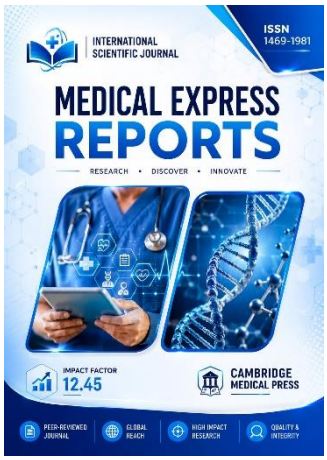
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AGE-ASSOCIATED MORPHOLOGICAL ALTERATIONS OF THE LOWER LEG AND FOOT VASCULAR ENDOTHELIUM IN DIABETIC ANGIOPATHY

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ABSTRACT

Background. Diabetic angiopathy is one of the major complications of diabetes mellitus and an important cause of vascular disorders in the lower extremities. Persistent hyperglycemia damages vascular endothelial cells, promotes thickening of capillary basement membranes, and contributes to disturbances in tissue circulation. These changes are particularly important in the lower leg and foot, where adequate blood supply is essential for maintaining tissue integrity and normal wound healing. Aging may further influence the development of diabetic vascular complications through reduced endothelial repair capacity, oxidative stress, and impaired angiogenesis..

Relevance of the research problem

Diabetes mellitus remains one of the most important medical and social problems worldwide. The number of people living with diabetes continues to increase, creating a growing burden on healthcare systems. According to the International Diabetes Federation estimates published by Sun et al., approximately 537 million adults aged 20–79 years were living with diabetes in 2021, with a projected increase to 783 million by 2045 [1].

One of the main reasons for the serious consequences of diabetes is its long-term effect on blood vessels. Vascular damage may develop gradually, even before severe clinical symptoms appear. Persistent hyperglycemia affects endothelial cells, disturbs normal vascular regulation, and promotes structural changes in the vessel wall. These abnormalities are important in the development of diabetic microangiopathy and peripheral arterial disease [2, 3].

The lower leg and foot are particularly vulnerable to diabetic vascular complications. Impaired blood supply, peripheral neuropathy, and repeated mechanical pressure create conditions in which even minor tissue injuries may develop into chronic wounds. Structural abnormalities in small vessels may further disturb local tissue nutrition and contribute to delayed healing. Nevertheless, the exact contribution of microangiopathy to diabetic foot ulcer development remains a subject of scientific discussion [4].

Aging creates additional difficulties in the assessment of diabetic vascular damage. With increasing age, endothelial cells gradually lose part of their ability to maintain vascular tone, regulate blood flow, and support tissue repair. Reduced angiogenic activity and changes in cellular metabolism may increase the vulnerability of peripheral tissues to ischemic injury [5].

Materials and methods

This study was conducted as a descriptive literature review.

Twelve scientific publications were included in the analysis. The selected publications covered the epidemiology of diabetes mellitus, mechanisms of diabetic vascular complications, endothelial dysfunction, diabetic foot microangiopathy, peripheral arterial disease, and vascular aging. The review included original clinical studies, experimental investigations, morphological examinations, and scientific review articles. The main analytical approach was the comparison of published findings concerning the structure and function of the vascular endothelium. Special attention was given to histological and ultrastructural indicators of diabetic microangiopathy. The principal morphological parameters considered were endothelial cell integrity, vessel wall thickness, capillary basement membrane thickness, vascular lumen area, microvascular density, and the presence of perivascular connective tissue remodeling. The role of oxidative stress, nitric oxide dysfunction, and endothelial senescence was also considered because these mechanisms may influence vascular structure during aging. Published findings from diabetic foot tissue investigations were evaluated separately from general experimental and clinical evidence of diabetic vascular disease. The available information was interpreted descriptively. No new patient samples were collected, and no additional histological measurements or statistical calculations were performed. The purpose of the analysis was to summarize established morphological findings and identify unanswered questions concerning age-associated changes in peripheral vascular structures.

Results and discussion

The comparative analysis revealed that diabetic angiopathy is associated with structural changes in the vascular endothelium, including endothelial injury, capillary basement membrane thickening, and narrowing of vascular lumina. These alterations were linked to persistent hyperglycemia, oxidative stress, and extracellular matrix remodeling. The reviewed findings showed that basement membrane thickening is one of the characteristic morphological signs of diabetic microangiopathy. Changes in endothelial cell structure and vascular lumen dimensions may further disturb peripheral microcirculation. Endothelial dysfunction was also associated with

reduced nitric oxide availability and increased inflammatory activity. Thus, the analysis identified endothelial damage, basement membrane remodeling, and capillary narrowing as important components of diabetic vascular pathology.

The analysis of the investigation by Fiordaliso et al. [9] revealed significant morphological differences between diabetic and non-diabetic skin microvessels. Capillary density in diabetic tissues was **22.2% lower,** measuring 159 ± 43 capillaries/mm² compared with 205 ± 52 capillaries/mm² in non-diabetic controls. Capillary basement membrane thickness increased approximately **2.2-fold,** reaching 3.44 ± 1.19 μm compared with 1.53 ± 0.34 μm. The vascular lumen area decreased by **57.7%,** from 34.7 ± 27.5 μm² to 14.6 ± 11.1 μm². These findings demonstrated that diabetic microangiopathy affects both capillary structure and vascular distribution. The observed abnormalities provide morphological evidence of peripheral microvascular remodeling.

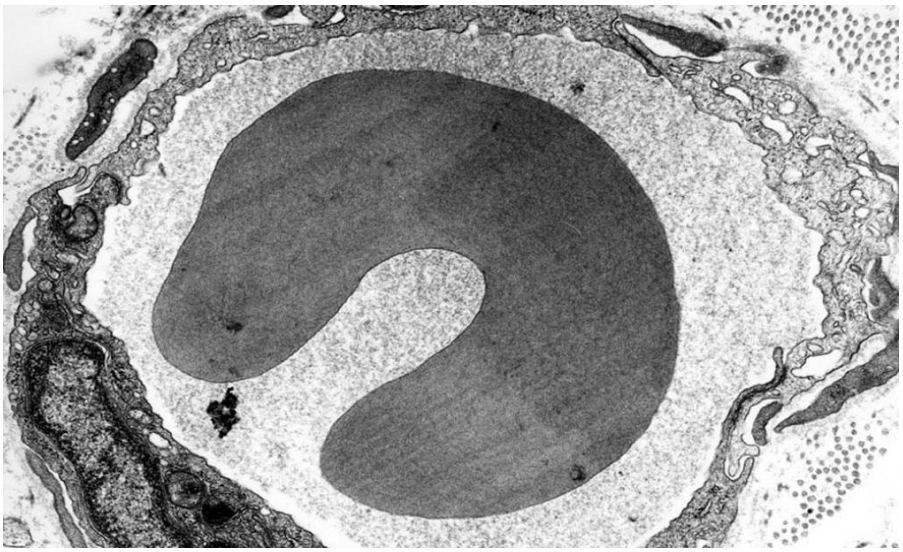


Figure 1. Morphological changes in peripheral capillaries associated with diabetic angiopathy. **A normal capillary with a preserved endothelial lining, thin basement membrane, and open lumen; B diabetic capillary showing basement membrane thickening, endothelial remodeling, and lumen narrowing. Schematic comparison based on published morphological findings.**

The reviewed studies demonstrated that vascular aging is associated with endothelial senescence, reduced nitric oxide bioavailability, impaired angiogenesis, and decreased regenerative capacity. These abnormalities may become more pronounced when aging occurs together with chronic hyperglycemia. Oxidative stress and changes in extracellular matrix metabolism may contribute to progressive vascular remodeling. The evidence suggests that older patients with diabetes may have reduced endothelial repair capacity. However, direct morphological comparisons between specific age groups are still insufficient to establish precise age-dependent differences in lower-extremity vessels.

The analysis identified capillary rarefaction, basement membrane abnormalities, and structural remodeling of small vessels as important manifestations of diabetic microangiopathy. In the foot, these changes may affect tissue nutrition and wound healing. Peripheral arterial disease and neuropathy may further aggravate tissue damage. The comparison of published findings showed that both the number of capillaries and the structural condition of individual vessels are relevant to the morphological assessment of diabetic angiopathy.

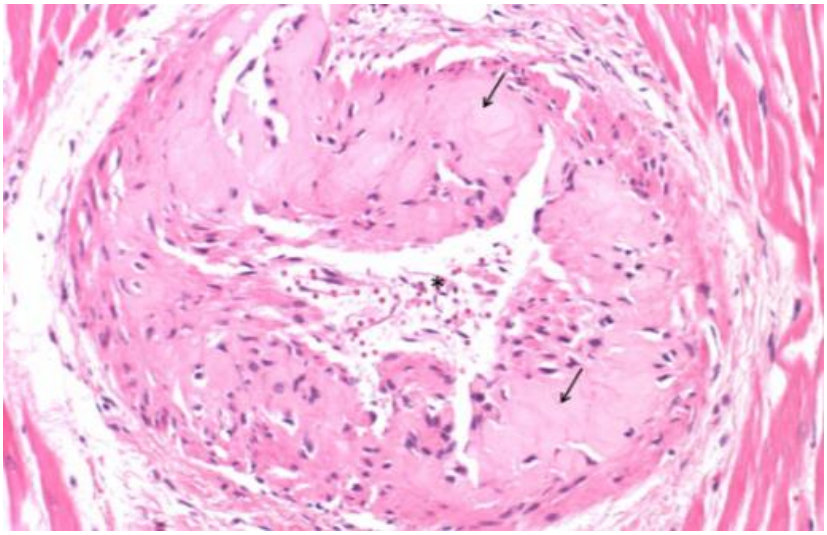


Figure 2. Structural remodeling of the peripheral microvascular network in diabetic angiopathy. **A preserved dermal capillary network; B diabetic microangiopathy characterized by reduced capillary density, irregular vascular distribution, and capillary wall alterations. Schematic representation based on published findings.**

The reviewed evidence allowed the identification of several mechanisms that may influence diabetic angiopathy at different ages. In younger adults, endothelial dysfunction may develop before advanced structural remodeling becomes evident. In middle-aged patients, prolonged metabolic disturbances may contribute to more complex vascular abnormalities. In older patients, endothelial senescence and reduced angiogenic activity may further affect vascular repair. These patterns represent an interpretation of published mechanisms rather than directly measured differences between age groups. The analysis established that chronological age should be evaluated together with diabetes duration, glycemic control, and associated cardiovascular diseases.

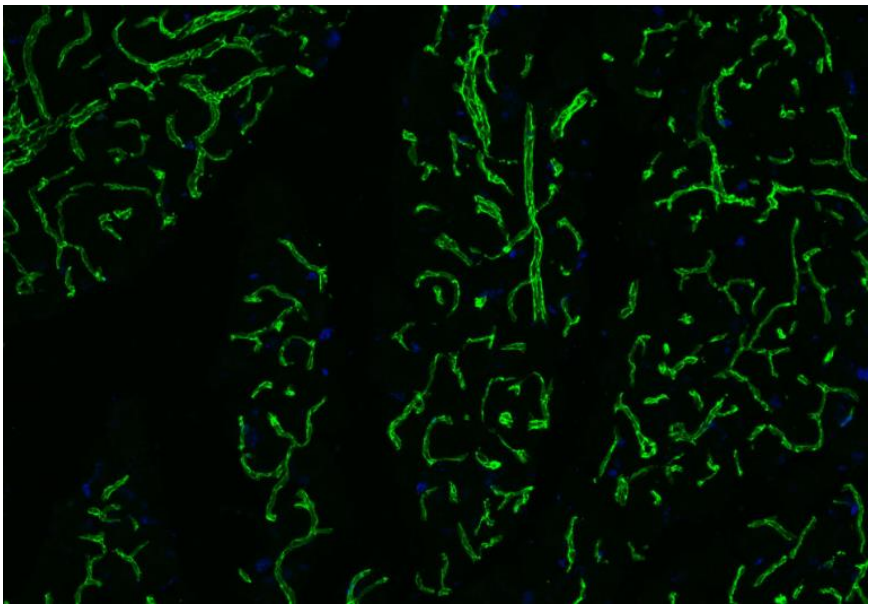


Figure 3. Age-associated structural alterations of the vascular endothelium in diabetic angiopathy. **A schematic representation of early endothelial dysfunction and microvascular remodeling; B possible combined effects of diabetic vascular injury and aging, including endothelial senescence, reduced angiogenic activity, and impaired vascular repair. Conceptual illustration based on published evidence.**

The comparative analysis established that diabetic angiopathy involves interconnected morphological and functional abnormalities of the peripheral vascular system. The principal structural changes included capillary basement membrane thickening, reduced vascular lumen area, decreased capillary density, and endothelial remodeling. Aging may contribute additional endothelial dysfunction and impaired vascular regeneration. The findings indicate that morphological and morphometric examination of lower-extremity vessels can provide valuable information about diabetic vascular damage. Nevertheless, further age-stratified histological investigations are required to determine the independent influence of aging on the severity of diabetic angiopathy.

Conclusion

Diabetic angiopathy is associated with structural and functional abnormalities of the vascular endothelium that may contribute to impaired peripheral microcirculation.

The reviewed scientific literature supports the following conclusions:

1. Persistent hyperglycemia contributes to endothelial injury through oxidative stress, inflammatory activation, metabolic disturbances, and changes in intracellular signaling pathways.

2. Characteristic morphological abnormalities of diabetic microangiopathy include capillary basement membrane thickening, vascular lumen narrowing, and alterations in microvascular density. In the study by Fiordaliso et al., dermal capillary density was reduced by 22.2%, basement

membrane thickness increased approximately 2.2-fold, and capillary lumen area decreased by 57.7% compared with non-diabetic controls.

3. Aging is associated with endothelial senescence, reduced nitric oxide bioavailability, impaired angiogenesis, and decreased vascular regenerative capacity. These processes may contribute to the progression of diabetic vascular abnormalities, although direct age-dependent differences in lower-extremity vascular morphology require further investigation.

4. Morphological assessment of the lower leg and foot should distinguish between macrovascular atherosclerotic disease and microvascular structural abnormalities. These processes may coexist but have different pathological characteristics.

5. The combined application of histological, morphometric, ultrastructural, and immunohistochemical methods may improve the assessment of peripheral vascular injury and provide additional information about structural changes associated with diabetic angiopathy.

Further studies based on clearly defined age groups and standardized tissue measurements are needed to determine the independent contribution of vascular aging to the progression of diabetic angiopathy.

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