signs of active healing, despite the generally accepted appropriate treatment. The most common causes of such wounds are chronic diseases of the veins of the lower extremities (venous trophic ulcer), chronic arterial insufficiency (obliterating atherosclerosis), and diabetes mellitus (DM). This also includes bedsores (decubital trophic ulcers) resulting from prolonged exposure to pressure on the supporting surface and/or disruption of innervation due to damage to the nervous system. All these pathological conditions represent a complex and extremely urgent medical and social problem. Thus, chronic venous trophic ulcers of the lower extremities occur in 1–2% of the population [8] and are the cause of the development of 50–70% of all chronic leg wounds [9]. Only half of venous trophic ulcers heal within 4 months, 20–25% do not epithelialize even within 2 years [10, 11]. In 25% of cases, the cause of leg ulcers is atherosclerotic damage to the arteries of the lower extremities with a hemodynamically significant decrease in perfusion, impaired oxygenation of the skin and soft tissues of the legs. The mentioned reasons have quite effective medical solutions, primarily surgical ones. When the main vessels are damaged, the narrowings are eliminated using modern, including intravascular, technologies. A much more serious problem, which does not have effective solutions today, is DDS - the appearance of chronic ulcers more often on supporting surfaces in patients with diabetes. The development of VDS is clinically manifested already in cases of disturbance of nerve trophism, and even more so in cases of damage to the microvascular bed due to glycation of vascular wall proteins.

The prevalence of SDS in the world is 6% [12]. Every fourth patient with diabetes mellitus bears a heavy burden of diabetes mellitus [13]; At the same time, every year SDS develops in 2–10% of patients with diabetes mellitus, about 10% of the affected lower extremities are amputated due to the development of putrefactive and gangrenous processes [14–16], which defines this pathology as highly disabling, associated with global economic losses. According to the European Diabetes Study Group (Eurodiale), within one year only high amputation is performed in 5% of patients with DBS [17, 18]. Moreover, the 5-year survival rate after amputation ranges from 30 to 70% [19]. In DDS, microvascular arteries are affected in 50–80% of cases, and the severity of this damage correlates with healing potential and determines prognosis [20, 21]. All this results in enormous economic costs. The Eurodiale study found that the average cost of treating a non-infected ulcer was €10,000, while the cost of treating an infected ulcer with associated peripheral arterial disease was €17,000 [18]. In the USA, the total cost of treatment of long-term non-healing diabetic ulcers with severe infection (combined surgical and conservative therapy and, due to its failure, amputation at the level of the leg) was estimated in 2012 at $190,000 [22].

**Wound healing process (physiological and metabolic disorders in chronic wounds)**. During the wound healing process, the phases of inflammation (exudation), proliferation/regeneration (formation of granulations) and scar reorganization (epithelialization) are distinguished. Macrophages play a key role in wound healing. They phagocytose pathogenic organisms and tissue breakdown products and stimulate the formation of granulation tissue. Fibroblasts are essential in the proliferation phase because they produce important structural elements including collagen, elastin, and extracellular matrix proteins. Wound healing depends on the characteristics of the wound itself (etiology, depth, size) and the general condition of the body. Under normal conditions, healing wounds have low levels of bacterial loads, inflammatory cytokines, proteases, and reactive oxygen species; wounds have a functionally active extracellular matrix and high mitotic activity of cells [23]. At the same time, the synthesis of granulations, collagen and the main substance of the extracellular space requires energy in the form of ATP molecules, the main part of which is produced in mitochondria in the presence of a sufficient amount of oxygen. Therefore, any disruption in the delivery of oxygen to cells leads to a several-fold decrease in the synthesis of ATP and, accordingly, collagen.

This is the main pathophysiological mechanism leading to disruption of normal tissue regeneration and the formation of chronic wounds/trophic ulcers [1, 2]. Studies conducted in different countries have shown that in diabetes mellitus collagen is glycated, therefore, despite the increased expression of type I collagen genes, the production of fully functional collagen in wounds decreases. Degraded matrix components, overactive matrix metalloproteinases (MMPs) in long-term non-healing wounds, contribute to a prolonged inflammatory response [24]. The physiology of fibroblasts also changes [25]. In response to ischemia/hypoxia, fibroblast migration and proliferation are reduced, which also contributes to a reduction in collagen production [26, 27]. That is why, along with the main methods of treatment, the use of collagen can rightfully be

ISSN NO: 2770-2936
Date of Publication:10-11-2023

considered an important auxiliary method of treatment in patients with various chronic wounds, long-term non-healing trophic ulcers and bedsores.

**Collagen.** Collagen (kolla - glue, genes - giving birth) is the most common protein in mammals, making up 25–35% of all proteins in the body, i.e. about 6% of body weight [28, 29]. This protein forms the basis of connective tissue, providing strength and elasticity to bones, tendons, skin, blood vessels and other tissues. Like any protein, especially one that carries constant loads, collagen is continuously synthesized and catabolized. It is stated that in young years the amount of newly synthesized collagen is 6 kg per year. In the second half of life, all synthesizing reactions decrease and the amount of newly formed collagen decreases by 2 times. It is important to note that about 40% of all collagen is found in the skin, which confirms the importance of its role not only in cosmetology, but especially in the process of wound healing. To date, scientists have identified more than 40 genes that together encode 28 types of collagen. They are designated by Roman numerals I–XXVIII [28, 30]. Such a pronounced diversity of collagen types is necessary to provide different physiological roles in different tissues and organs. Characteristics of the most common type I–IV collagens are presented in Table. 2.

**Table. 2.**
**The most common collagens are types I–IV**

| Type | Genes | Tissues and organs | Compound | Associated pathologies |
|---|---|---|---|---|
| **I** | COL1A1, COL1A2 | Everywhere, especially in the skin (dermis), tendons, bones, fascia, dentin, cornea | 1% hydroxylysine, 33% glycine, 13% proline; Low glycated, wide fibrils | Rheumatism, dysplasia, Marfan syndrome, syndrome Ehlers–Danlos |
| **II** | COL2A1 | Cartilage, vitreous body, cornea | ⩾1% hydroxylysine, highly glycated fibrils thinner than type I collagen | Collagenopathy, achondrogenesis, Stickler syndrome |
| **III** | COL3A1 | Skin (mostly fetus), uterus, circulatory vessels, reticular fibers hematopoietic organs | A lot of hydroxyproline, a little hydroxylysine, low glycirovan | Aortic aneurysm, dysplasia, Ehlers–Danlos syndrome |
| **IV** | COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6 | Basement membranes | Lots of hydroxylysine and hydroxyproline, little alanine; almost completely glycated | Goodpasture's syndrome |

Based on its supramolecular organization, collagen can be divided into 2 categories: fibrillar and non-fibrillar [29–32]. The main fibrillar types are collagen types I, II and III. The most common collagen in the adult human body is type I collagen, which has the greatest mechanical strength, including due to the widest fibrils. Non-fibrillar collagens can form networks of various topologies, for example collagens type IV (basal membranes), VIII (cornea, vessels), structures like “threads with beads” (VI - cartilage, vessels, skin, uterus, lungs, kidneys, XXVI and XXVIII - many tissues and organs), as well as anchor filaments (VII - skin, esophagus, cornea, chorion). Many nonfibrillar collagens are associated with the surface of collagen fibrils (IX, XII, XIV, XIX–XXII), and some of them are transmembrane proteins (XIII, XVII, XXIII, XXV). Thus, collagen fibrils are macromolecular alloys consisting of several types of collagens and associated proteins [33].

ISSN NO: 2770-2936
Date of Publication:10-11-2023

The composition of the fibrils depends on the developmental stage and tissue, so characterizing specific structures as “type I collagen fibrils” or “type II collagen fibrils” is an oversimplification. Thus, adult skin mainly contains type I collagen (80–85%); Moreover, up to 20% of the total collagen mass is made up of type III collagens (predominant in embryogenesis, but in adults it is 5–10%), V, VI, VII, XII, XIV and other types of collagens. Collagen fibrils of tendons mainly consist of collagen types I and III, cartilage - types II and XI, cornea - types I and V [29, 32]. To ensure strength and elasticity, the direction of the collagen fibers is important. Thus, in the central part of the skeletal bones (tubular, flat) collagen fibrils have a straight longitudinal direction, and in the peripheral part they have a transverse direction. Mechanical loads on tendons are provided by parallel fibers, and on cartilages - by a fibrillar network of collagen. In the dermis, collagen fibers form a network, the level of development of which is proportional to the load or pressure, so the richest network is on the skin of the heels. In healing skin, the network of collagen fibrils is characterized by a peculiar randomness.

Collagen is synthesized and secreted mainly by fibroblasts of varying degrees of maturity, cells that produce intercellular substances that ensure wound healing. Fibrillar collagens are initially synthesized as soluble precursors, procollagens [25, 34]. Procollagen molecules are converted into collagen with the participation of proteinases during or after secretion [35]. Mature collagen molecules bind to form fibrils, which is regulated by surface and extracellular proteins such as other collagens, integrins, fibronectin, etc. [33, 36–38]. It is important to emphasize that collagen is not simply a passive structural component of a molecular scaffold. The biological function of collagen is to interact with various receptors located on the surface of cells and with other proteins of the extracellular matrix. The interaction of collagen with specific cellular receptors triggers signaling events that regulate cell migration, adhesion or proliferation. There are 3 main families of collagen receptors: collagen-binding integrins, collagen-binding immune receptors, and discoidin domain receptors. The latter are kinase receptors that bind to basic fibrillar collagen types I–III and regulate cell proliferation, differentiation and matrix modulation [39–41], ensuring the healing process of wounds/ulcers.

**Medical products and preparations based on collagen**. Many scientific works convincingly show the role of collagen and drugs and medical devices derived from it in the normal stimulation of the regenerative and proliferative phases of the wound process. The main differences between collagen preparations are the degree of purification and cross-linking, the relative percentage of different types of collagen, the source and the form in which it is presented. Sources of collagen can be the skin, intestines and other organs. Once harvested, producers prepare each product using a proprietary, custom process, removing cellular components and leaving behind the natural matrix. The degree and method of purification of collagen preparations vary, having a direct impact on the preservation of the collagen structure. In some cases, the collagen structure is preserved (native collagen), in others it is not (fractional collagen). It is assumed that split collagen with a destroyed collagen matrix does not lose the properties inherent in a three-dimensional helix molecule [42]. To increase the strength of fibrillar protein, some companies use collagen cross-linking or multiple lamination techniques. Each approach has potential advantages and disadvantages.

When producing biomaterials based on native collagen, its natural structure is completely preserved; this removes cellular elements carrying specific cellular markers (melanocytes, macrophages, lymphocytes), as well as sections of blood vessels and hair follicles. This ensures low antigenicity of the products. When introduced into a wound, native collagen plays the role of an exogenous matrix that stimulates the chemotaxis of fibroblasts and macrophages, providing the basis for the directed migration of cellular components of the wound bed. As a result, the proliferation of fibroblasts and their secretory activity are activated in the implant area, ensuring the process of new vascular formation and the intensification of immune cells - lymphocytes and macrophages involved in the regulation of regeneration. As a result, native exogenous collagen is gradually absorbed and replaced by its own connective tissue. Thus, native collagen is a kind of template for the formation of one’s own tissue, which is its exceptional advantage over split collagen preparations [29, 43].

Examples of native collagen are: Integra (Integra LifeSciences Corporation, Plainsboro, New Jersey, USA) - porcine skin collagen matrix; biomaterial Collost (LLC "Biopharmaholding") - collagen of the dermis of cattle, mainly Clinical medicine. 2018; 96(2) DOI http://dx.doi.org/10.18821/0023-2149-2018-96-2-106-115 Reviews and lectures 110 collagen type I; Primatrix (TEIBiosciencesInc, Boston, MA, USA) is acellular collagen from fetal bovine dermis, primarily type III collagen. Type I collagen is the most studied. In in vitro

ISSN NO: 2770-2936
Date of Publication:10-11-2023

experiments, it helped accelerate the formation of the intercellular matrix using dermal fibroblasts [44]. Native type I collagen bound a number of proteases and inflammatory cytokines (including neutrophil elastase, MMP-2, interleukin (IL) 6, IL-8, and IL-1, superoxide anion, peroxynitrate), which are abundant in wound fluid from chronic ulcers/wounds [45, 46]. In an in vivo study of dermal microvascular endothelial cells, it caused activation of angiogenesis [47]. These studies show that topical application of type I collagen modulates the chronic wound environment, with effects occurring as early as 2 weeks of collagen application [46]. Type III collagen is a homotrimeric fibrillar collagen that predominates during the first stage of healing, providing the initial initiation of cell migration and differentiation. Studies in COL3-negative mouse models have shown that type III collagen modulates scar formation through its effects on myofibroblast migration and differentiation. The absence of collagen type III led to the destruction of the structure, and the relative deficiency led to an increase in the size of scars and faster wound closure compared to the values in normal (COL3+) mice [48]. Research results cast doubt on the high effectiveness of type III collagen in the healing of chronic wounds. At the same time, there is evidence indicating the possibility of transformation of type III collagen into type I collagen [49].

Additionally, an experimental study in porcine models using recombinant collagen type III gel showed efficacy in wound healing [50], but the gel was used as a delivery vehicle for cultured autologous skin cells (keratinocytes, fibroblasts) to promote granulation tissue formation in the wound. Fractionated collagen works as a bioactivator that uses fragments of the collagen molecule to recruit macrophages and fibroblasts, promoting wound healing. Being a pseudosubstrate for MMPs, it binds and inactivates them, suppressing the proteolysis of intercellular matrix proteins. An example of fractionated collagen is CellerateRx (Wound Care Innovations, Ft. Lauderdale, FL, USA), in which collagen fibers are cleaved to approximately 1/100 the length of intact fibers, resulting in the destruction of virtually all internal bonds and increasing the rate of integration, however, the structural advantages of collagen are lost. This material is thought to work as a bioactivator that uses collagen fragments to recruit macrophages and fibroblasts. Other examples are the so-called foamed collagens, whose manufacturers claim that the production method is based on the destruction and subsequent integration of collagen with cellulose, which preserves the classic triple helical structure of collagen, which promotes the binding of elastase, which activates the action of MMP [51, 52]. Such preparations are Prisma and Promogran (Systagenix, North Yorkshire, UK), containing about 55% collagen and 44% cellulose, and in the case of Prisma an additional 1% ionic silver bound to cellulose. Biostep and BiostepAg (Smith & Nephew, Largo, FL, USA) are also similar products.

They contain collagen, carboxymethylcellulose and sodium alginate, which facilitates cell migration and tissue regeneration. Biostep additionally contains ethylenediaminetetraacetic acid, which inhibits proteolytic enzymes in chronic wounds, thereby improving wound healing. PuracolPlus and PuracolPlusAG (Medline Industries, Mundeline, IL, USA) use pure collagen without additives. In 2013, J. Tarlton and H. Munro [53]. showed that Promogran fractionated collagen is able to reduce MMP activity in all types of chronic wounds, however, the effectiveness of the drug depends on the acidity of the environment, since any modulation of the protease is lost at neutral pH. It has been hypothesized that collagen digestion increases the rate of collagen integration, but fractionation loses the structural benefits of the collagen matrix. In addition, the positive effect of increasing the integration rate is controversial, since it necessitates frequent repeated use of the drug. In contrast, native collagen is resistant to the effects of lymphocytes and remains longer in the wound bed, performing the functions of an exogenous matrix [54]. Another weakness of fractionated and subsequently cross-linked collagen is the dense packing of structures in its composition, which prevents the penetration of fibroblasts and their interaction with the drug [55]. In 2016, C. Wiegand et al. [56] conducted a study of the physiological effect of native and fractionated collagen on the healing process of chronic wounds. It has been shown that fibroblasts seeded on a native collagen matrix demonstrate exponential growth, while very low proliferation rates are observed on a fractionated collagen preparation. When using native collagen, more effective and significant sequestration of MMP is observed. In addition, native collagen significantly stabilizes platelet-derived growth factor (PDGF-BB) in vitro.

Taking into account the results of the studies, we can think that for the treatment of trophic ulcers and long-term non-healing wounds, it is preferable to use native rather than fractionated collagen, mainly type I. The use of native collagen in diabetic foot syndrome. It has been shown that the use of native collagen preparations helps reduce the area of chronic wounds [57]. Preparations of native collagen (Collost) promote

ISSN NO: 2770-2936
Date of Publication:10-11-2023

the rapid transition of the wound process to the stage of active regeneration and reduce the contamination of the wound with microorganisms [58, 59]. In a study by S. Ivanus and B. Risman [60], by the 12th day of treatment with Collost, the degree of contamination did not exceed 105 CFU/g. The use of Collost led to a 1.8-fold reduction in the time required to prepare a wound for autodermoplasty (32.0 ± 4.6 days versus 56.8 ± 8.7 days in the comparison group) [61]. In preliminary results of a multicenter, prospective, randomized clinical trial involving 71 patients with Wagner II–III DDS, native collagen (Collost) effectively reduced the length, width, area, and volume of diabetic ulcers, accelerating the time of epithelialization [62, 63]. After 4 weeks of treatment, complete epithelization was recorded in 22.2% of patients in the main group (Collost) and 8.6% of patients in the comparison group (standard therapy). At the same time, in the main group it was possible to achieve a reduction in the wound area by 67%, and in the comparison group – by 39% relative to the indicator on the 1st day [64]. Another multicenter randomized controlled clinical trial involving 307 patients also noted a decrease in the time to complete closure of diabetic ulcers when using a native collagen preparation (Integra) [65]. The use of native collagen reduces pain in patients with chronic wounds, including complicated forms of DFS [57, 58, 66]. It is important to note that researchers note the absence of adverse effects when using native collagen preparations [57, 58, 62, 63, 67], which indicates their high safety. The cost-effectiveness of including biomaterials based on native collagen into the treatment regimen for SDS has also been demonstrated. For example, Collost has been shown to reduce the ratio of required costs to the resulting effectiveness of treatment [68]. Comparative studies of native collagen preparations and other advanced agents used for local treatment of DBS demonstrate the high relative effectiveness and safety of native collagen-based preparations.

A comparative clinical study of the use of the Collost membrane and the epidermal growth factor Eberprot-P in patients with DFS showed the benefits of collagen [69]. There were more frequent positive dynamics in the course of the wound process, a greater number of cases of complete epithelialization (complete healing or positive dynamics in 89% of patients in the Collost group and 19% of patients in the comparison group), fewer amputations (0 and 32%, respectively), as well as cases of individual intolerance when using collagen with a preserved structure (biomaterial Collost) [69]. In a comparative study of cell therapy (Apligraf) or native collagen (PriMatrix) in the treatment of diabetic (n = 40) and venous (n = g28) foot ulcers, both treatment methods were highly effective. The results of the study demonstrated that ulcers in patients treated with PriMatrix healed faster than those in patients treated with Apligraf, despite the larger wound size [55]. A patented technique developed by Russian scientists, consisting of the sequential use of conservative therapy, surgical treatment in combination with ultrasonic hydrosurgical treatment and a native collagen preparation, allowed the authors to reduce the number of organ-removing operations and complications by 15–33%, reduce the length of stay of patients in the hospital by 20% and the number of repeat visits by 13.4–18.5%, which was demonstrated in a large study involving 1195 patients [59, 70, 71].

The use of fractionated collagen in diabetic foot syndrome. R. Lobmann et al. [72], having analyzed the effects of the drug Promogran on a sample of 33 patients, noted the absence of statistically significant differences in the level of MMP mRNA, as well as IL-1β and tumor necrosis factor α compared with the levels in the control group. In addition, the level of MMPs in the wound tissue (analyzed by ELISA) also did not differ significantly between the groups, however, the level of IL-1β was increased on day 8 only in the Promogran treatment group ($p = 0.01$), and a significant decrease in the ratio was found MMP-9/TIMP-2 in the collagen group. However, this group showed a higher healing rate [72]. Similar results were obtained by M. Motzkau et al. [73], who included 19 patients with DFS in a randomized study, 13 of whom received fractionated collagen. At 26-day follow-up, no differences in the expression of MMP mRNA, tumor necrosis factor α and other MMPs in wound tissue were shown. At the same time, the authors' statement of a statistically significant reduction in wound area in the collagen group ($p = 0.003$) is more than doubtful, given the size of the groups. It is possible to increase the effectiveness of fractionated collagen preparations. Thus, D. Kakagia et al. [74] showed that the effectiveness of the isolated use of the drug Promogran is lower than when it is combined with growth factors. The largest study devoted to studying the effectiveness of fractionated collagen in DFS is the work of A. Veves et al. [75], in which a sample of 276 patients aged 23 to 85 years were randomized into 2 groups: the Promogrann group (n = 138) and the comparison group - wet gauze (n = 138). After 12 weeks of treatment, 37% of patients in the Promogrann group experienced complete wound closure (in the comparison group, 28%, $p = 0.12$). This difference turned out to be more pronounced

ISSN NO: 2770-2936
Date of Publication:10-11-2023

for ulcers “younger” than 6 months (45 and 33%, respectively, p = 0.056), but it was not statistically significant. Thus, a large multicenter study failed to demonstrate significant efficacy of fractionated collagen in the treatment of patients with DBS. Thus, analysis of the results of using fractionated collagen preparations did not reveal clear advantages of their use in patients with DFS compared to the results when using native collagen preparations. Conclusion Treatment of chronic wounds is a continuously evolving field. Problems of excess mechanical forces, infection, inflammation, decreased production of growth factors and, of course, lack of collagen will affect the results of treatment. Numerous studies have shown that collagen preparations are bioactivators and promote their own tissue regeneration by integrating into the surrounding natural tissues. Their main advantages are regulation of the biochemical environment of the wound, stimulation of chemotaxis and angiogenesis. They have the properties of a thin layer of natural skin, but are devoid of the disadvantages inherent in foreign cellular elements that contribute to skin graft rejection. At the same time, not all collagen-based preparations and products are the same. They differ in composition and degree of preservation of the natural matrix. Native (unsplit) collagen serves as a matrix for the directed migration of macrophages and fibroblasts into the wound bed, and activates chemotaxis, proliferation and secretory activity of cellular elements.

**Conclusion.** Dissolving during the healing process, it is replaced by the recipient’s own connective tissue. Native collagen preparations modulate the activity of proteases and stimulate the expression of native collagen. Unlike native collagen, fractionated (split) collagen interacts less actively with fibroblasts due to the dense packaging of the components and, accordingly, has a less pronounced effect on the rate of their migration and proliferation, however, the effectiveness of the drugs depends on the acidity of the medium, decreasing at a neutral pH value. The advantages of the physiological action of native collagen preparations are confirmed by its clinical effectiveness. Native collagen preparations help accelerate the transition of the wound process to the regeneration stage, reduce the time of epithelization of chronic wounds, help reduce the area of chronic wounds, reduce the level of bacterial contamination, eliminate pain and reduce the frequency of relapses. When using native collagen preparations, there is a decrease in the ratio of required costs and the resulting effectiveness of treatment. Thus, the use of native collagen preparations is a very promising direction in the treatment of chronic ulcers and wounds, including diabetic foot syndrome, which can increase the effectiveness of treatment and reduce the economic costs of managing these patients. Conflict of interest. The authors declare no conflict of interest. Financing. The study had no sponsorship.

**References:**

1. Alisher o‘g‘li, A. B., & Rafiqovich, Z. A. (2023). QANDLI DIABET ASORATLARIDA JIGAR PATOMORFOLOGIYASINI KOMPLEKS DAVOLASH. *Journal of Universal Science Research*, *1*(4), 42-49.
2. Yusufjanovich, E. U., & Rafiqovich, Z. A. (2023). EVALUATION OF THE LIPID PEROXIDASE INDEX IN DIABETIC COMPLICATIONS. *Conferencea*, 68-73.
3. Ergashev, U. Y., Mominov, A. T., Malikov, N. M., Yakubov, D. R., & Abdusalomov, B. A. (2023). MODERN APPROACH TO COMPLEX TREATMENT OF DIABETIC FOOT ULCERS.(LITERATURE REVIEW).
4. Ogli, A. B. A., & Rafiqovich, Z. A. (2023). THE MECHANISM OF ACTION OF THE GEL FORM OF COLLAGEN IN DIABETIC WOUNDS. *International Journal of Medical Sciences And Clinical Research*, *3*(03), 96-103.
5. Yusufjanovich, E. U., Mamatkulovich, M. B., Fozilovich, M. S., & Rafiqovich, Z. A. (2023). VOLUME OF OUTPATIENT AND POLYCLINIC SURGICAL CARE PROVIDED IN THE PRIMARY HEALTH CARE. *Open Access Repository*, *4*(3), 171-186.
6. Ergashev, U., & Zohirov, A. (2023). STUDYING THE EFFICACY OF MODERN SCLEROTHERAPY IN VASCULAR SURGERY. *Journal of Academic Research and Trends in Educational Sciences*, *2*(1), 211-217.
7. Моминов, А. Т., Маликов, Н. М., Якубов, Д. Р., & Абдусаломов, Б. А. (2022). Проблемы обезболивания в амбулаторной хирургии. *European Journal of Interdisciplinary Research and Development*, *10*, 81-89.

ISSN NO: 2770-2936
Date of Publication:10-11-2023

8. Ergashev, U. Y., et al. "Efficiency of Percutaneous Minimally Invasive Technologies in the Treatment of Patients with Obstructive Jaundice." (2022).
9. Yusufjanovich, E. U., Rafiqovich, Z. A., & Tohirovich, G. B. (2023). PRINCIPLES OF STUDYING LIVER MORPHOLOGY IN EXPERIMENTAL DIABETIC FOOT SYNDROME. *World Bulletin of Public Health*, *19*, 63-65.
10. Эргашев, У. Ю., & Зохиров, А. Р. (2023). ИЗУЧЕНИЕ ПАТОМОРФОЛОГИИ ПЕЧЕНИ ПРИ ЭКСПЕРИМЕНТАЛЬНОМ СИНДРОМЕ ДИАБЕТИЧЕСКОЙ СТОПЫ. *European Journal of Interdisciplinary Research and Development*, *12*, 27-31.
11. Yusufjanovich, E. U., Irisbaevich, M. G., Rafiqovich, Z. A., & Irsaliyevich, E. K. (2023). EVALUATION OF EFFECTIVENESS OF SPLENECTOMY IN CHRONIC LEUKEMIAS. *World Bulletin of Public Health*, *19*, 79-83.
12. Эргашев, У. Ю., & Зохиров, А. Р. (2023). ОЦЕНКА ЭФФЕКТИВНОСТИ МАЛОИНВАЗИВНЫХ ОПЕРАЦИЙ ПРИ МЕХАНИЧЕСКОЙ ЖЕЛТУХЕ И ПРИМЕНЕНИЕ АЛГОРИТМА. *European Journal of Interdisciplinary Research and Development*, *12*, 6-16.
13. Ergashev, Ulugbek Yusufjonovich, Adkhamjon Rafiqovich Zokhirov, and Khojimurod Irsaliyecvich Ernazarov. "THE STUDY OF PATHOMORPHOLOGICAL DIAGNOSIS OF VITAL ORGANS AFTER MODERN TREATMENT OF DIABETIC FOOT SYNDROME." (2022).
14. Зохиров, А. Р., Абдусаломов, Б. А., & Моминов, А. Т. (2022). Совершенствование комплексного лечения с учетом патофизиологических изменений гнойно-некротических поражений нижних конечностей при сахарном диабете.
15. Yusufjanovich, E. U., & Rafiqovich, Z. A. (2023). Treatment of purulent-necrotic lesions of the lower extremities with modern drugs. *Conferencea*, 88-94.
16. Yusufjanovich, E. U., Rafiqovich, Z. A., & Irsalievich, E. K. (2023). Assessment of the Process of Epithelialization After Complex Treatment of Diabetic Foot Syndrome. *Texas Journal of Medical Science*, *16*, 19-23.
17. Rafiqovich, Z. A., Sobirjonovich, S. S., Faxriddinovich, F. F., & Ubaydullaxonovich, O. S. (2023). Experimental Treatment of Purulent-Necrotic Lesions of The Lower Extremities with New Generation Drugs. *Texas Journal of Medical Science*, *18*, 30-38.
18. Zohirov, A., Anvarjonov, M., Abdukarimov, S., & Rahmonov, S. (2023). EVALUATION OF THE EFFICACY OF SCLEROTHERAPY IN VENOUS PATHOLOGY. *Journal of Academic Research and Trends in Educational Sciences*, *2*(1), 185-190.
19. Rafiqovich, Z. A., & Rustamovich, T. S. (2023). A Modern Approach to the Study and Analysis of Biochemical Parameters in Diabetic Foot Syndrome. *Texas Journal of Medical Science*, *19*, 39-47.
20. Rafiqovich, Z. A., & Ogli, O. Q. A. (2023). PRINCIPLES OF SURGICAL TREATMENT OF TRACHEAL STENOSIS. *International Journal of Medical Sciences And Clinical Research*, *3*(03), 104-110.
21. Ergashev, U., & Zohirov, A. (2023). COURSE AND PRINCIPLES OF TREATMENT OF ACUTE APPENDICITIS IN PREGNANCY. *Journal of Academic Research and Trends in Educational Sciences*, *2*(1), 218-225.
22. Атаходжаева, Ф. А., Сохибова, Г. К., Эргашев, У. Ю., & Зохиров, А. Р. (2023, February). ВЛИЯНИЯ ВИТАМИНА Д НА ТАКТИКУ ВЕДЕНИЯ ЖЕНЩИН С МИОМОЙ МАТКОЙ. In *E Conference Zone* (pp. 35-41).
23. Эрназаров, Х., Зохиров, А., Эргашев, У. Ю., & Исраилов, Р. (2022). ПАТОМОРФОЛОГИЧЕСКАЯ КАРТИНА ЖИЗНЕННО ВАЖНЫХ ОРГАНОВ ПРИ ЭКСПЕРИМЕНТАЛЬНОЙ МОДЕЛИ ДИАБЕТИЧЕСКОЙ СТОПЫ.
24. Ergashev, U. Y., Mustafakulov, G. I., Mominov, A. T., Yakubov, D. R., Zohirov, A. R., & Ernazarov, X. I. (2022). Effective of Simultaneous Surgeries in Chronic Immune Thrombocytopenia.
25. Ergashev, U. Y., Zokhirov, A. R., & Minavarkhujaev, R. R. (2023). The study of pathological physiology of indicators of endogenous intoxication in purulent-necrotic lesions of the lower extremities.
26. Ergashev, U. Y., Zokhirov, A. R., & Minavarkhujaev, R. R. (2022). Determination of changes in the lipid peroxidase index in purulent-necrotic lesions of the lower extremities.

ISSN NO: 2770-2936
Date of Publication:10-11-2023

27. Ergashev, U. Y., Mustafakulov, G. I., Muminov, A. T., Minavarkhujaev, R. R., Yakubov, D. R., Ernazarov Kh, I., & Zohirov, A. R. (2021). The role of minimally invasive technologies in the treatment of liver cavities. *Frontiers in Bioscience-Landmark*, *8*, 82-89.
28. Rafiqovich, Z. A. (2023, February). IMPROVING THE DETECTION OF MORPHOLOGICAL CHANGES IN PURULENT WOUNDS. In *E Conference Zone* (pp. 51-57).
29. Rafiqovich, Z. A. (2023). CONTROL OF INDICATORS OF ENDOTOXICOSIS IN DIABETIC FOOT SYNDROME. *Conferencea*, 83-90.
30. 46. Rafiqovich, Z. A. (2023). STUDY OF THE EFFECT OF LIPID PEROXIDASE ANALYSIS ON THE BODY IN DIABETIC FOOT SYNDROME. *Conferencea*, 76-82.
31. Rafiqovich, Z. A. (2023). MONITORING OF THE REGENERATION PROCESS IN PURULENT-NECROTIC PROCESSES OF THE LOWER EXTREMITIES. *Conferencea*, 189-194.
32. Rafiqovich, Z. A. (2023). OBSERVATION OF BIOCHEMICAL RESULTS IN EXPERIMENTAL DIABETIC FOOT SYNDROME. *Conferencea*, 181-188.
33. Зохиров, А. Р. (2023). ОБОСНОВАНИЕ ПРОЦЕССОВ ЭПИТЕЛИЗАЦИИ И РЕГЕНЕРАЦИИ ПРИ ГНОЙНО-НЕКРОТИЧЕСКИХ ПРОЦЕССАХ НИЖНИХ КОНЕЧНОСТЕЙ ПРИ САХАРНОМ ДИАБЕТЕ. *Conferencea*, 174-180.