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Vasa venarum of the saphenous veins from the patients with associated metabolic disorders

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The aim of the study was to investigate vasa venarum of great saphenous vein and their endothelial proliferation and to evaluate the modification of the microvessel density in case of atherosclerosis and associated diabetes mellitus.

Material and methods. The present study included nine venous fragments of human saphenous veins collected from the patients whose lower limbs were amputated. The causes of the limb ablation were: trauma (1 case) and atherosclerosis complicated with occlusion or thrombosis of the lower limbs arteries (8 cases). There were two cases presenting associated diabetes mellitus among the eight cases of atherosclerosis. Formalin-fixed tissues were paraffin embedded and cut into 3µm transverse sections. The slides were stained by a double immunostaining technique using the monoclonal antibodies anti-CD34 and anti-Ki67. The microvessel density was determined by counting the vessels of three "hot spots" and represented by the average values of three "hot spot" areas divided on the surface of high power field (0.0625 mm²). The endothelial cell proliferation index was calculated as the percentage of all nuclei of Ki67-stained endothelial cells that also co-expressed positive cytoplasmic staining in CD34-positive cells.

Results. Vasa venarum of the examined segments of human great saphenous veins were found both in the adventitia and the tunica media. In case of the traumatic injury of the lower limb the adventitial vasa venarum were 4.5 times more numerous (299 vessels/mm²) than those of great saphenous vein media (64 vessels/mm²). In case of associated metabolic disorders we found increased number of vasa venarum of saphenous vein media, 247±109 vessels/mm² and 253±51 vessels/mm², respectively. However, the adventitial microvessel density was lower in case of atherosclerosis (151±23 vessels/mm²) and associated diabetes mellitus (125±3 vessels/mm²). The endothelial cell proliferation index was between 20% and 25% in saphenous vein from the patient with the traumatic injury. Moreover, the proliferation index was higher, ranged between 25% and 30%, in saphenous vein from the patients with metabolic disorders. In the adventitia and the media sprouting and non-sprouting angiogenesis were observed.

Conclusions. Under normal conditions, the microcirculatory vessels predominate in the adventitia, but under pathological conditions (atherosclerosis, diabetes mellitus) the microvessels of the media can exceed numerically the microvessels of the adventitia. The vasa venarum of the tunica media can be located in its outer layer. The Ki67-endothelial proliferation index can be higher (25–30%) in case of the atherosclerosis and associated diabetes mellitus than that in normal conditions (20–25%). The formation of the neovasa vasorum occur through both sprouting and non-sprouting angiogenesis.

Key words: *saphenous vein, vasa venarum, Ki-67 antigene, microvessels, endothelial cells, metabolic diseases.*

Vasa venarum подкожных вен нижней конечности у пациентов с нарушениями обмена веществ

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Целью данного исследования было изучение vasa venarum большой подкожной вены ноги, эндотелиальной пролиферации и оценка изменения плотности микрососудов при атеросклерозе и ассоциированном сахарном диабете.

Материал и методы. Изучено 9 фрагментов подкожных вен человека, взятых у пациентов, которым ампутировали нижние конечности. Причинами ампутации были: травма (1 случай) и атеросклероз, осложненный окклюзией или тромбозом артерий нижних конечностей (8 случаев). Среди случаев атеросклероза 2 были ассоциированы с сахарным диабетом. Фиксированные формалином ткани заливали в парафин и готовили серийные срезы толщиной 3 мкм. Полученные срезы окрашивали методом двойного иммуноокрашивания с использованием моноклональных антител анти-CD34 и анти-Ki67. Плотность микрососудов определяли путем подсчета сосудов в трех «hot spots», средние значения которых были разделены на поверхности поля высокой мощности разрешения (0.0625 мм²). Пролиферативный индекс эндотелиальных клеток рассчитывали в процентном отношении ко всем окрашенным Ki67 ядрам эндотелиальных клеток, которые также ко-экспрессировали позитивное цитоплазматическое окрашивание в CD34-позитивных клетках.

Результаты. В исследованных фрагментах больших подкожных вен человека, vasa venarum были обнаружены в наружной и средней оболочках. При травматическом повреждении нижней конечности

адвентициальные vasa venarum были в 4.5 раза многочисленнее (299 сосудов/мм²), чем в средней оболочке больших подкожных вен (64 сосуда/мм²). В случае сопутствующих метаболических нарушений было обнаружено увеличение количества vasa venarum в средней оболочке подкожной вены, 247±109 сосудов/мм² и 253±51 сосуд/мм² соответственно. Однако, при атеросклерозе (151±23 сосуда/мм²) и ассоциированном сахарном диабете (125±3 сосуда/мм²) плотность адвентициальных микрососудов была ниже чем в средней оболочке. Пролиферативный индекс эндотелиальных клеток в подкожной вене у пациента с травматическими повреждениями составлял 20%–25%, в то время как у пациентов с нарушениями обмена веществ был выше в диапазоне от 25% до 30%. В адвентиции и медии наблюдались как ангиогенез путем почкования, «sprouting», так инвагинационный «non-sprouting» ангиогенез.

Выводы. В нормальных условиях микроциркуляторные сосуды преобладают в адвентиции, а при патологических состояниях (атеросклерозе, сахарном диабете) микрососуды средней оболочки могут численно превосходить микрососуды адвентиции. Vasa venarum средней оболочки чаще располагаются в ее наружном слое. Пролиферативный индекс эндотелия Ki67 выше (25–30%) в случае атеросклероза и ассоциированного сахарного диабета, чем в нормальных условиях (20–25%). Образование и рост новых микрососудов, neovasa vasorum, происходит как путем «sprouting», так и «non-sprouting» ангиогенеза.

Ключевые слова: *подкожная вены, vasa venarum, Ki-67, микрососуды, эндотелиальные клетки, нарушение обмена веществ.*

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Introduction

At the beginning of the twentieth century it was admitted that the architecture of the vessel wall is structurally dynamic and changes with the growth and ageing. At birth, the intima of the vessels consists of endothelial cells attached to an underlying matrix, while the media comprises lamellar units consisting of smooth vascular muscle cells, connective tissue, and elastic fibers. The collagen-rich adventitia includes fibroblasts, perivascular nerves, pericytes, adipocytes, as well as resident leukocyte populations [14].

From histological and functional points of view, the circulatory system notably manifests itself in specialized microcirculatory beds of organs. This also refers to the walls of the veins, which are characterized by a very well developed nutritional system, "vasa venarum" [10].

An example of the practical significance of vasa venarum for the integrity and patency of vessels can be observed in the saphenous veins used as grafts for coronary bypass. While collecting saphenous vein, the connective tissue that contains microvesels is often removed. This manifests in venospasm [12], which can progress into vein-graft disease and even vein-graft failure [16]. In addition, vasa venarum play an important role in vein relaxation, and any damage of the microvessels during saphenous vein collecting severely affects flow-induced vasodilation of the graft [8].

Adventitial angiogenesis as a process activated during atherosclerosis, and increased in vasa vasorum density is considered a response to vessel wall thickening in atheromatous plaque forms [15, 20]. While the thickness of the vessel wall is an important parameter that governs neovascularization, other stimuli, such as inflammation, can trigger the formation of new vessels [14].

Angiogenesis is a biological process characterized by the formation of new blood vessels from the pre-existing vasculature, which involve the endothelial cell migration and proliferation, lumen formation, and occasionally the recruitment of smooth muscle cells and other adventitial cells. [11]. Active participants in the angiogenesis process are the endothelial cells, as well as the components of the peripheral nervous system. During the embryonic development peripheral nerves support the formation and differentiation of blood vessels. Neuropeptide Y (NPY), a neurotransmitter released from sympathetic nerves, facilitates angiogenesis [15].

Intussusceptive angiogenesis is an intravascular process capable of modifying dramatically the structure of the microcirculation [9]. Post-capillary venules have relatively thin walls, which are particularly permissive to sprouting angiogenesis. The wall shear stress in the post-capillary venules together with biochemical factors is capable of stimulating angiogenesis [7].

The monoclonal antibody Ki-67 is a marker strictly associated with cell proliferation because it recognizes a nuclear antigen present in the G1, S, G2 and M phases of the cell cycle, but not in the Go phase [1, 2]. For decades, Ki-67 protein has been widely used as a proliferation marker for human tumor cells. In recent studies, the multiple molecular functions of this protein have become better understood. Present in both interphase and mitotic cells, its cellular distribution undergoes dramatic changes during cell cycle progression [17].

Evaluation of the immunohistochemical expression of Ki-67 as a proliferative marker and of CD34 as a marker of endothelial cells allows studying the vascular proliferation in tumors [2, 4]. Microvessel density is a very useful parameter in the evaluation of angiogenesis [2].

The aim of this study is to evaluate the vascular proliferation in the saphenous veins in

Table

Characteristics of patients

Diagnosis	Male	Female	Total	Age
Traumatic injury. Crush syndrome	1	–	1	53
Atherosclerosis of the extremities	5	1	6	69.5
Atherosclerosis and diabites mellitus	1	1	2	68

correlation with certain clinicopathological parameters (age, associated metabolic disorders), as well as the correlation between microvessel density and Ki67-endothelial proliferation index.

Material and methods

The present study included nine venous fragments of the great saphenous veins collected from the patients whose lower limbs were amputated. These patients were admitted to the Timofei Mosneaga Republican Clinical Hospital, Chisinau, Republic of Moldova, between July 2018 – January 2019. The causes of limb ablation were: trauma (1 case) and atherosclerosis complicated with occlusion or thrombosis of the arteries of the lower limbs (8 cases). There were two cases with associated diabetes mellitus among the eight cases with atherosclerosis. The patients` ages ranged between 53 years and 77 years, the average value being 67.33±6.07 years.

The venous fragments were processed according to the usual histological technique, fixed in neutral 10% formalin, embedded in paraffin and cut into 3 µm transverse sections. The initial sections were stained with hematoxylin-eosin for histopathological changes, the subsequent sections were double immunohistochemically stained using the anti-CD34 and anti-Ki67 monoclonal antibodies.

The immunostaining technique started with the deparaffinization and rehydration of the vein sections, followed with the blocking of endogenous peroxidases using 3% hydrogen peroxide for 5 min. The next step was to apply the primary antibody on the slides for 30 min, then the secondary antibody for 8 min. Bond Polymer Refine Detection System (Leica Biosystems) was used for visualisation. As chromogen 3.3 diamino-benzidine dyhirochloride was applied and hematoxylin was used for counterstaining. The sections were dehydrated, clarified, mounted, and observed under an optical microscope. The entire immunohistochemical procedure was performed with Leica Bond Max (Leica Biosystems, Newcastle upon Tyne, UK) autostainer.

The microcirculatory vessels of the venous wall were highlighted by immunostaining of the endothelial cells with anti-CD34 monoclonal antibody (QBEnd 10, Leica Biosystem Newcastle Ltd, Newcastle Upon Tyne, UK) and with anti-Ki67 antibody (MM1, Leica Biosystem Newcastle Ty, UK). CD34 antigen was stained using an alkaline phosphatase method (red), and Ki67 antigen was stained using a streptavidin-biotin-peroxidase (brown) method.

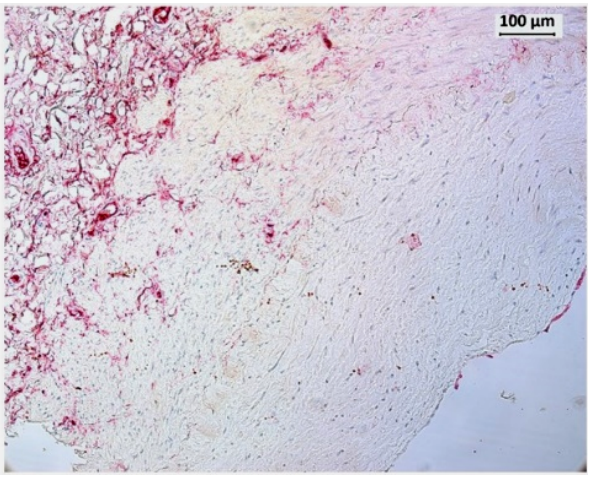


Fig. 1. Numerous blood vessels of the adventitia of the great saphenous vein from the patient without metabolic disorders. Double immunostaining for CD34 and Ki-67 (ob. 20, oc. 10).

The microvascular density of the immunohistochemically stained vessels with CD34 was determined by counting the vessels of three "hot spot" areas (areas with the highest number of microvessels), previously defined under low power (×100) magnification. Red-colored cells, single or in nests, clearly separated from each other, with or without lumen were considered microvessels and were counted. The microvessels were counted under ×400 magnification, which represents a field size of 0.0625 mm^2. The microvessel density represented the average of the values of the three "hot spot" areas divided on the surface of the high-power field (0.0625 mm^2). The endothelial cell proliferation index was determined under ×400 magnification. The index was calculated as the percentage of all nuclei of Ki67-stained endothelial cells that also had co-expressed positive cytoplasmic staining in CD34-positive cells.

Results and discussion

As reference point we used the saphenous vein from the patient with the limb ablation because of the crush syndrome and traumatic injury of the left lower limb (see the table) who was younger than all the other patients and had no atherosclerosis or diabetes mellitus.

We have investigated the vascular architecture pattern in the different layers of the venous wall in correlation with associated metabolic disorders, the microvessel density and the endothelial cell proliferation index using double immunochemistry with CD34 and Ki67.

The vasa venarum were found both in the adventitia and in the tunica media, but their architecture was different. In the patient without metabolic disorders (fig. 1) more numerous

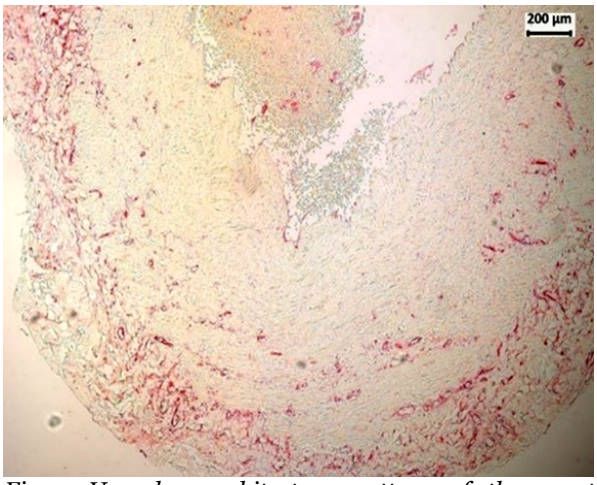


Fig. 2. Vascular architecture pattern of the great saphenous vein from the patient with atherosclerosis of the extremities. Numerous blood vessels of the media and adventitia of the great saphenous vein. Double immunostaining for CD34 and Ki-67 (ob. 10, oc. 10).

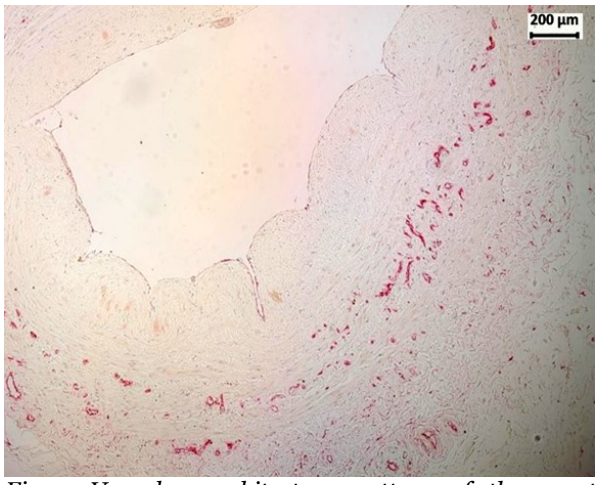


Fig. 3. Vascular architecture pattern of the great saphenous vein from the patient with atherosclerosis of the extremities and associated diabetes mellitus. Numerous blood vessels of the media and less numerous of the adventitia of the great saphenous vein. Double immunostaining for CD34 and Ki-67 (ob. 10, oc. 10).

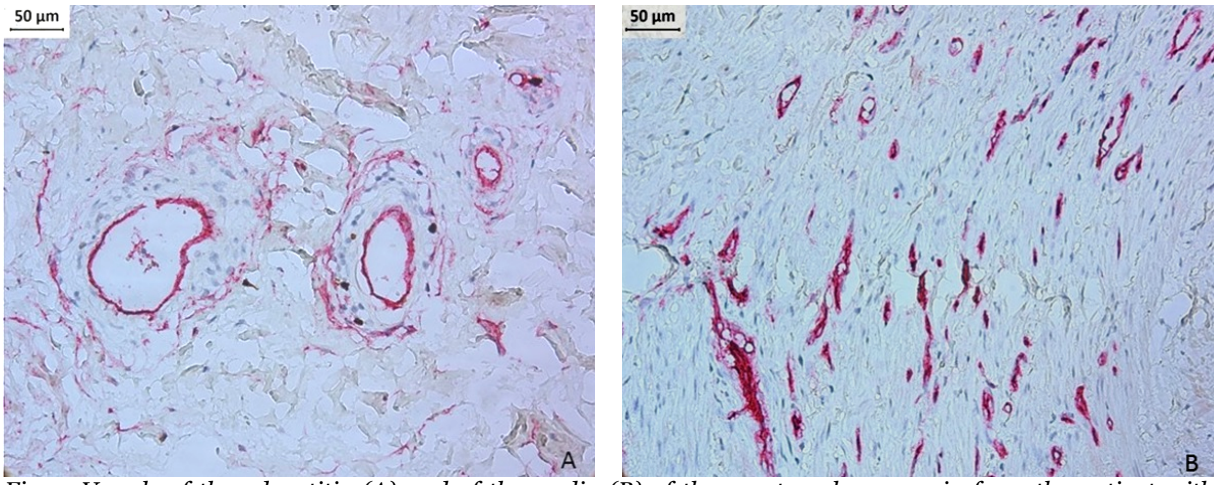


Fig. 4. Vessels of the adventitia (A) and of the media (B) of the great saphenous vein from the patient with atherosclerosis of the extremities. Double immunostaining for CD34 and Ki-67 (ob. 40, oc. 10).

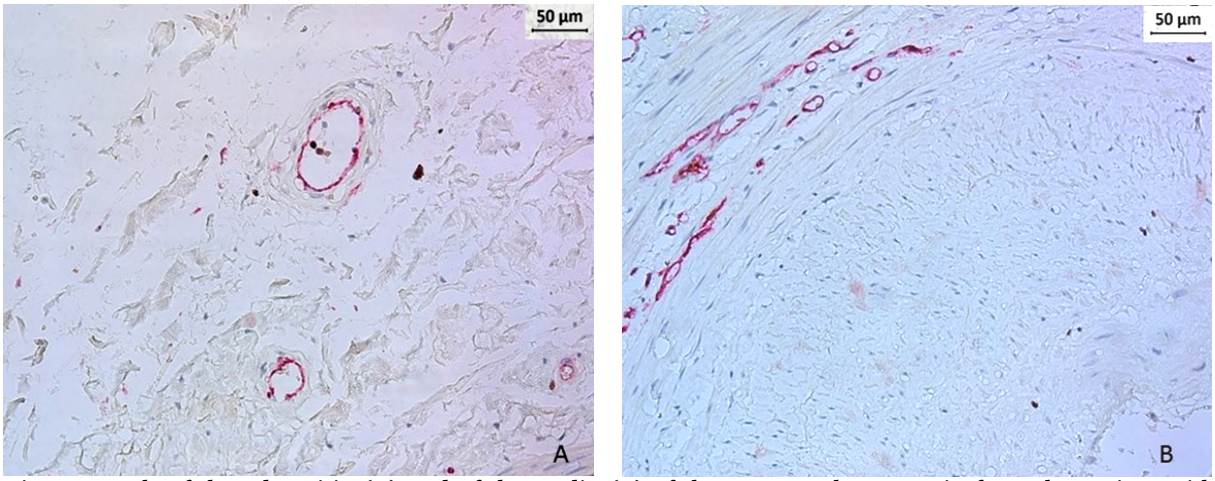


Fig. 5. Vessels of the adventitia (A) and of the media (B) of the great saphenous vein from the patient with atherosclerosis of the extremities and associated diabetes mellitus. Double immunostaining for CD34 and Ki-67 (ob. 40, oc. 10).

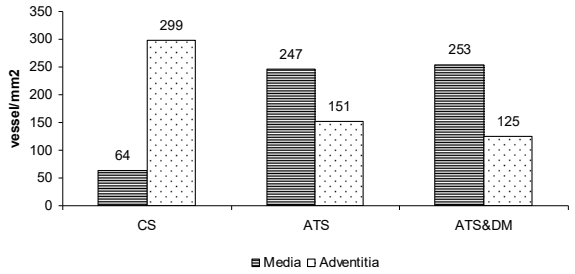


Fig. 6. Microvessel density (vessel/mm²) of the media and adventitia of the great saphenous vein in correlation with clinicopathological parameters. CS – crush syndrome, ATS – atherosclerosis, ATS&DM – atherosclerosis and diabetes mellitus.

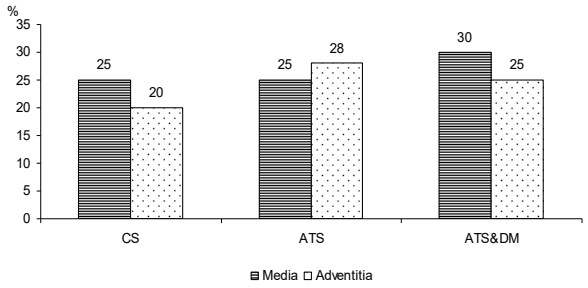
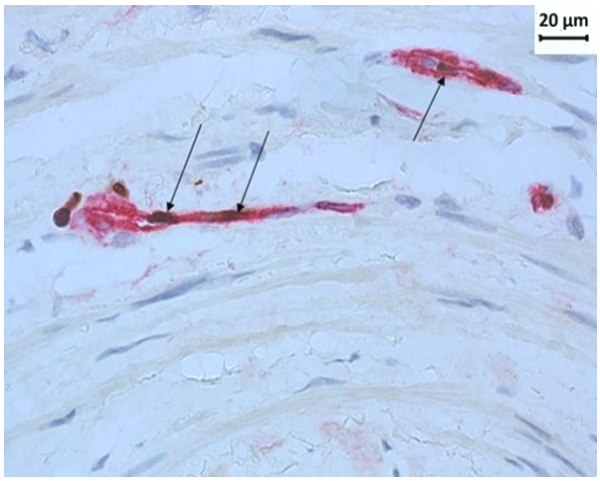


Fig. 8. Endothelial cells proliferating index (%) of the media and adventitia of the great saphenous vein in correlation with clinicopathological parameters.



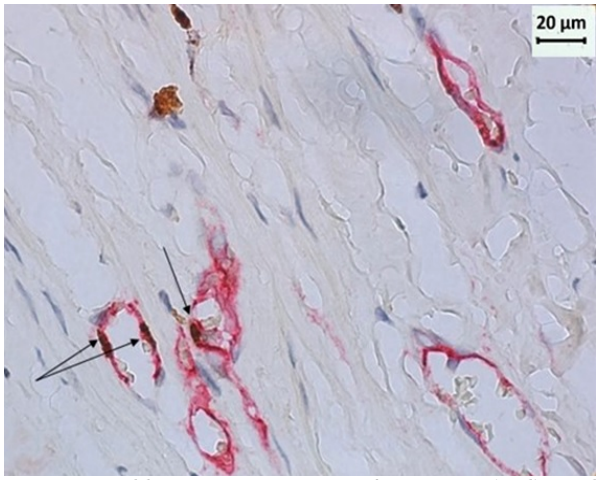


Fig. 7. Double immunostaining for CD34 (red) and Ki-67 (brown). Proliferating endothelial cells in the media of the great saphenous vein. Ki-67–positive endothelial nuclei (arrows). Ob. 100, oc. 10.

microvessels were located in the adventitia, however in the patients with metabolic disorders more numerous microvessels were found in the tunica media (fig. 2, 3).

The microvessels of the adventitia had a large lumen and were surrounded by their own thick media, but the vessels of the tunica media, arranged between smooth vascular muscle cells, were elongated with or without lumen, lined with endothelial cells with or without proliferation. In all the cases included in our study the non-proliferating microvessels predominated (fig. 4, 5).

In case of the traumatic injury of the lower limb the adventitial vasa venarum were 4.5 times more numerous (299 vessels/mm²) than those of the media of the great saphenous vein (64 vessels/mm²). In case of the associated metabolic disorders we found increased numbers of the vasa venarum of the media of the saphenous vein: 247±109 vessels/mm² in case of the atherosclerosis and 253±51 vessels/mm² in case of the associated diabetes mellitus, respectively (fig. 6).

However, the adventitial microvessel density was lower in case of the atherosclerosis (151±23 vessels/mm²) and associated diabetes mellitus (125±3 vessels/mm²).

In the adventitia and media sprouting and non-sprouting (intussusceptive) angiogenesis were observed (fig. 7).

The endothelial cell proliferation index was between 20 and 25% in the saphenous vein from the patient with traumatic injury. However, the proliferation index was higher, ranged between 25 and 28%, in the saphenous vein from the patients with atherosclerosis and 25 and 30% in the saphenous veins from the patient with associated diabetes mellitus (fig. 8).

The vasa venarum in the vein wall corresponds to the nutritive microvessels of the arterial wall, the vasa vasorum [10]. The vasa venarum penetrate the adventitia of the great saphenous vein every 0.5–1.5 cm [6]. The microcirculatory arteries originate from the arteries supplying the subcutaneous adipose tissue, and veins usually drain into the terminal segments of the largest tributaries [6].

The feeding artery at the surface of the adventitia branches into first-order arterioles (A1) running parallel to the longitudinal axis of the great saphenous vein. The first-order arterioles branch off second-order arterioles (A2), running circumferentially to the

longitudinal axis of the great saphenous vein. The second-order arterioles continue into the media where they form a rich capillary network [5 11]. The capillary network change into postcapillary venules that are much more numerous than the arterioles and are noted with V4–V1 depending on their location and luminal diameter [5]. The tunica media of the saphenous vein consists of two structurally different layers: an inner loose layer and an outer dense layer, both of similar thickness. The innermost capillaries of the vasa venarum network reach the border between the two layers of the media [6, 18], a fact observed in most of the patients included in our study.

The diffusion distance is limited by 100 μm and the microvessels are responsible for the transport of oxygen and nutrients to the adventitia, and through diffusion to the media. The intima is usually fed by diffusion from the lumen of the vessel [11]. The thickness of the adventitia of the great saphenous vein is about 2–3 μm, the tunica media about 500–300 μm, and the intima about 200 μm. It means that total thickness of the wall of the great saphenous vein is at least 700 μm. In this way, vasa venarum of the great saphenous vein penetrate deep into the tunica media [5, 19]. In our study the microcirculatory vessels were observed both in the adventitia and the media. In the tunica media the microvessels were predominantly located in its outer layer.

According to Dreifaldt M, 2011 [3], the density of vasa venarum of the adventitia (94.5±24.7) is twice higher than of the media of the great saphenous vein (48.0±13.9). In our study, the adventitial microvessel density was 4.5 times higher than those of the media of the great saphenous vein from the patient with the traumatic injury. In patients with metabolic disorders (atherosclerosis, diabetes mellitus) the microvessel density of the media was higher than that of the adventitia of the great saphenous vein.

Vasa vasorum angiogenesis is associated with a decrease in mean diameter of the first-order vasa vasorum and an increase in density of the second-order vasa vasorum in animals fed on a hypercholesterolemic diet for 6–12 weeks [11]. The microvessel density of the media of the great saphenous vein from the patients with diabetes mellitus was higher compared with the microvessel density in the patient with the traumatic ablation of the limb.

Conclusions

To summarize the above-mentioned, we can conclude that the increased microvessel density of the media of the great saphenous vein can be influenced by atherosclerosis and diabetes mellitus. Vasa venarum of the tunica media are mostly located in its outer layer. Under normal conditions, the microcirculatory vessels predominate in the adventitia, but under pathological conditions (atherosclerosis, diabetes mellitus) the microvessels of the media can exceed numerically the microvessels of the adventitia. The Ki67-endothelial proliferation index can be higher (25–30%) in case of atherosclerosis and associated diabetes mellitus than that in normal condition (20–25%). The formation of neovasa vasorum occurs through both sprouting and non-sprouting angiogenesis.

Declaration of conflicting interests

The authors declare lack of any conflict of interests.

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