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Pathogenetic Mechanisms of Venous Wall Remodeling in Varicose Disease: A Histochemical Study

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Abstract **Background:** Varicose disease of the lower extremities is associated with structural remodeling of the venous wall and valvular apparatus, leading to venous reflux and chronic venous insufficiency. **Objective:** To investigate and refine the histochemical characteristics of venous vessels in lower extremity varicose disease. **Methods:** A qualitative histochemical study was conducted using venous wall specimens obtained during surgical treatment. Periodic acid–Schiff (PAS) reaction, Schiff reaction, and Van Gieson staining were applied. Microscopic examination was performed at magnifications of ×100–×400. **Results:** Uneven accumulation of PAS- and Schiff-positive structures, thickening and irregularity of the basement membrane, plasma imbibition, and mucoid swelling were identified. Disorganization and fragmentation of fibrous components were observed. Van Gieson staining revealed focal proliferation of fuchsinophilic fibers in all layers of the venous wall and valvular structures. Endothelial damage and thrombotic deposits were detected. **Conclusions:** The identified changes reflect metabolic injury of the venous wall with development of phlebofibrosis and collagen remodeling, contributing to valvular insufficiency and thrombogenesis.

Keywords Varicose disease, Chronic venous insufficiency, Venous wall, Histochemistry, PAS reaction, Van Gieson staining

1. Introduction

Varicose disease of the lower extremities is one of the most prevalent vascular pathologies worldwide, significantly contributing to morbidity and reduced quality of life. According to epidemiological data, the prevalence of chronic venous disorders reaches 30–40% in the adult population and continues to increase globally [1–3].

Despite advances in diagnostics and treatment, varicose disease remains a clinically significant condition due to its progressive course, high recurrence rates, and associated complications. The disease imposes a considerable socio-economic burden, particularly in regions with limited access to specialized vascular care [4,5].

Current concepts consider varicose disease as a systemic disorder involving structural and functional changes of the venous wall. Remodeling of the extracellular matrix, including alterations in collagen and elastin components, is regarded as a key pathogenetic mechanism underlying venous dilation and valvular insufficiency [6–8].

The aim of this study was to investigate and refine the histochemical characteristics of venous vessels in lower extremity varicose disease.

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2. Materials and Methods

Study design and participants

The study was conducted on venous specimens obtained from 175 patients undergoing surgical treatment for lower extremity varicose disease between 2022 and 2024. Inclusion criteria comprised clinically and instrumentally confirmed varicose disease. Exclusion criteria included acute inflammatory conditions and systemic connective tissue disorders.

Data collection instruments

Histological and histochemical analysis was performed using light microscopy. Standard staining techniques included periodic acid–Schiff (PAS) reaction, Schiff reaction, and Van Gieson staining. Microscopic examination was carried out at magnifications ranging from ×100 to ×400.

Procedures

Venous wall fragments and biopsy samples from the muscle–venous pump region were collected intraoperatively. Tissue samples were fixed in formalin, processed according to standard histological protocols, embedded in paraffin, and sectioned for staining and microscopic evaluation.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Local Ethics Committee of the Fergana Medical Institute of Public Health. Written informed consent was obtained from all

participants.

Data analysis

The study employed qualitative histochemical analysis. Structural alterations were assessed descriptively based on staining characteristics and tissue morphology.

3. Results and Discussion

Histochemical examination revealed pronounced structural alterations in the venous wall of varicose veins.

Accumulation of PAS- and Schiff-positive structures was predominantly localized in the subendothelial and medial layers, demonstrating an uneven distribution pattern. Thickening and irregularity of the basement membrane were consistently observed.

Pronounced plasma imbibition and mucoid swelling were identified within the vascular wall, indicating increased hydrophilicity of the extracellular matrix.

Fragmentation and disorganization of collagen and elastic fibers were detected across all layers of the venous wall. These alterations were accompanied by dilation of the vascular lumen.

Van Gieson staining demonstrated focal proliferation of fuchsinophilic fibers, particularly within the medial and valvular regions. Structural deformation of venous valves and microfissure-type damage were identified.

Endothelial injury and focal thrombotic deposits were observed on the luminal surface.

The presence of dark homogeneous pink inclusions surrounding Schiff-positive structures reflects pronounced accumulation of neutral mucopolysaccharides, manifested as PAS-positive formations (see Fig. 1).

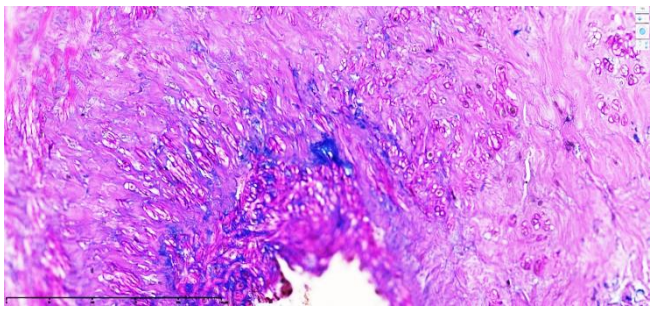

Figure 1. Venous vessel. The intimal surface is of uneven thickness (1); interlaminar spaces of the subendothelial layer are variably expanded (2); developing edematous changes are observed around Schiff-positive structures (3); the basement membrane is thickened with an irregular contour. Schiff staining. Magnification ×40×10

Under the influence of acidic mucopolysaccharides accumulating within the subendothelial and medial layers of varicose veins, foci of destruction of fibrous structures are identified. These alterations were found to result in direct injury to endothelial cells lining the luminal surface of the venous wall and the valvular apparatus, accompanied by focal cellular desquamation as well as swelling and edema of the basal layer underlying the desquamated regions (see Fig. 2).

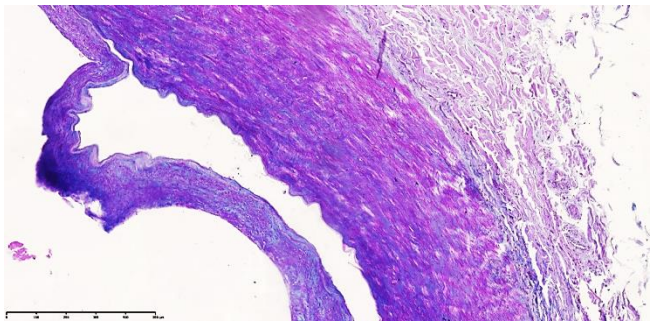

Figure 2. Venous vessel. The intimal surface is of uneven thickness (1); interlaminar spaces of the subendothelial layer are variably expanded (2); developing edematous changes are observed around Schiff-positive structures (3); the basement membrane is thickened with an irregular contour. Schiff staining. Magnification ×10×10

As a consequence, the damaged surfaces periodically create conditions conducive to the development of thrombogenesis.

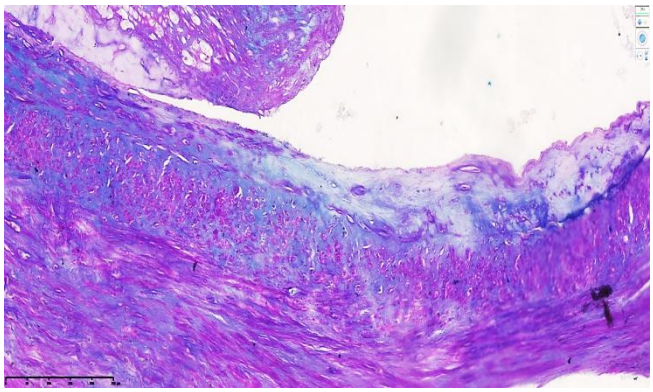

Figure 3. Superficial vein of the middle third of the lower leg. Massive simultaneous accumulation of PAS- and Schiff-positive structures is observed in the muscular layer of the vascular wall. The vessel wall demonstrates plasma imbibition and fragmentation of fibrous structures of different origin. Along the endothelium, the basement membrane boundaries are altered with irregular thickening. PAS + Schiff staining. Magnification ×20×10

Simultaneously, it was established that excessive accumulation of mucopolysaccharides of varying degrees of expression in most cases is accompanied by increased hydrophilicity of the vascular wall and results in the development of persistent plasma imbibition.

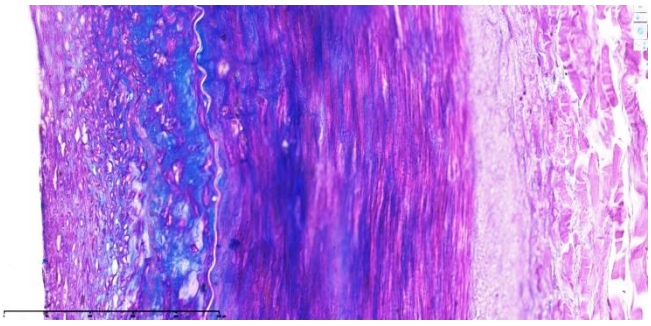

Figure 4. The medial layer demonstrates focal destruction and fragmentation of fibrous structures (1), as well as PAS- and Schiff-positive formations of varying intensity with irregular contours. Intervening areas reveal a disorganized distribution of sparse, weakly stained fibers (2). Schiff staining. Magnification ×20×10

Irregular swelling of elastic and collagen fibers within the vascular wall leads to their dissociation, disorganization, and fragmentation, ultimately contributing to deformation of the wall of varicose veins.

These alterations are characterized by pronounced dilation of the vascular lumen and impairment of intravascular hemodynamics. This is attributable to the fact that damage and disorganization of the aforementioned fibrous structures, which provide elastic tension to the vascular wall, disrupt the propagation of wave oscillations generated by contraction of the right cardiac chambers along the venous circulation, thereby reducing venous vascular reactivity. Changes in the collagenous and elastic components of the vascular wall are regarded as the structural basis of its dilation [10]. Valvular incompetence is determined by structural remodeling of the leaflets and the surrounding wall [7].

These disturbances intensify continuous mechanical stress on the surface of venous valves, potentiating chronic intimal injury in varicose veins. Subsequent slowing of blood flow promotes platelet adhesion and aggregation at damaged regions of the vascular wall and valvular apparatus, thereby creating conditions favorable for thrombogenesis. Chronic alterations of the venous wall establish a substrate for localized thrombus formation [6].

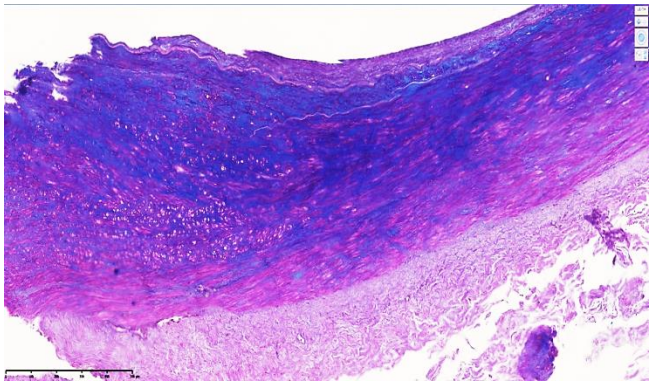

Figure 5. Medial layer of the lower leg vein. Foci of destruction and fragmentation of fibrous structures are identified (1), together with PAS- and Schiff-positive formations of varying intensity with irregular contours. The intervening areas demonstrate a disorganized arrangement of sparse, weakly stained fibers (2). Schiff staining. Magnification ×20×10

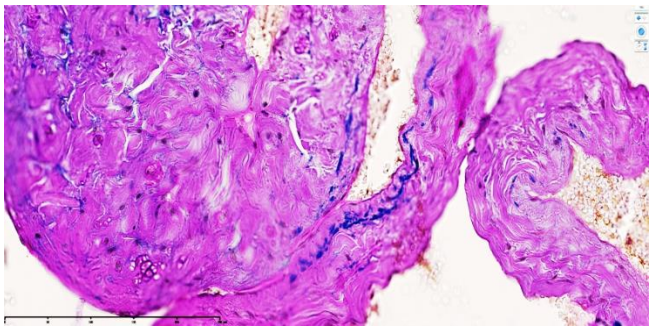

Figure 6. Venous valve of the lower leg. Linear distribution of Schiff-positive structures is observed within the valve tissue. In most areas, a substantial number of PAS-positive formations are detected, indicating pronounced plasma imbibition of the valve (intense dark-pink staining). PAS + Schiff staining. Magnification ×40×10

According to the results of the conducted histochemical investigations, Schiff and periodic acid–Schiff (PAS) staining reflect the qualitative reaction of mucopolysaccharides accumulating in varying concentrations between the anatomical layers of the vascular wall, as clearly demonstrated in the presented microphotographs (Figs. 1–6).

PAS-positive structures, by their nature, belong to the family of neutral mucopolysaccharides, which under physiological conditions accumulate in moderate amounts and subsequently undergo utilization. However, in varicose veins, the hydrophilic properties of accumulated neutral mucopolysaccharides promote intensive binding of water from blood plasma, resulting in pronounced impregnation of the vascular wall and the development of swelling.

Subsequently, metabolic disturbances within the vascular wall are accompanied by transformation of neutral mucopolysaccharides into acidic Schiff-positive polysaccharides, which morphologically manifest as characteristic bluish staining. The acidic nature of Schiff-positive structures contributes to a shift of the local pH environment toward acidity and induces processes of destruction and fragmentation of fibrous components.

These alterations are accompanied by activation of fibroblasts in adjacent regions and enhanced synthesis of tropocollagen, leading to heterogeneous localization of fibrous structures, uneven thickening of anatomical layers of the vascular wall, and formation of its deformed architectonic organization.

The described changes contribute to the progression of both qualitative and structural disturbances of the vascular wall and create conditions favorable for intravascular thrombogenesis and thromboembolic complications during varicose transformation of veins. In patients of older age groups (55–70 years), these parameters are aggravated due to decreased vascular wall tone and predominance of catabolic processes, manifested by reduced fibroblast proliferative activity and increased fragility of the vascular wall. The obtained observations corroborate the presented histochemical findings.

Van Gieson staining, as one of the histochemical investigative methods, is of substantial importance in assessing the histotopographic distribution of fuchsinophilic fibers within the wall of varicose veins, allowing evaluation of the degree of development of pathologically formed fibrous structures.

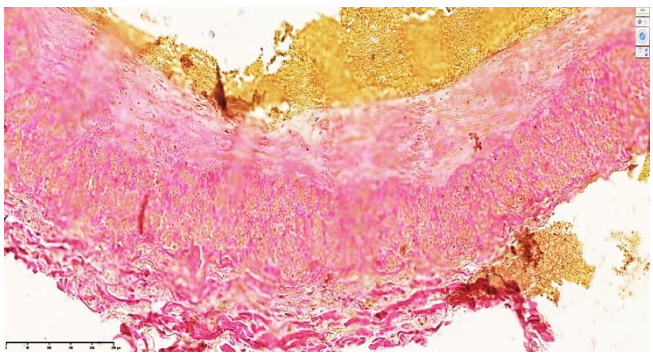

Figure 7. Venous vessel of the middle third of the lower leg. The vascular wall demonstrates irregular, focal distribution of fuchsinophilic fibers. The luminal surface exhibits traces of thrombotic deposits and areas of structural damage. Van Gieson staining. Magnification ×40×10

It has been established that during varicose transformation of veins, a massive, contourless increase in the number of fuchsinophilic fibers throughout all layers of the vascular wall, particularly between muscular bundles, develops as a consequence of pronounced metabolic disturbances. Excessive proliferation of fuchsinophilic fibers leads to the formation of deforming foci within the vascular wall, resulting in altered geometry of the valvular apparatus and focal cicatricial changes of the valvular leaflets.

These morphological alterations contribute to discoordinated contraction of the venous vessel under external mechanical influences and impairment of the muscle–venous pump system. Under conditions of complete vessel contraction, tunnel-like cavities form within the lumen, creating prerequisites for microreflux development. Consequently, in regions of disturbed hemodynamics, vortex and turbulent flow patterns arise in addition to laminar blood flow, further aggravating functional insufficiency of the venous circulation.

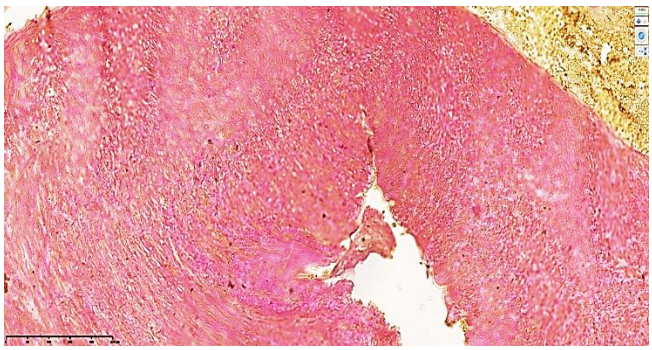

Figure 8. Venous vessel of the upper third of the lower leg. The vascular wall demonstrates massive accumulation of fuchsinophilic fibers. A fragment of a damaged valve with an angular configuration is identified. Interstitial edematous changes are visualized within the vascular stroma. Van Gieson staining. Magnification ×20×10

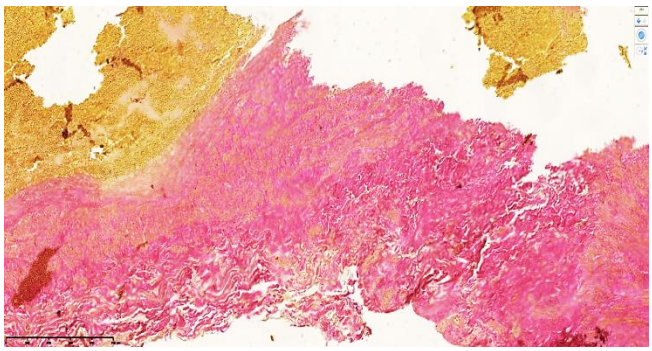

Figure 9. Venous vessel of the popliteal region. The vascular wall demonstrates massive accumulation of fuchsinophilic fibers. A fragment of a damaged valve with an angular configuration is identified. Wavy-oriented fuchsinophilic fibrous structures are observed. Interstitial edematous changes are visualized within the vascular stroma. Van Gieson staining. Magnification ×20×10

Morphologically, these alterations are manifested by bundle-like, coarse focal staining of fuchsinophilic fibrous structures throughout all layers of the vascular wall. Notably, the increase in fuchsinophilic fibers is predominantly associated with a shift of the local pH environment toward acidity, under which fibroblast proliferative activity becomes most pronounced, additionally indicating the development of hypoxic processes within the vascular wall. As a result, in vascular segments exhibiting barrel-shaped deformation, fissure-like damage of the valvular apparatus develops, where fibroblast and histiocyte proliferation is associated with enhanced tropocollagen synthesis followed by collagen polymerization, thereby confirming the formation of deformed cicatricial foci within valvular structures (see Figs. 7–10).

As a consequence, the identified morphological alterations contribute to an increased propensity of varicose veins toward dilation, accompanied by slowing of blood flow throughout the venous circulation and development of plasma imbibition of the intima.

Accumulation of PAS- and Schiff-positive structures within the vascular wall, increased hydrophilic properties, and plasma impregnation concurrently lead to mucoid swelling and disruption of metabolic processes. Under these conditions, activation of the fibroblastic component occurs, accompanied by hyperproduction of tropocollagen fibers and intensified synthesis of coarse fuchsinophilic collagenous structures.

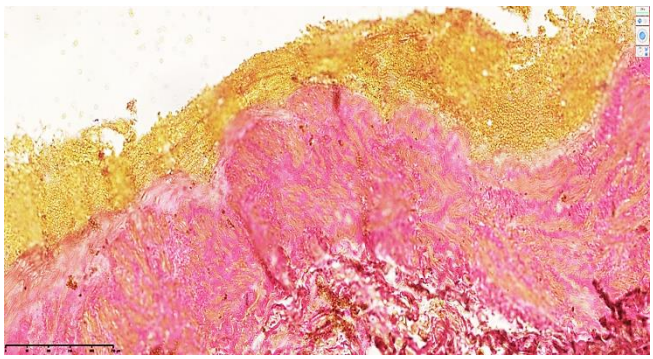

Figure 10. Venous vessel of the popliteal region. The vascular wall demonstrates massive accumulation of fuchsinophilic fibers. A fragment of a damaged valve with an angular configuration is identified. Wavy-oriented fuchsinophilic fibrous structures are observed. Interstitial edematous changes are visualized within the vascular stroma. Van Gieson staining. Magnification ×20×10

Thus, considering that Van Gieson staining enables visualization of the normal architectonics of collagen fibers within the vascular wall, the present study established disruption of their rhythmically ordered arrangement. It was noted that within the venous valvular apparatus and at the level of their bases, fuchsinophilic fibers in the intimal, medial, and muscular layers of the vascular wall were distributed unevenly and were characterized by altered perimetric texture and disorganization.

The identified alterations reflect disturbances of metabolic processes within the vascular wall and heterogeneous activation of tropocollagen synthesis across different anatomical layers. Collectively, these findings indicate discoordination of the muscle–venous–valvular complex during varicose transformation of veins, accompanied by impaired directed ascending blood flow and formation of focal turbulent flow patterns within the muscle–venous pump system.

These hemodynamic disturbances contribute to the development of microfissure-type damage of valvular structures. It should also be noted that mechanical impact on varicose segments (intensive vibrational or massage exposure) may lead to reactivation of thrombus formation on the surface of damaged valves, thereby increasing the risk of thromboembolic complications, including pulmonary embolism.

4. Discussion

The aim of this study was to investigate histochemical alterations of the venous wall in varicose disease.

The findings demonstrate that accumulation of mucopolysaccharides and plasma imbibition play a central role in the development of structural changes in the venous wall. These processes lead to disruption of extracellular matrix organization and contribute to loss of vascular elasticity.

The observed increase in PAS- and Schiff-positive structures reflects metabolic disturbances and altered pH balance within the vascular wall, which promotes degradation of fibrous components. Similar findings have been reported in studies investigating extracellular matrix remodeling in chronic venous disease [6–8].

Proliferation of fuchsinophilic fibers identified by Van Gieson staining indicates enhanced collagen synthesis and fibrotic transformation. These changes are consistent with previously described mechanisms of venous wall remodeling and valvular dysfunction [7,8].

Endothelial damage and thrombotic deposits observed in the present study confirm the role of structural alterations in thrombogenesis. Impaired hemodynamics and turbulent blood flow further contribute to disease progression.

Limitations: The study was qualitative and did not include morphometric analysis.

Strengths: Detailed histochemical characterization of venous wall remodeling.

Future directions: Quantitative morphometric studies are required to further elucidate pathogenetic mechanisms.

5. Conclusions

The study demonstrated that varicose disease is associated with metabolic and structural remodeling of the venous wall, including plasma imbibition, mucoid swelling, and fibrotic transformation.

These changes contribute to valvular insufficiency, impaired hemodynamics, and increased risk of thrombogenesis.

Therapeutic strategies should be aimed at improving trophic support of the venous wall, limiting fibrosis, and preventing thromboembolic complications.

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Author Contributions

All authors contributed equally to the study design, data collection, analysis, and manuscript preparation.

Conflict of Interest

The authors declare no conflict of interest.

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