UDC 616.147.3-007.64
DOI https://doi.org/10.63181/ujcvs.2025.33(4).106-112

Mykyta V. Druzhkin[1,2], PhD student of the Department of Faculty Surgery and Oncology, https://orcid.org/0009-0009-6027-7750

Andrii V. Klymenko[1], MD, PhD, Professor, Head of the Department of Faculty Surgery and Oncology, https://orcid.org/0000-0002-8502-0769

[1]Zaporizhzhia State Medical and Pharmaceutical University, Zaporizhzhia, Ukraine

[2] "KRAM INVEST" LLC, Zaporizhzhia, Ukraine

Effect of Surgical Intervention on Proteolytic Activity of Blood in Chronic Venous Disease of the Lower Extremities

Abstract

Background. Chronic venous disease (CVD) with chronic venous insufficiency (CVI) involves disruption of the proteolytic balance in the venous wall driven by an imbalance between matrix metalloproteinases (MMPs) and tissue inhibitors (TIMPs), particularly MMP-2 and TIMP-4.

Aim. To assess changes in MMP-2, TIMP-4 and their ratio before and after surgical treatment of CVD and to compare the effectiveness of different surgical techniques.

Materials and Methods. A total of 139 patients with chronic venous disease (CEAP C3–C6), aged 18–75 years, were enrolled and allocated into three groups based on the extent of surgical intervention performed. All participants underwent standard clinical assessment and duplex ultrasound. Serum MMP-2 and TIMP-4 concentrations were measured before and after treatment using validated ELISA assays under identical laboratory conditions. Thirty age-matched healthy volunteers served as the control group.

Results. Before treatment, patients showed elevated MMP-2 and reduced TIMP-4 compared with controls. Combined intervention (RFA + miniphlebectomy + perforator ligation) resulted in the most significant decrease in MMP-2, increase in TIMP-4 and near-normalisation of their ratio. Less pronounced but significant changes occurred in subgroup 2A, whereas subgroup 2B and the RFA-only group retained an abnormal MMP-2/TIMP-4 ratio.

Conclusions. Combined surgical treatment most effectively restores proteolytic balance in CVD. Dynamic assessment of MMP-2, TIMP-4 and their ratio may serve as a laboratory indicator of treatment efficiency.

Keywords: *CVD, chronic venous insufficiency, matrix metalloproteinases, tissue inhibitors of metalloproteinases, surgical treatment, endovenous ablation, MMP-2, TIMP-4.*

Introduction. Chronic venous disease (CVD) of the lower extremities is a common condition that affects quality of life and imposes a significant financial burden on the healthcare system, with lower limb trophic ulcers occurring in 1-2 % of the adult population and rising to 3 % among individuals over the age of 65 [1]. Despite its high prevalence, the pathophysiological mechanism of varicose vein development remains insufficiently understood [2,3,4].

Modern hypotheses regarding the onset and progression of CVD focus on local inflammatory responses associated with persistent venous hypertension, which leads to capillary dilation and venous blood pooling in the skin microcirculation [5]. In a human study in which venous stasis was experimentally induced, increased expression of endothelin-1, a mediator of inflammation, was observed. Moreover, patients with CVD exhibit elevated blood levels of inflammatory markers such as C-reactive protein, interleukin-6, and D-dimer. In varicose veins, decreased levels of type III collagen, elastin, and laminin are observed, which reduces the contractile capacity of venous smooth muscle [6].

The aforementioned changes lead to venous wall remodelling and venous valve dysfunction [3,7]. Persistent microcirculatory alterations, chronic inflammation, local hypoxia, and oxidative stress cause endothelial dysfunction, which contributes to fibrosis, loss of venous elasticity, and the development of venous ulcers [8,9,10].

It has been established that matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) play a leading role in the pathogenesis of chronic venous disease (CVD), with their normal ratio maintaining the homeostasis of the extracellular matrix (ECM).

MMPs are a group of zinc-dependent enzymes that influence the migration, proliferation, and apoptosis of vascular smooth muscle cells, as well as endothelial and inflammatory cells, with MMP-1, MMP-2, and MMP-9 being the most extensively studied [11,12,13]. The main differences among these MMPs lie in their substrate specificity and their roles in various physiological and pathological processes. MMP-2 and MMP-9 are known to be the key enzymes involved in the proteolytic degradation of the extracellular matrix (ECM). However, MMP-9 predominates in the early clinical stages (clinical class C2 according to CEAP), whereas MMP-2 is more prevalent in the stage of chronic venous insufficiency (clinical classes C3–C6 according to CEAP). Studies have shown that patients with lipodermatosclerosis exhibit excessive expression of matrix metalloproteinases, which leads to the formation of venous ulcers and impaired healing [14,15].

However, the exact impact of different types of MMPs on the development and progression of CVD remains unclear, and the study of their activity may help to elucidate new pathogenetic mechanisms of this condition.

Tissue inhibitors of metalloproteinases (TIMPs) are specific inhibitors of matrix metalloproteinases involved in regulating the local activity of MMPs in tissues. It has been established that only TIMP-4 is significantly reduced across all clinical classes of CVD compared with healthy individuals [16]. It is the imbalance in the levels and activity of MMPs and TIMPs that triggers inflammatory processes in tissues, particularly in peripheral veins, and may potentially affect venous wall remodelling in chronic venous disease [17].

Aim. To investigate the changes in MMP-2 and TIMP-4 levels and their ratio before and after surgical intervention for chronic venous disease (CVD) of the lower extremities, as well as to compare the effectiveness of different surgical treatment techniques.

Materials and Methods. The study included patients with chronic venous disease (CVD) in the stage of chronic venous insufficiency (clinical class C3–C6 according to the CEAP classification), aged 18 to 75 years. Among them, there were 47 men (33.8 %) and 92 women (66.2 %).

Inclusion criteria: patients with CVD of clinical classes C3–C6 according to CEAP, aged from 18 to 75 years.

Exclusion criteria: patients with CVD of clinical classes C0–C2 according to CEAP; patients under 18 or over 75 years of age; patients with oncological, autoimmune diseases, diabetes mellitus, liver diseases, as well as patients who did not provide written informed consent to participate in the study.

A total of 139 patients (100 %) were examined and divided into 3 clinical groups with subgroups:

Group 1 (main group) – 32 patients (23 %) who underwent treatment using endovenous radiofrequency ablation (RFA) of the trunks of the Great Saphenous Vein (GSV) and/or Small Saphenous Vein (SSV) combined with miniphlebectomy of tributaries and perforator veins.

Group 2 (comparison group) – 64 patients:

- Subgroup 2a: 31 patients (22.3 %) who underwent endovenous RFA combined with miniphlebectomy of tributaries without perforator vein ligation;
- Subgroup 2b: 33 patients (23.7 %) who underwent endovenous RFA combined with perforator vein ligation without miniphlebectomy of tributaries.
- Group 3 (comparison group) – 43 patients (30.9 %) who were treated using endovenous radiofrequency ablation of the trunks of the GSV and/or SSV only.

The examination of patients included clinical assessment, instrumental and laboratory investigations, which were conducted at the Department of Faculty Surgery and Oncology of Zaporizhzhia State Medical and Pharmaceutical University.

Ultrasound examination of the lower limb vessels was performed using the ultrasound diagnostic system "ACUSON Redwood" (Siemens Medical Solutions USA, Inc., USA). Determination of matrix metalloproteinase type 2 (MMP-2) was carried out using enzyme-linked immunosorbent assay (ELISA) on the fully automated microplate ELISA analyser "Sirio-S" (Seac, Italy) with the "Human MMP-2" reagent kit. The level of tissue inhibitor of metalloproteinase type 4 (TIMP-4) was measured using enzyme-linked immunosorbent assay (ELISA) on the fully automated microplate ELISA analyser "Sirio-S" (Seac, Italy) with the "Human TIMP-4" reagent kit. ELISA testing was performed at the Department of Faculty Surgery and the Department of Toxicological and Inorganic Chemistry of Zaporizhzhia State Medical and Pharmaceutical University.

Statistical analysis of the obtained data was performed using the applied software packages STATISTICA 13.0, TIBCO Software Inc. (license JPZ804I382130ARCN10-J) and MICROSOFT EXCEL 2013 (license 00331-10000-00001-AA404) [18]. Quantitative variables were presented as mean ± standard deviation (M±SD). Differences between more than two groups were assessed using one-way analysis of variance (ANOVA) with subsequent post-hoc comparison based on letter-based significance grouping. The significance of differences between two independent groups was evaluated using Student's t-test (for equal variances) or Welch's t-test (for unequal variances), and intragroup changes over the course of treatment were analysed using the paired Student's t-test.

To determine the mean values of the studied indicators in healthy individuals, 30 volunteers were examined, forming the control group. The data are presented in Table 1.

The study was conducted in accordance with current bioethical standards [19], including the provisions of Article 8 of the Law of Ukraine No. 123/96-VR "On Medicinal Products", Directive 2001/20/EC of the European Parliament and of the Council [20], the Convention on Human Rights and Biomedicine [21], the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [22], the recommendations of the World Health Organization "Global Health Ethics" [23], the provisions of Good Clinical Practice (GCP)

Table 1

Indicators of healthy individuals in the control group

Indicator	Value	
	95 % CI	mean (M±SD)
MMP2, ng/ml	4,32-22,98	7,63±4,11
TIMP4, pg/mL	35,52-194,97	163,90±33,90
MMP2/TIMP4	26,56-312,02	41,01±131,73

[24], as well as Order No. 690 of the Ministry of Health of Ukraine. All patients provided written informed consent to participate in the study.

Results and Discussion. The serum levels of MMP-2 and TIMP-4 and their ratio in patients before treatment are presented in Table 2.

Analysis of the data in Table 2 demonstrates that there is no statistically significant difference in MMP-2 levels between the groups and subgroups in patients before treatment (p>0.05). However, it was found that the mean values in all groups were significantly higher than those in healthy individuals. The mean TIMP-4 values in patients before treatment also showed no statistically significant difference (p>0.05), but were lower than those in healthy individuals. The obtained results for the MMP-2 to TIMP-4 serum ratio in patients of the main and comparison groups before surgical treatment revealed no significant differences between the groups and subgroups (p>0.05). However, these values were significantly higher compared to healthy individuals.

After the administered treatment, the following mean laboratory values were recorded in patients, as presented in Table 3.

According to the data presented in Table 3, the mean MMP-2 levels after treatment in patients of the main group were significantly lower than those in patients of subgroup 2A (t=-3.48; p=0.001), subgroup 2B (t=-15.16; p<0.001) of the second comparison group, and the third comparison group (t=-11.29; p<0.001). This indicates a pronounced reduction in proteolytic activity as a result of the comprehensive surgical approach, which included RFA of the trunks of the GSV and/or SSV in combination with miniphlebectomy of tributaries and ligation of incompetent perforator veins. Such an approach effectively eliminates both central and peripheral sources of venous reflux, which evidently contributes to the reduction of MMP-2 activation.

In subgroup 2A of the 2nd comparison group, the mean MMP-2 values were significantly lower than in subgroup 2B (t=-6.13; p<0.001). Significantly lower enzyme levels were also observed in subgroup 2A compared to the 3rd comparison group (t=-4.19; p<0.001). The mean MMP-2 values in subgroup 2B and the 3rd comparison group showed no statistically significant differ-

Table 2

Serum levels of MMP-2 and TIMP-4 and their ratio in patients before treatment (M±SD)

Indicators	Groups				
	1st group (main), n=32	2nd group (comparison), n=64		3rd group (comparison), n=43	p (ANOVA)
		subgroup 2A, n=31	subgroup 2B, n=33		
MMP2, ng/ml	24,68±11,54 A	26,09±11,28 A	26,53±5,02 A	23,38±2,33 A	0,310
TIMP4, pg/mL	65,91±27,82 A	79,27±47,15 A	64,02±19,65 A	67,91±12,21 A	0,207
MMP2/ TIMP4	457,39±234,56 A	418,92±326,56 A	453,60±116,05 A	404,54±200,47 A	0,727

Note: Patient groups without common letters are statistically different from each other (p<0.05).

Table 3

Serum levels of MMP-2 and TIMP-4 and their ratio in patients after treatment (M±SD)

Indicators	Groups				
	1st group (main), n=32	2nd group (comparison), n=64		3rd group (comparison), n=43	p (ANOVA)
		subgroup 2A, n=31	subgroup 2B, n=33		
MMP2, ng/ml	7,70±2,43 A	13,05±8,20 B	23,90±5,62 C	20,68±8,49 C	<0,001
TIMP4, pg/mL	150,82±44,25 A	130,14±34,56 B	65,59±19,70 C	73,76±14,86 C	<0,001
MMP-2/ TIMP-4	60,57±40,84 A	89,95±63,48 B	396,37±113,80 C	303,94±198,71 D	<0,001

Note: Patient groups without common letters are statistically different from each other (p<0.05).

ence (t=1.98; p=0.051). Compared to the mean MMP-2 values of healthy individuals, both subgroup 2B and the 3rd comparison group had values that were significantly above normal.

When comparing the mean MMP-2 values in patients of the main group before and after treatment, a statistically significant decrease in MMP-2 level was observed (t=-7.93; p<0.001). In subgroup 2A of the 2nd comparison group, a significant reduction in this enzyme was also found over the course of treatment (t=5.50; p<0.001). The mean MMP-2 values in subgroup 2B of the 2nd comparison group before and after treatment were significantly lower after treatment (t=2.00; p=0.049). In patients of the 3rd comparison group, a significant decrease in MMP-2 levels after treatment was also noted (t=2.01; p=0.049).

TIMP-4 levels in patients after treatment were significantly higher in the main group compared to subgroups 2A (t=2.07; p=0.043) and 2B (t=10.48; p<0.001) of the 2nd comparison group, and also significantly higher than in the 3rd comparison group (t=9.46; p<0.001). Such a positive dynamic of TIMP-4 in patients of the main group who underwent combined surgical intervention indicates the activation of reparative mechanisms and a reduction in extracellular matrix destruction.

The mean enzyme levels in subgroup 2A were significantly higher than in subgroup 2B (t=9.79; p<0.001) and the 3rd comparison group (t=8.53; p<0.001). No statistically significant difference was observed between the values of subgroup 2B and the 3rd comparison group (t=-1.98; p=0.052); however, both were significantly lower than the values in healthy individuals.

When comparing the mean TIMP-4 values in patients of the main group over time, a significant increase in TIMP-4 was observed after treatment (t=-9.18; p<0.001). In subgroup 2A of the 2nd comparison group, a significant increase in enzyme levels was also noted after treatment (t=4.84; p<0.001). However, no statistically significant difference was found in TIMP-4 levels over time in patients of subgroup 2B (t=-0.32; p=0.746). In the 3rd comparison group, TIMP-4 levels significantly increased after treatment (t=-1.99; p=0.049).

The obtained results for the MMP-2/TIMP-4 ratio in patients after surgical treatment were significantly lower in the main group compared to subgroup 2A (t=-2.17; p=0.034), subgroup 2B (t=-15.92; p<0.001) of the 2nd comparison group, and the 3rd comparison group (t=-7.81; p<0.001).

Thus, combined surgical treatment provided the most pronounced restoration of the balance between proteolytic activity and inhibitory response, indicating effective suppression of venous wall degradation processes following the elimination of all anatomically significant sources of pathological venous outflow.

When comparing both subgroups of the 2nd group, the mean enzyme ratio values were significantly lower in subgroup 2A than in subgroup 2B (t=-13.35; p<0.001). The values in subgroup 2A were also significantly lower than those in the 3rd comparison group (t=-6.59; p<0.001). It was noted that in subgroup 2B, the values were significantly higher compared to the 3rd comparison group (t=-2.55; p=0.013). The enzyme ratio in the main group was significantly lower after combined treatment (t=9.42; p<0.001) and approached normal values. The MMP-2/TIMP-4 ratio in subgroup 2A significantly decreased after treatment (t=5.50; p<0.001), although it remained significantly above normal. The enzyme ratio before and after treatment in subgroup 2B was significantly lower after treatment (t=2.02; p=0.047), but remained significantly higher than in healthy individuals. The mean MMP-2/TIMP-4 value in the 3rd group was significantly lower after treatment (t=2.33; p=0.021), but still remained elevated compared to normal.

Thus, the results of the study indicate a positive dynamic in MMP-2, TIMP-4 levels and their ratio after surgical intervention in patients with chronic venous disease (CVD) in the stage of chronic venous insufficiency. The most pronounced decrease in MMP-2 proteolytic activity, increase in TIMP-4 tissue inhibitor levels, and normalization of their ratio were observed in patients who underwent combined surgical intervention-namely, endovenous RFA in combination with miniphlebectomy and ligation of incompetent perforator veins. This surgical approach provided more complete elimination of venous reflux sources and reduced inflammatory and destructive processes in the venous wall.

Our study is the first to establish a link between MMP-2, TIMP-4 levels and their ratio in chronic venous disease (CVD) and the methods of surgical treatment. For instance, in the study by Lauren E. Mueller et al., a significant reduction in MMP-2 levels was observed after successful use of radiofrequency ablation (RFA) for large thyroid nodules, compared to pre-treatment values. This was accompanied by decreased degradation of type IV collagen, preservation of the basement membrane of healthy tissues, and, accordingly, inhibition of tumour cell growth and metastasis [25].

Changes in the expression and activity of matrix metalloproteinases have been described in chronic venous disease (CVD). It has been found that the levels of MMP-1, -2, -3, and -7 are elevated, with MMP-2 activity increasing in varicose veins, and this elevation being observed across all layers of the varicose vein wall. At the same time, some studies have shown no changes or even a decrease in the levels of certain MMPs in CVD. In particular, one study reported a decrease in the levels of the active form of MMP-2 in varicose veins. This variability in data may be due to the investigation of different anatomical regions of varicose veins (e.g., hypertrophic or atrophic areas), or differences in the stage of chronic venous insufficiency [26].

The imbalance between MMPs and TIMPs is considered one of the main contributing factors in the development of CVD. Studies have shown minor changes in the levels of MMP-7 and MMP-9, as well as TIMP-1, TIMP-2, and TIMP-3; elevated levels of MMP-1, MMP-2, and MMP-

3; along with an increase in the elastic network and deposition of type I collagen, fibrillin-1, and laminin in the venous wall and skin of patients with CVD compared to control veins obtained from patients undergoing coronary artery bypass grafting. These observations suggest that the imbalance between MMPs and TIMPs disrupts the process of extracellular matrix renewal. In patients with trophic ulcers, elevated plasma levels of MMP-2, TIMP-1, and TIMP-2 have also been observed, as well as an increased MMP-2 to TIMP-2 ratio. Moreover, changes have been found not only in the venous wall but also in the skin of patients with CVD, indicating systemic connective tissue remodelling [27].

The obtained data confirm the advantage of extended combined intervention compared to isolated RFA or its combination with only one stage (miniphlebectomy or perforator vein ligation).

Thus, it is the comprehensive surgical approach that promotes optimal restoration of the balance between matrix metalloproteinases and their inhibitors, which is an important component of reparative processes in the venous wall and may potentially influence the long-term prognosis in such patients.

Conclusions

1. In patients with CVD in the stage of chronic venous insufficiency, the preoperative level of MMP-2 was markedly elevated (24.68±11.54 ng/mL) and the level of TIMP-4 was reduced (65.91±27.82 pg/mL) compared to the control group of healthy individuals (7.63±4.11 ng/mL and 163.90±33.90 pg/mL, respectively), indicating an imbalance between matrix metalloproteinases and their inhibitors toward increased proteolytic activity, which is pathogenetically significant for the progression of venous wall remodelling.
2. Combined surgical treatment, which includes endovenous radiofrequency ablation of the trunks of the great and/or small saphenous veins in combination with miniphlebectomy of tributaries and ligation of perforator veins, leads to a significant decrease in MMP-2 levels (from 24.68±11.54 to 7.70±2.43 ng/mL), an increase in TIMP-4 levels (from 65.91±27.82 to 150.82±44.25 pg/mL), and normalization of their ratio (from 457.39±234.56 to 60.57±40.84), indicating effective reduction of the impact of the pathophysiological mechanism of proteolytic imbalance on disease progression.
3. RFA procedures of the GSV and/or SSV without perforator vein ligation or without miniphlebectomy of tributaries show a significantly smaller positive dynamic in laboratory parameters, and in some cases, the MMP-2/TIMP-4 ratio remained significantly above normal after treatment, which may indicate incomplete elimination of the pathophysiological mechanisms of the disease.
4. Determining the levels of MMP-2 and TIMP-4 and their ratio in dynamics before and after surgery may serve as an indicator for assessing the effectiveness of eliminating a known pathophysiological link in the development of the inflammatory process, which directly affects venous wall remodelling in patients with CVD in the stage of chronic venous insufficiency.

Prospects for Further Research. Future studies should focus on long-term follow-up of patients undergoing different surgical approaches to evaluate the persistence of biochemical improvements and their correlation with clinical outcomes. In addition, investigating other members of the MMP and TIMP families, as well as their genetic regulation, could provide a deeper understanding of the mechanisms involved in venous wall remodelling. Further research may also explore the potential for pharmacological modulation of proteolytic activity as an adjunct to surgical treatment in chronic venous disease.

Funding and conflict of interest. The authors report no conflicts of interest related to this publication. This study received no external financial support.

Compliance with Ethical Standards. The study was conducted in accordance with the principles of the Declaration of Helsinki (75th WMA General Assembly, Helsinki, Finland, October 2024) and complied with the requirements of the Ethics Committee of Zaporizhzhia State Medical and Pharmaceutical University. The study protocol was reviewed and approved by the local ethics committee. Written informed consent was obtained from all participants prior to their inclusion in the study.

Use of Artificial Intelligence. No artificial intelligence (AI) tools or large language models were used in the collection, processing, or statistical analysis of the data. However, AI-based software tools were used for language polishing, grammar correction, and reference formatting during manuscript preparation. These tools did not influence the scientific content, interpretation of results, or conclusions.

Primary Data and Materials. The primary datasets generated and analysed during the current study are available from the corresponding author upon reasonable request. All laboratory results, anonymised patient data, and statistical tables supporting the findings of this study are securely archived at the Department of Faculty Surgery of Zaporizhzhia State Medical and Pharmaceutical University.

Acknowledgments. The authors express their sincere gratitude to the staff of the Department of Toxicological and Inorganic Chemistry at Zaporizhzhia State Medical and Pharmaceutical University for their technical assistance and support in conducting this research. Special thanks are extended to all patients who participated in the study for their trust and cooperation.

References

1. Ortega MA, Fraile-Martínez O, García-Montero C, Álvarez-Mon MA, Chaowen C, Ruiz-Grande F et al. Understanding Chronic Venous Disease: A Critical Overview of Its Pathophysiology and Medical Management. J Clin Med. 2021 Jul 22;10(15):3239. http://doi.org/10.3390/jcm10153239
2. Aslam MR, Muhammad Asif H, Ahmad K, Jabbar S, Hayee A, Sagheer MS et al. Global impact and contributing factors in varicose vein disease development. SAGE Open Medicine. 2022;10. http://doi.org/10.1177/20503121221118992
3. Yun S. Chronic Venous Disease is a Progressive Disease that Requires Early Intervention. Ann Phlebology. 2023;21:80-84. https://doi.org/10.37923/phle.2023.21.2.80
4. Azar J, Rao A, Oropallo A. Chronic venous insufficiency: a comprehensive review of management. J Wound Care. 2022;31(6):510-519. http://doi.org/10.12968/jowc.2022.31.6.510
5. Fukaya E, Klein A, Lau J, Ratchford EV. Vascular Disease Patient Information Page: Venous leg ulcers. Vascular Medicine. 2023;28(1):89-92. http://doi.org/10.1177/1358863X221118120
6. Manolache N, Stoleriu G, Brănişteanu DE, Robu S, Diaconu C, Costache DO. New pathophysiological aspects in chronic venous disease. Romanian Journal of Military Medicine. 2022(4). https://doi.org/10.55453/rjmm.2022.125.4.25
7. Krizanova O, Penesova A, Hokynkova A, Pokorna A, Samadian A, Babula P. Chronic venous insufficiency and venous leg ulcers: Aetiology, on the pathophysiology-based treatment. Int Wound J. 2024;21(2):e14405. http://doi.org/10.1111/iwj.14405
8. Shao Y, Saredy J, Yang WY, Sun Y, Lu Y, Saaoud F et al. Vascular Endothelial Cells and Innate Immunity. Arterioscler. Thromb. Vasc. Biol. 2020;40(6):138–152. https://doi.org/10.1161/atvbaha.120.314330
9. Chen PS, Chiu WT, Hsu PL, Lin SC, Peng IC, Wang CY et al. Pathophysiological implications of hypoxia in human diseases. J. Biomed. Sci. 2020;27(1):63. http://doi.org/10.1186/s12929-020-00658-7
10. Amato R, Dattilo V, Brescia C, D'Antona L, Iuliano R, Trapasso F, et al. Th17-gene expression profile in patients with chronic venous disease and venous ulcers: genetic modulations and preliminary clinical evidence. Biomolecules 2022;12(07):902. http://doi.org/10.3390/biom12070902
11. Cabral-Pacheco GA, Garza-Veloz I, Castruita-De la Rosa C, Ramirez-Acuña JM, Perez-Romero BA, Guerrero-Rodriguez JF et al. The Roles of Matrix Metalloproteinases and Their Inhibitors in Human Diseases. International Journal of Molecular Sciences. 2020;21(24):9739. https://doi.org/10.3390/ijms21249739
12. Kumar P, Khan IA, Das A, Shah H. Chronic venous disease. Part1: pathophysiology and clinical features. Clin Exp Dermatol 2022;47(7): 1228-1239. http://doi.org/10.1111/ced.15143
13. Wang F, An Y, Hao H. MicroRNA-361-5p acts as a biomarker for carotid artery stenosis and promotes vascular smooth muscle cell proliferation and migration. BMC Med Genomics. 2023;16(1):134. https://doi.org/10.1186/s12920-023-01563-2
14. Oselusi SO, Sibuyi NR, Martin DR, Meyer M, Madiehe AM. Potential matrix metalloproteinase 2 and 9 inhibitors identified from Ehretia species for the treatment of chronic wounds-Computational drug discovery approaches. Comput. Biol. Med. 2024;185:109487. http://doi.org/10.1016/j.compbiomed.2024.109487
15. Attaran RR, Carr JG. Chronic Venous Disease of the Lower Extremities: A State-of-the Art Review. J Soc Cardiovasc Angiogr Interv. 2022 Nov 26;2(1):100538. http://doi.org/10.1016/j.jscai.2022.100538
16. Wolosowicz M, Prokopiuk S, Kaminski TW. The Complex Role of Matrix Metalloproteinase-2 (MMP-2) in Health and Disease. Int J Mol Sci. 2024;25(24):13691. https://doi.org/10.3390/ijms252413691
17. Butler AE, Nandakumar M, Sathyapalan T, Brennan E, Atkin SL. Matrix Metalloproteinases, Tissue Inhibitors of Metalloproteinases, and Their Ratios in Women with Polycystic Ovary Syndrome and Healthy Controls. International Journal of Molecular Sciences. 2025;26(1):321. https://doi.org/10.3390/ijms26010321
18. Фетісов ВС. Пакет статистичного аналізу даних STATISTICA. Ніжин: НДУ ім. М. Гоголя. Fetisov VS. Statistical data analysis package STATISTICA. Nizhyn: M. Gogol NDU; 2018. 114 p.
19. Терешкевич ГТ. Основи біоетики та біобезпеки. Тернопіль: ТДМУ, 2018. 400 с. Tereshkevych GT. Fundamentals of bioethics and biosafety. Ternopil: TSMU; 2018. 400 p.
20. Directive 2001/20/EC of the European Parliament and of the Council. On the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [Internet]. 2001 Apr 4 [cited 2025 Mar 8]. Available from: http://data.europa.eu/eli/dir/2001/20/oj
21. Convention on Human Rights and Biomedicine (ETS No. 164) [Internet]. 1999 Dec 1 [cited 2025 Mar 8]. Available from: https://www.coe.int/en/web/conventions/full-list?module=treatydetail&treatynum=164
22. World Medical Association. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants [Internet]. [cited 2025 Mar 8]. Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki/
23. World Health Organization. WHO guidelines on ethical issues in public health surveillance. Geneva: World Health Organization; 2017. 66 p. [cited 2025 Sep 19] https://www.who.int/publications/i/item/who-guidelines-on-ethical-issues-in-public-health-surveillance
24. Good Clinical Practice [Internet]. [cited 2025 Mar 8]. Available from: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-clinical-practice?
25. Mueller LE, Issa PP, Hussein MH, Elshazli RM, Haidari M, Errami Y, et al. Clinical outcomes and tumor microenvironment response to radiofrequency ablation therapy: a systematic review and meta-analysis. Gland Surg. 2024;13(1):4-18. https://dx.doi.org/10.21037/gs-22-555

26. Raffetto JD, Khalil RA. Mechanisms of Lower Extremity Vein Dysfunction in Chronic Venous Disease and Implications in Management of Varicose Veins. Vessel Plus. 2021;5:36. https://dx.doi.org/10.20517/2574-1209.2021.16
27. Sak K. The low expression of matrix metalloproteinases: a key to longevity? Explor Med. 2024;5:158–66. https://doi.org/10.37349/emed.2024.00213

Вплив оперативного втручання на протеолітичну активність крові при варикозній хворобі нижніх кінцівок

Дружкін М. В.[1,2], Клименко А. В.[1]

[1]Запорізький державний медико-фармацевтичний університет, м. Запоріжжя, Україна

[2]ТОВ «КРАМ ІНВЕСТ», м. Запоріжжя, Україна

Резюме

Варикозна хвороба нижніх кінцівок (ВХНК) у стадії хронічної венозної недостатності (ХВН) супроводжується порушенням протеолітичного балансу у венозній стінці, що опосередковано дисбалансом матриксних металопротеїназ (ММР) та їх тканинних інгібіторів (TIMP). Одним із ключових учасників цього процесу є ММР-2 та TIMP-4, співвідношення яких може бути маркером деструкції екстрацелюлярного матриксу.

Мета. Дослідити зміни рівнів ММР-2, TIMP-4 та їх співвідношення до та після хірургічного втручання при ВХНК, а також порівняти ефективність різних методик оперативного лікування.

Матеріали та методи. Дослідження проведене на базі кафедри факультетської хірургії і онкології та кафедри токсикологічної та неорганічної хімії Запорізького державного медико-фармацевтичного університету. У ньому взяли участь 139 пацієнтів із ВХНК стадії ХВН (CEAP C3–C6), віком 18-75 років, які були розподілені на 3 клінічні групи залежно від обсягу хірургічного втручання: в 1-шій групі (основна, n=32) виконувалось комбіноване лікування (РЧА + мініфлебектомія + перев'язка перфорантів). 2-га група (група порівняння, n=64) розподілена на 2 підгрупи: у підгрупі 2А проводили ендовенозну РЧА разом із мініфлебектомією притоків без перев'язки перфорантних вен; у групі 2В - ендовенозну РЧА разом із перев'язкою перфорантних вен без мініфлебектомії притоків. Хворим 3-ої групи (група порівняння, n=43) виконувалась тільки РЧА. Контрольну групу складали 30 здорових добровольців. Всім хворим проведені стандартні клініко-лабораторні обстеження, дуплексне сканування вен нижніх кінцівок. Визначення рівнів ММР-2 і TIMP-4 проводили імуноферментним методом (ELISA) до та після лікування.

Результати. До лікування всі пацієнти мали достовірно вищі рівні ММР-2 і нижчі TIMP-4, ніж контрольна група. Після хірургічного втручання у 1-й групі спостерігалось найбільше зниження ММР-2, підвищення TIMP-4 та нормалізація їх співвідношення, що свідчить про ефективне гальмування деструкції венозної стінки. У підгрупі 2А зміни були менш виражені, але достовірні. У підгрупі 2Б та 3-й групі співвідношення ММР-2/TIMP-4 залишалося значуще вищим за норму, що вказує на неповну ефективність втручання.

Висновки. Найефективніше зменшення протеолітичної активності та нормалізація інгібіторного потенціалу досягається при комбінованому хірургічному лікуванні ВХНК. Визначення динаміки ММР-2, TIMP-4 та їх співвідношення може слугувати лабораторним критерієм ефективності усунення патофізіологічного компонента ХВН. Застосування лише РЧА як моновтручання або її комбінації з одним етапом лікування має менш виражений вплив на біомаркери ремоделювання венозної стінки.

Ключові слова: *ВХНК, хронічна венозна недостатність, матриксні металопротеїнази, тканинні інгібітори металопротеїназ, хірургічне лікування, ендовенозна абляція, ММР-2, TIMP-4.*

Стаття надійшла в редакцію / Received: 04.10.2025
Після доопрацювання / Revised: 27.11.2025
Прийнято до друку / Accepted: 05.12.2025