6. Gertz MA. Waldenström macroglobulinemia: 2023 update on diagnosis, risk stratification, and management. Am J Hematol 2023;98:348–58. https://doi.org/10.1002/ajh.26796.
7. Kaiser LM, Hunter ZR, Treon SP, Buske C. CXCR4 in Waldenström's Macroglobulinema: chances and challenges. Leukemia 2021;35:333–45. https://doi.org/10.1038/s41375-020-01102-3.
8. McMaster ML. The epidemiology of Waldenström macroglobulinemia. Semin Hematol 2023;60:65–72. https://doi.org/10.1053/j.seminhematol.2023.03.008.
9. Pratt G, El-Sharkawi D, Kothari J, D'Sa S, Auer R, McCarthy H, Krishna R, et al. Diagnosis and management of Waldenström macroglobulinaemia − A British Society for Haematology guideline. Br J Haematol 2022;197:171–87. https://doi.org/10.1111/bjh.18036.
10. Ravi G, Kapoor P. Current approach to Waldenström Macroglobulinemia. Cancer Treat Res Commun 2022;31:100527. https://doi.org/10.1016/j.ctarc.2022.100527.
11. Seon BK, Okazaki M, Duzen J, Matsuno F, Goey AKL, Maguire O. Identification of unique molecular heterogeneity of human CD79, the signaling component of the human B cell antigen receptor (BCR), and synergistic potentiation of the CD79-targeted therapy of B cell tumors by co-targeting of CD79a and CD79b. Leuk Res 2024;136:107436. https://doi.org/10.1016/j.leukres.2024.107436.

Стаття надійшла 21.06.2024 р.

DOI 10.26724/2079-8334-2025-2-92-265-270
UDC 617.58-002.44-02-089:616.147.3 005.6-06-089

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EFFECTS OF AUTOLOGOUS PLASMINOGEN ON ANGIOSTATIN LEVELS AND MATRIX METALLOPROTEINASE ACTIVITY IN THE HEALING OF A CHRONIC VENOUS SKIN ULCER

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This clinical case report describes the application of autologous plasminogen to a chronic venous skin ulcer of six years' duration and its effects on wound healing, proteinase activity, and angiogenesis regulation in the affected tissue. Plasminogen was isolated from the patient's blood plasma and applied locally every two days for twenty days. Wound size was tracked through planimetric analysis, while levels of protein markers in skin biopsies were assessed using immunoblot analysis and zymography assay. By the twenty-fourth day, the ulcer area has reduced significantly, and this improvement was accompanied by a marked decline in both angiogenesis inhibitors and enzymes associated with tissue degradation. These findings suggest that the normalization of molecular processes induced by plasminogen plays a crucial role in restoring reparative functions in chronic wounds. This is the first report documenting the clinical benefits of autologous plasminogen in treating non-healing lower limb ulcers associated with venous insufficiency.

Key words: chronic wounds, venous insufficiency, plasminogen, angiostatins, matrix metalloproteinases.

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ВПЛИВ АУТОЛОГІЧНОГО ПЛАЗМІНОГЕНУ НА РІВЕНЬ АНГІОСТАТИНІВ ТА АКТИВНІСТЬ МАТРИКСНИХ МЕТАЛОПРОТЕЇНАЗ НА ЗАГОЄННЯ ХРОНІЧНОЇ ВЕНОЗНОЇ ВИРАЗКИ ШКІРИ

У представленому клінічному випадку описано застосування аутологічного плазміногену для лікування хронічної венозної виразки шкіри, що не загоювалася шість років, та його вплив на загоєння рани, активність протеаз і регуляцію ангіогенезу в пошкодженій тканині. Плазміноген було ізольовано з плазми крові пацієнта, білок застосовували місцево кожні два дні протягом двадцяти днів. Динаміка загоєння оцінювалася планіметрично, рівні маркерних протеїнів у біоптатах визначали методом імуноблотингу та зимографії. До двадцять четвертого дня площа виразки суттєво зменшилася, що супроводжувалося зниженням вмісту інгібіторів ангіогенезу та літичних ферментів, які сприяють деградації тканин. Отримані результати свідчать, що нормалізація молекулярних процесів під дією плазміногену є важливою передумовою відновлення репаративного потенціалу хронічних ран. Представлена робота є першим повідомленням про клінічну ефективність місцевого застосування аутологічного плазміногену для лікування трофічних виразок нижніх кінцівок на фоні венозної недостатності.

Ключові слова: хронічні рани, венозна недостатність, плазміноген, ангіостатини, матриксні металопротеїнази.

The work is a fragment of the research project "Usage of molecular-cells technologies in surgical treatment patients with purulent wounds", state registration No. 0123U01055.

Venous ulcers are the most common chronic lower limb ulcers, affecting 1 to 3 % of the population in industrially developed countries [9]. It has been proven that venous hypertension resulting from venous reflux (insufficiency) or occlusion is the primary mechanism of venous ulcer development. Ulcers develop as the result of a complex process that includes secondary hypertension (venous hypertension) and inflammation along the venous circulation pathway, in venous walls and valve leaflets, along with the inflammatory debris interstitial extravasation [7]. Factors, which contribute to the development of venous ulcers, include being 55 years of age or older, a history of venous insufficiency, pulmonary embolism,

fractures of the shin bones leading to superficial and deep thrombosis, and insufficient physical activity. During physical examination, venous ulcers are typically irregularly shaped and shallow with well-defined borders and are often located over bony prominences on the medial and lateral sides of the shin. Ulcers are often accompanied by other venous diseases, such as varicose veins, edema, or venous dermatitis. Chronic venous ulcers significantly reduce the quality of life. A number of patients have a history of undergoing various surgical interventions to correct superficial venous reflux. Despite this, the percentage of trophic ulcers remains high even after surgery [3].

Proteases play an active role in wound healing processes, so their proteolytic activity data can be used as biomarkers of healing. Matrix metalloproteinases (MMPs) play a crucial role in inflammatory and destructive processes in tissues, associated with the degradation of extracellular matrix components and the basement membrane. Among the numerous matrix metalloproteinases, MMP-2 (gelatinase A, EC 3.4.24.24) and MMP-9 (gelatinase B, EC 3.4.24.35) are involved in the remodelling processes of normal tissue during healing. However, excessive expression and dramatic activity of MMPs are key factors in disrupting regenerative processes in both diabetic wounds and other vascular disorders of the skin on the lower limbs. Moreover, it is believed that MMPs contribute to the non-healing of wounds by inhibiting reparative angiogenesis through the formation of AS. AS are formed in a result of a limited proteolysis of Pg by MMPs and other proteases such as plasmin and neutrophil elastase, giving various physiologically active fragments containing a certain number of Kringle (K) Pg domains [1]. AS induce apoptosis in endothelial cells and effectively suppress the proliferation and migration of endotheliocytes. Based on the paradigm of angiogenic balance, AS are considered among the primary endogenous inhibitors of vascular growth factors. They block the pro-angiogenic signaling from vascular endothelial growth factor (VEGF) and other activators of angiogenesis [2]. Current studies have identified Pg as one of the key participants in the wound healing process. Pg, a 92 kDa glycoprotein, is synthesized in the liver and circulates in the plasma (1.8–2.2 μM) as the catalytically inactive zymogen of the serine protease plasmin (Pm) (EC 3.4.21.7).

Physiologically, tissue or urokinase-type Pg activators (tPA or uPA, respectively) convert the zymogen into Pm, a protease with broad substrate specificity that is the central enzyme of the fibrinolytic system [4]. However, recent studies have highlighted the importance of Pg/Pm in processes beyond hemostasis, such as extracellular matrix (ECM) remodelling, cell migration and apoptosis, inflammation, and angiogenesis [3]. During the physiological process of wound healing, Pg regulates both the initiation and resolution of the inflammation phase and participates in tissue remodelling, in addition to providing fibrin clearance [6]. We have recently shown that topical application of autologous plasma-derived Pg in patients with 2 type diabetes mellitus had great benefit by accelerating wound closure of lower proximity chronic ulcers. Though, if Pg topical application could provide therapeutic effect in the treatment of non-diabetic chronic venous wounds had yet to be examined.

The purpose of the study was to evaluate the impact of the local application of autologous Pg for the treatment of chronic venous ulcer, as well as the effect of Pg on the molecular mechanisms of angiogenesis and the activity of tissue proteases.

Materials and methods. Patient Data. The female patient with a trophic ulcer on the lower limb due to chronic venous insufficiency, caused by thrombophlebitis of the superficial veins of the right lower limb (CVI C6 according to the CEAP classification) (Table 1), provided written consent to participate in the study and for the publication of the results. All protocols and procedures of this study were reviewed and approved by the local ethics committee (Commission on Bioethical Expertise and Ethics of Research at Bogomolets NMU, meeting held on 10.11.2020, protocol No. 138). The authors adhered to all ethical guidelines and principles outlined in the latest version of the Declaration of Helsinki (2013).

Table 1

Patient Medical Record

Gender	Female
Age (years)	72
Weight	89 kg
Diagnosis, duration	Chronic venous trophic ulcer on the right shin, 6 years
Blood pressure	150/90
Blood glucose concentration	5.6 mmol/L
Bacterial infection	None
Treatment	Antibiotics, changing dressings, compression therapy, surgical treatment

Purification of Pg and Treatment. Native Glu-Pg was isolated and purified from 150 mL of fresh citrated plasma from the patient using affinity chromatography on lysine-Sepharose (GE Healthcare, Amersham Biosciences, Uppsala, Sweden). Isolated Pg had a purity of 95-99 % as assessed by SDS-

PAGE. The isolated Pg showed no spontaneous proteolytic activity, as evaluated spectrophotometrically using the specific chromogenic substrate S-2251. Pg was dissolved in sterile buffered saline, adjusted to the concentration of 1.0 mg/mL, and stored at –20 ºC before use.

The patient received a local application of autologous Pg on the affected area at a dose of 1.0 mg/mL in sterile buffered saline every 2 days for 20 days (a total of 10 applications). The wound healing process was monitored dynamically.

Digital planimetry was used to measure the wound area and assess the efficacy of therapy. The wound was photographed from a distance of 30 cm with a calibration ruler or marker at the same level, placed on the skin near the wound edge. The wound area was measured using the Imito Wound 2.0.0.17 software (ImitoAG, Germany, https://imito.io/en/imitowound). The wound size was expressed in cm^2. The wound closure rate as changes in the relative size of the wound was calculated using a specific formula. The edges of the wound were traced to determine the surface area. The software calculates the area by counting the image pixels after it has been scaled using the marker placed in the same plane as the wound.

Sample Preparation. Skin biopsies (n=3, 15-20 mg) from the wound bed were obtained before the first application of Pg (day 0) and on the 18th day of the current treatment period. Each tissue sample included layers of the cutis and subcutis. Immediately after collection, all biopsies were stored at –80 ºC until analysis. Protein samples from the biopsies for Western blot analysis were prepared by grinding the tissue in liquid nitrogen and homogenizing in an ice-cold 50 mM Tris-HCl buffer (pH 7.4), containing 150 mM NaCl, 0.1 % SDS, 1.0 % Triton X-100, and supplemented with a protease/phosphatase inhibitor cocktail. Protein extracts for MMP analysis were prepared using the same lysis buffer, without enzyme inhibitors. The tissue-to-buffer ratio was 1:5 (w/v). After homogenization, the samples were sonicated for 60 seconds using a Sartorius ultrasonic disintegrator (Labsonic® M, Göttingen, Germany) and centrifuged at 16,000 g for 45 minutes at 4 ºC. The total protein concentration in each supernatant was determined spectrophotometrically [24]. The samples were diluted 1:1 in Laemmli Sample Buffer, frozen, and stored at –80 ºC until analysis.

Immunoblotting. The levels of AS were measured using Western blot analysis. Samples were electrophoretically separated in 10 % SDS-PAGE (100 μg of protein per lane). Proteins were transferred from the gel to nitrocellulose membranes with a pore size of 0.45±0.2 μm (Amersham Biosciences, Uppsala, Sweden) using electroblotting. The membranes were blocked in a 5 % defatted dry milk solution (Apex^{TM} Bioresearch Products, USA) for 90 minutes at 37 ºC. After blocking, the blots were incubated overnight at 4 °C with primary antibodies against β-actin as a loading control (Invitrogen, USA, #MA5-15739) or human AS, obtained as described previously [25]. The membranes were washed in phosphate-buffered saline containing 0.05 % Triton X-100 (PBST) and then incubated with the appropriate secondary species-specific antibodies conjugated with horseradish peroxidase (HRP) Invitrogen, USA, cat. #G-21234 anti-rabbit IgG, and cat. #31430 anti-mouse IgG) and were incubated for 90 minutes at 37 ºC. After washing in PBST, the membranes were incubated with HRP substrate and exposed on X-ray film (Konica Minolta, Japan) using enhanced chemiluminescence (ECL) technology. The signal from immunopositive protein bands was visualized, digitized, and analysed using TL120 software (TotalLab Ltd., USA). Molecular weights were determined using standard pre-stained molecular weight transblot markers (PageRuler, cat. #26616, Fermentas, Germany). Protein levels were expressed in arbitrary units (a.u.) after normalization to β-actin content.

Gelatin Zymography. The activity of MMPs was assessed using gelatine zymography in skin lesion biopsy samples to evaluate the effects of Pg treatment on diabetic wounds and compare it with such activity in biopsies from acute wounds. Gelatinolytic activity was analysed by separating proteins (50 μg per lane) in 8 % polyacrylamide gel copolymerized with gelatine (5 mg/mL), as previously described [1]. Briefly, after denaturing electrophoresis, the gels were washed twice for 30 minutes in cold 2.5 % (v/v) Triton X-100 to remove SDS, followed by five washes for 5 minutes each in cold double-distilled water. After washing, the gels were incubated overnight at 37 ºC in developing buffer (50 mM Tris-HCl, pH 7.6, containing 0.15 M NaCl, 5 mM $CaCl_2$, 1 mM $ZnCl_2$, and 0.02 % Tween-80). The zymograms were stained with 0.5 % Coomassie Brilliant Blue R-250 (Merck Millipore, Germany) dissolved in 25 % methanol and 10 % acetic acid), and then destained in the same solution without Coomassie Blue. The final gel had a uniform blue background except for the areas where MMPs had migrated to further cleave the substrate. Gelatinolytic activity was identified as clear bands against the blue-stained Coomassie background. The resulting MMP bands were visualized, digitalized, quantified densitometrically, and expressed as a.u.

Statistical Analysis. The Mann-Whitney U test was used to analyse the Western blot and zymography data to evaluate differences between mean parameters. All variables were expressed as mean±standard error of the mean (S.E.M.). A P-value of <0.05 was considered statistically significant for

all tests. All statistical calculations were performed using the software "OriginPro" (version 9.0 SR2 Pro English).

Results of the study and their discussion. The blotogram of AS levels in the trophic ulcer is presented in Fig. 1. Pg-based treatment reduced the production of anti-angiogenic regulators, specifically AS, thus shifting the angiogenic balance towards an activation state. It was shown that AS polypeptides are represented as a set of 50 and 38 kDa bands, corresponding to the K1-4.5 and K1-3 isoforms. Densitometry analysis of the blotogram revealed that Pg treatment decreased the total content of AS by 2.3 times on the 18th day compared to the baseline level ($P<0.05$).

MMPs, or gelatinases, were identified using zymography assay. MMP activity areas appeared as transparent zones on a dark blue background. In chronic, hard-to-heal wounds, MMP overexpression is well known to contribute to the pathophysiology of impaired healing of chronic venous ulcers. In the present study, we demonstrated that wound treatment using Pg reduced MMP-9 activity by 2.7 times on the 18th day of treatment compared to the baseline value ($P<0.05$). This indicates that tissue remodelling is nearly complete, and high MMP activity is no longer needed. Changes in biochemical parameters, which are accompanied with accelerating wound closure rate, are summarized in Table 2.

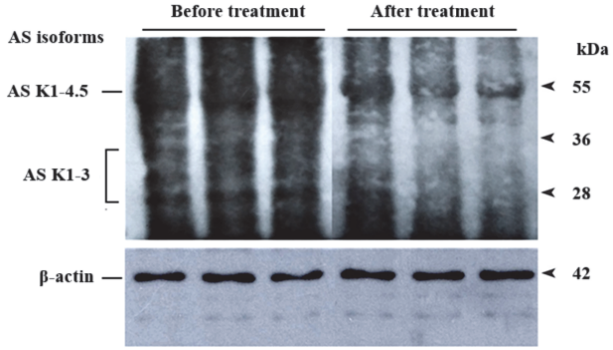

Fig. 1. Angiostatin (AS) levels in chronic wound biopsies before and after Pg treatment. Total content of AS is expressed in arbitrary units (a.u.): before treatment – 11.83±0.558 a.u.; after treatment – 5.1±1.785 a.u. ($P<0.05$, n=3).

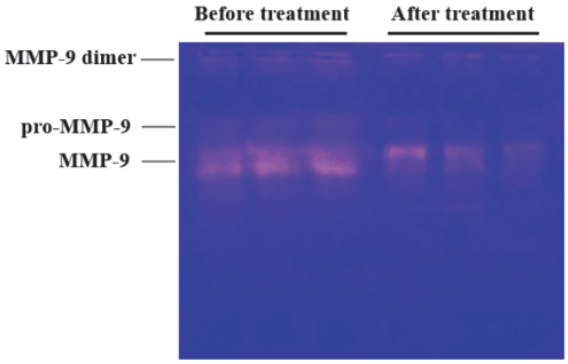

Fig. 2. Active MMP levels in chronic wound biopsies before and after Pg treatment. Total MMP activity is expressed in arbitrary units (a.u.): before treatment – 4.56±0.877 a.u.; after treatment – 1.69±0.882 a.u. ($P<0.05$, n=3).

Table 2

Results of quantitative analysis of angiostatin levels and MMP activity (in arbitrary units of optical density) and planimetry analysis of wound area before and after the application of autologous plasminogen (Pg)

Value	Before treatment	After treatment
Level of Angiostatin K1-4.5 and K1-3, a.u. (n=3)	11.83±0.558	5.1±1.785 (by 18th day)
Level of active MMP-9, a.u. (n=3)	4.56±0.877	1.69±0.882 (by 18th day)
Wound Area (in cm^2)	32.4	12.7 (by 24th day)

At the same time, the wound surface of the chronic ulcer underwent obviously seen changes during treatment with autologous Pg, as shown in Fig. 3.

Before treatment, the wound surface was smooth, covered with flaccid fine-grained granulations and a layer of fibrin, without marginal epithelialization. Starting from the 6th day of treatment, the wound surface showed signs of an inflammatory process, which manifested as the disappearance of fibrin from the wound, vigorous growth of granulation tissue, and perifocal hyperemia. After 2 days, marginal epithelialization appeared against the background of dense and "healthy" granulations. Starting from the 6th day of treatment, planimetry recorded a significant reduction in the area of the trophic ulcer. By the 24th day of treatment, the surface of the trophic ulcer was completely covered with a layer of epithelial cells and progressively reduced in size from 32.4 cm^2 to 12.7 cm^2 (nearly 60 % decrease as compared with the initial wound area).

Among many proteins involved in wound healing, Pg plays a multifaceted role in the healing processes. It has been emphasized that the physiological significance of Pg in wound healing is not limited to its conversion into Pm and extends far beyond its fibrinolytic function [10]. Binding of Pg to its cellular receptors promotes monocyte migration, macrophage responses during inflammation, angiogenesis, thus resulting in a proper wound healing. Pg is transported to the site of injury by binding to macrophages and neutrophils, where the local concentration of Pg is increased, leading to accelerated wound healing [11]. In addition to its role in activating inflammation, Pg is also crucial for subsequent stages, including the

resolution of inflammation and activation of the proliferation phase, acting as a chemoattractant for cells involved in skin wound healing [13].

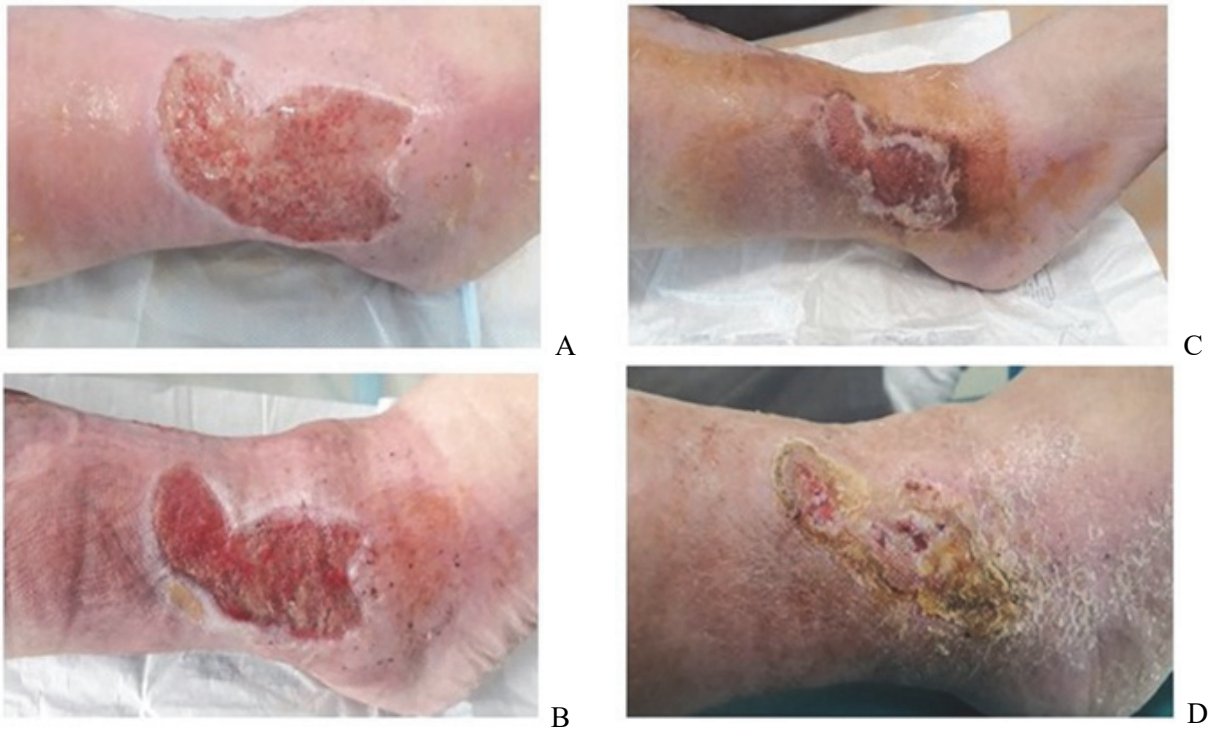

Fig. 3. Dynamical pattern of healing of a chronic venous ulcer of the lower extremity during local applications of autologous plasminogen (Pg): A – before treatment, B – 6th day of Pg-based treatment; C – 14th day of Pg-based treatment; D – 24th day of Pg-based treatment.

AS are proteolytically derived fragments of Pg/Pm that contain varying numbers of Kringle (K) domains of precursor proteins [2]. Initially, AS were studied as tumor-associated angiogenesis inhibitors that suppress tumor-induced neovascularization and limit metastasis formation by inducing apoptosis in endothelial cells and reducing their migratory activity [14]. However, it was recently shown that exudates from ischemic foot ulcers strongly inhibit endothelial cell proliferation and capillary tube formation due to the anti-angiogenic effects of AS, which are locally produced in the damaged skin tissue [12]. Moreover, AS appeared to significantly reduce ability of pro-inflammatory cells to migration toward the site of injury, thus disrupting the sequence of events during the inflammatory stage of healing process [12]. AS levels typically correlate with tissue proteolytic enzyme levels, mainly MMP activity, as they are involved in the fragmentation of Pg [15]. MMPs are known as “sculptors of tissue remodelling” playing many roles in the normal healing process by engaging in ECM remodelling and controlling the activity, release, and bioavailability of cytokines and growth factors [4]. However, uncontrolled and persistent intensified MMP expression in skin lesions contributes to the pathophysiology of impaired healing and is considered a negative prognosis for wound healing [15]. The presented results of our zymographic analysis support data from the above-cited studies, thus confirming the classical viewpoint. This indicates that the deeper the hypoxic condition develops in the skin lesion, the higher the MMP activity and AS levels would be. It can be inferred that downregulation of AS formation may lead to the improvement of pro-angiogenic signalling and recovering neovascularization at the sites of injury [13]. It could be hypothesized that Pg administration could improve impaired wound healing in patients with chronic wounds of a different origin that can be associated with functional deficiency of Pg.

Conclusion

This study presents the first clinical observation of enhanced healing of a chronic venous ulcer following treatment with locally applied plasminogen derived from the patient's blood plasma. The application of plasminogen was associated with accelerated wound closure, likely due to the activation of tissue repair pathways and the enhancement of pro-angiogenic signaling. A notable reduction in the levels of angiogenesis inhibitors and metalloproteinase activity further supports its role in normalizing the molecular environment of chronic wounds. These findings suggest that plasminogen may serve as a promising biologically active agent for treating non-healing skin lesions, especially those associated with

impaired vascular function. Further investigation is essential to understand the full therapeutic potential and mechanisms of plasminogen in regenerative medicine.

References

1. Amato B, Coretti G, Compagna R, Amato M, Buffone G, Gigliotti D, et al. Role of matrix metalloproteinases in non-healing venous ulcers. Int Wound J. 2015 Dec;12(6):641-5. doi: 10.1111/iwj.12181.
2. Baker SK, Strickland S. A critical role for plasminogen in inflammation. J Exp Med. 2020; 217 (4): e20191865. https://doi.org/10.1084/jem.201918656.
3. Bonkemeyer Millan S, Gan R, Townsend PE. Venous ulcers: diagnosis and treatment. Am Fam Physician. 2019 Sep 1;100(5):298-305.PMID: 31478635
4. Fallah M, Viklund E, Bäckman A, Brodén J, Lundskog B, Johansson M, et al. Plasminogen is a master regulator and a potential drug candidate for the healing of radiation wounds. Cell Death Dis. 2020 Mar 23;11(3):201. doi: 10.1038/s41419-020-2397-0.
5. Fu K, Zheng X, Chen Y, Wu L, Yang Z, Chen X, et al. Role of matrix metalloproteinases in diabetic foot ulcers: potential therapeutic targets. Front Pharmacol. 2022 Oct 20;13:1050630. doi: 10.3389/fphar.2022.1050630.
6. Keragala CB, Medcalf RL. Plasminogen: an enigmatic zymogen. Blood 2021; 137 (21): 2881-2889. https://doi.org/10.1182/blood.2020008951.
7. Kirketerp-Møller K, Doerfler P, Schoefmann N, Wolff-Winiski B, Niazi O, Pless V, et al. Biomarkers of skin graft healing in venous leg ulcers. Acta Derm Venereol. 2022 Jul 7;102:adv00749. doi: 10.2340/actadv.v102.201.
8. Krishnaswamy VR, Mintz D, Sagi I. Matrix metalloproteinases: the sculptors of chronic cutaneous wounds. Biochim Biophys Acta Mol Cell Res. 2017; 1864 (11 Pt B): 2220-2227. https://doi.org/10.1016/j.bbamcr.2017.08.003.
9. Lal BK. Venous ulcers of the lower extremity: definition, epidemiology, and economic and social burdens. Semin Vasc Surg. 2015;28(1):3-5. DOI: 10.1053/j.semvascsurg.2015.05.002.
10. Miles LA, Ny L, Wilczynska M, Shen Y, Ny T, Parmer RJ. Plasminogen receptors and fibrinolysis. Int J Mol Sci. 2021 Feb 8;22(4):1712. doi: 10.3390/ijms22041712.
11. Ny L, Parmer RJ, Shen Y, Holmberg S, Baik N, Bäckman A, et al. The plasminogen receptor, Plg-RKT, plays a role in inflammation and fibrinolysis during cutaneous wound healing in mice. Cell Death Dis. 2020 Dec 12;11(12):1054. doi: 10.1038/s41419-020-03230-1.
12. Perucci LO, Vago JP, Miles LA, Sousa LP. Crosstalk between the plasminogen/plasmin system and inflammation resolution. J Thromb Haemost. 2023 Oct;21(10):2666-2678. doi: 10.1016/j.jtha.2023.07.013.
13. Petrenko O, Badziukh S, Korsa V, Kolosovych I, Tykhomyrov A. Topical application of autologous plasma-derived plasminogen accelerates healing of chronic foot ulcers in type 2 diabetes patients. Int J Low Extrem Wounds. 2024 May 17:15347346241256025. doi: 10.1177/15347346241256025.
14. Raffetto JD. Pathophysiology of chronic venous disease and venous ulcers. Surg Clin North Am. 2018;98(2):337-347. DOI: 10.1016/j.suc.2017.11.002
15. Ulrich D, Lichtenegger F, Unglaub F, Smeets R, Pallua N. Effect of chronic wound exudates and MMP-2/-9 inhibitor on angiogenesis in vitro. Plast Reconstr Surg. 2005 Aug;116(2):539-45. doi: 10.1097/01.prs.0000173447.81513.7a.

Стаття надійшла 24.06.2024 р.