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Review Article

From Diabetic Foot Microvascular Disease to Medial Arterial Sclerosis and Calcification in Chronic Limb-Threatening Ischemia: A Potentially Unified Pathogenic and Prognostic Entity for Tissue and Limb Loss

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Abstract

Contemporary publications revealed that microvascular disease (mVD) represents a common, yet poorly controlled microcirculatory complication, currently encountered in the multifactorial diabetic neuro-ischemic foot pathology. The presence of mVD in vascular structures of < 100 µm was evoked to represent an independent detrimental pathogenic factor, leading to increased inferior limb major complications and limb loss. Convergently, medial artery sclerosis (MAS) and medial artery calcification (MAC) were described as closely affiliated pathological entities, equally encountered at the inferior limb level in diabetic patients.

This review aims to provide updated information about the clinical and prognostic significance of peripheral diabetic mVD, studied apart, or in association with concomitant MAS and MAC.

These three entities appear to represent rather interconnected stages of a unified pathological process inflicted by persistent hyperglycaemia, leading to specific structural and functional arterial damage and limb loss. Diabetic foot mVD necessitates an independent, systematic assessment, to identify patients with high limb loss prognostic.

Key Words: diabetic foot; chronic limb-threatening ischaemia; diabetic neuropathy; wound healing; chronic hyperglycaemia; medial arterial sclerosis; medial arterial calcification; microvascular disease.

Abbreviations

ABI - ankle-brachial index;

AGEs - advanced glycation end-products;

ASL - arterial spin labeling;

BOLD - blood oxygenation level-dependent;

BTA - below-the-ankle;

BTK - below-the-knee;

CLTI - chronic limb-threatening ischaemia;

CT-scan - computed tomography scan.;

DPN - diabetic peripheral neuropathy;

DSA - digital subtraction angiography;

EAOD - end-artery occlusive disease;

EVUS - extravascular ultrasound;

IVUS - intravascular ultrasound;

MAC - medial artery calcification;

MAS - medial artery sclerosis;

MACE - major adverse cardiac events;

MALE - major adverse limb events;

MRI-ASL - magnetic resonance imaging-arterial spin labeling;

MRI-BOLD - magnetic resonance imaging-blood O2 level dependent;

mVD - micro-vascular disease;

NIRS - near-infrared spectroscopy

PAD - peripheral artery disease;

PET-scan - positron emission tomography;

ROS - reactive oxygen species;

SAD - small-artery disease;

SFDI - spatial frequency domain imaging;

SPECT-CT - single photon emission tomography;

SVD - small-vessel disease;

TcPO2 - trans-cutaneous oxygen pressure;

X-rays - plane radiography;

Introduction

Diabetes mellitus is associated to progressive structural and functional impairment of the vascular system. Conventionally, the arterial network is divided into macrocirculation (vessels with a diameter greater than 100 μm), and microcirculation (vessels inferior to 100 μm diameter). Diabetic foot microangiopathy is a common but insufficiently monitored complication of persistent hyperglycaemia; it is essentially represented by irreversible medial arteriolar layer damage and by capillary destruction. Historically, the first description of degenerative alterations (sclerosis and calcifications) located in the medial arterial wall of small vascular structures is attributed to J.G. Mönckeberg in 1903. [1] It took several decades before medial arterial sclerosis (MAS) and the associated medial arterial calcifications (MAC) gained their well-deserved clinical relevance as key detrimental cardiovascular factors. [2] These two pathological entities appear to be strongly related to higher rates of major adverse cardiac events (MACE), [2] major adverse limb events (MALE), [2-4] and increased perioperative morbidity and mortality. [2-4]

From a contemporary perspective, MAS and MAC represent markers of severe systemic vascular disease distinct from atherosclerotic affliction. [2, 4] Medial arterial pathology is often associated with diabetes mellitus, macro- and microvascular chronic limb-threatening ischaemia (CLTI), the diabetic neuro-ischaemic foot syndrome, renal insufficiency, ageing, and various inflammatory diseases. [2-7]

Based on improved electron microscopic investigation, an original publication by LeCompte in 1955 [6] offered one of the earliest studies that clearly delineated the distinction between macro- and microangiopathic disease in ischaemic diabetic limbs. [6] The microvascular disease was attributed to arteriolar and capillary destruction, as was later corroborated by Goldenberg et al. [7] It is also important to mention the pioneering work of Pedersen and Olsen, [8] who in 1962 proposed an original definition of “small-vessel disease” (SVD) as a taxonomic vascular entity in the assessment of the diabetic neuro-ischaemic foot. [8]

More recently, diabetic foot microangiopathy has gained considerable attention in relation to tissue and limb preservation in CLTI—paralleling the diagnostic progress made in the better-recognised diabetic retinopathy, cardiomyopathy, and peripheral neuropathy. [3, 9]

The aim of this review is to provide updated information regarding the current clinical, pathogenic, and prognostic significance of diabetic microvascular disease (mVD), as well as its contemporary screening, diagnostic, and therapeutic options—particularly in the context of diabetic CLTI and associated MAS and MAC affecting the lower limbs.

Material and Methods

Publication screening and data assembling.

A parallel search was conducted in the Medline database, supplemented by unrestricted online data exploration, to identify publications related to microangiopathy in the diabetic foot syndrome within the context of CLTI. This investigation focused particularly on relevant publications from the last two decades. Fourteen keywords were employed during the database search, such as: “chronic limb-threatening ischaemia, diabetic neuro-ischaemic foot, medial arterial sclerosis, medial arterial calcification, arterial calcification, diabetic foot microangiopathy, hyperglycaemia pathology, diabetic microvascular complications, pathophysiology of diabetic microcirculation, diabetic peripheral neuropathy, diagnostic of diabetic microangiopathy, treatment of diabetic microangiopathy, prognostic of diabetic vascular complications, and perspectives in diabetic microvascular disease.”

Protocol for data selection and analysis

Following a three stages approach, the location, approval, and analytical processes are briefly illustrated in Figure. 1.

The finally selected data were integrated into a narrative review format.

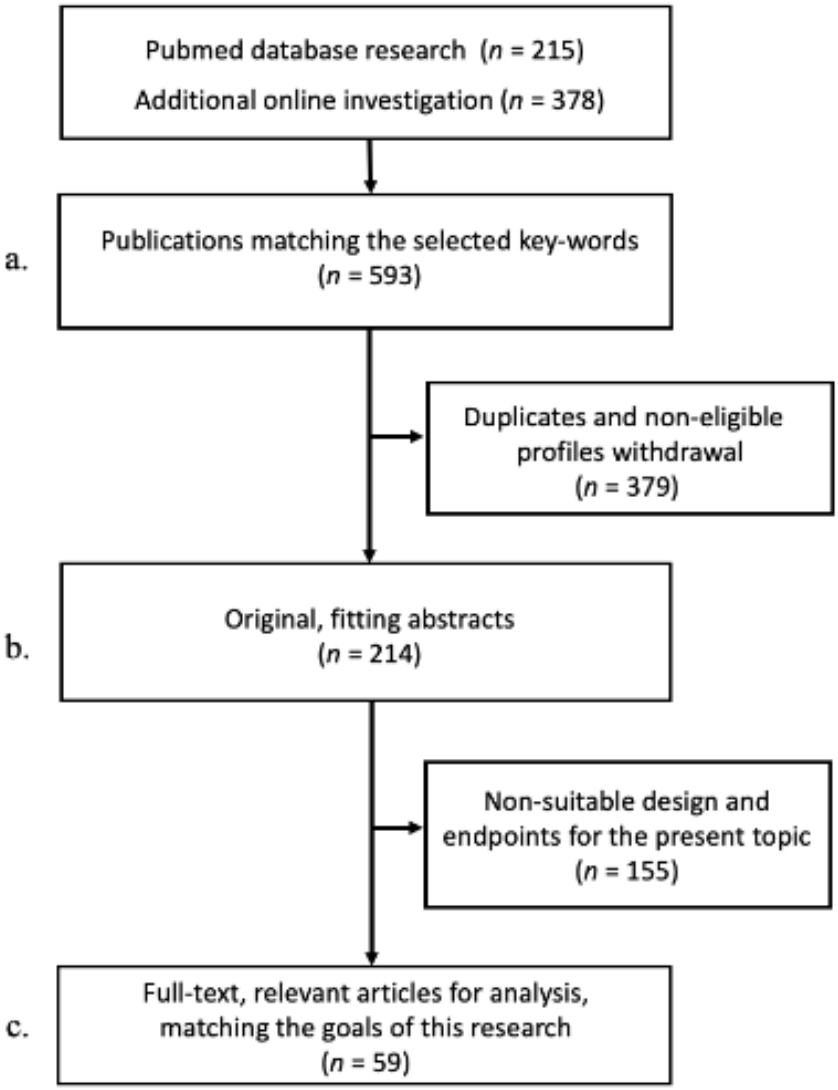

Figure 1. Flow diagram resuming the selection process. **(a)**. Screening for publications matching the selected key-words; **(b)**. Data selection and analysis focusing on original, fitting abstracts; **(c)**. The finally appointed full-text, relevant papers for analysis.

Structural and Functional Aspects

From a morphological point of view, the human vasculature associates a wide range of perfusion structures whose diameter varies from 2 cm (the aorta) down to 5 μm (the distant capillaries) (Figure. 2). [3, 6, 9, 10]

Commonly, the macrocirculation assembles (Figure. 2) vessels with a diameter greater than 100 μm, while the microcirculation refers to the kilometric "ubiquitarian" vascular network that associates different types of arterioles, capillaries, and venular conduits, whose diameter varies between 100 μm and 5 μm. [3, 9, 10]

The microcirculatory conduits exhibit a specific histological wall arrangement, intimately adapted to each tissue region and its various haemodynamic specificities. [3, 9, 11]

Arterioles pursue the smallest distal arterial branches and are usually connected to the distal meta-arterioles, which benefit from precapillary sphincters that coordinate and harmonise regional blood flow resistance to tissues. [10, 12]

A part of the proximal arterioles possesses, similarly to the macrocirculatory arteries, a thin smooth-muscle medial layer [10, 12] that participates directly in the coordination of the microcirculation and contributes to the development of MAS and MAC pathologies. [2, 12]

Capillary structure is centered around a basement membrane that harbours the endothelial cells, surrounded by pericyte cells. [2, 3, 10] All these essential histological constituents act as a selective natural barrier between the blood flow and the surrounding tissues. [9-12] This effective microcirculatory arrangement finally acts as a unique functional unit, playing a pivotal role in tissue perfusion, oxygen and nutrient diffusion, and in all parallel metabolic, hormonal, and immunological signalling. [10] It is governed by a central neural-mediated vasoactive counterbalance and by a local veno-arteriolar axonal reflex. [9, 12] This important and continuous interplay between macro- and microcirculation is known as haemodynamic coherence. [13]

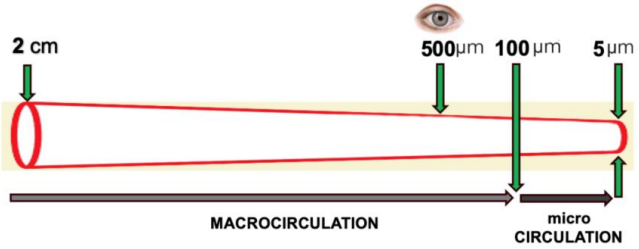

Figure 2. A schematic representation of the arterial vasculature.

Commonly the arterial vasculature is divided into macro vs. microcirculation, upon the vessel's diameter: "the macrocirculation" holds diameters > 100 µm), while the microcirculation refers to diameters < 100 µm, encompassing the arterioles and the capillaries). Taking in account that visual acuity becomes challenging for DSA exploration regarding vascular structures around 500 µm, the morphological and functional analysis of microcirculation requires specific diagnostic technology and exams.

Abbreviations: DSA, digital subtraction angiography

Microcirculatory Pathological Pathways

Microcirculatory damage in the diabetic neuro-ischaemic foot syndrome is mainly generated by the noxious effects of chronic hyperglycaemia. [10-12] Persistent high glycaemic levels can induce both direct cellular toxicity at systemic level (including the widespread endothelial cells) and additional indirect ischaemic harm through the resulting hypoxia in all damaged microcirculatory endothelial organs and systemic regions [3, 12].

Hyperglycaemia essentially harms the mitochondria of the targeted cells, further inducing uncontrolled amounts of reactive oxygen species (ROS) with high tissue toxicity. [10, 11, 14] Concomitant deleterious metabolic pathways, such as the hexosamine, polyol, and protein kinase pathways, further contribute to regional ROS accumulation. [3, 10-12]

In parallel, an accelerated glycation process generates excessive, irreversible advanced glycation end-products (AGEs), which activate macrophages and arteriolar smooth muscle cells, causing additional stress and injury to the vascular endothelium. [15] AGEs are also able to directly damage the endothelium of the arterioles and capillaries in the CLTI limb [11, 15] and to gradually impair the normal intravascular wall architecture by favouring intramural sclerosis, followed by hyalinosis, and finally by microcalcification deposits. [10, 11, 15]

These initial morphological changes (Figure. 3) are accompanied by early functional endothelial degeneration, leading to the loss of regional "haemodynamic coherence". [13, 15] A precocious diagnosis and stratification of the initial endothelial cell damage are essential in the assessment and prognostic evaluation of the foot's neuro-ischaemic mVD. [3, 11, 12, 15]

Ultimately, these intramural medial-layer transformations lead to local inflammation, increasing hydroxyapatite crystal deposition, irreversible medial layer destruction, and further extended calcifications (Figure. 3), ending in vessel loss. [4, 5]

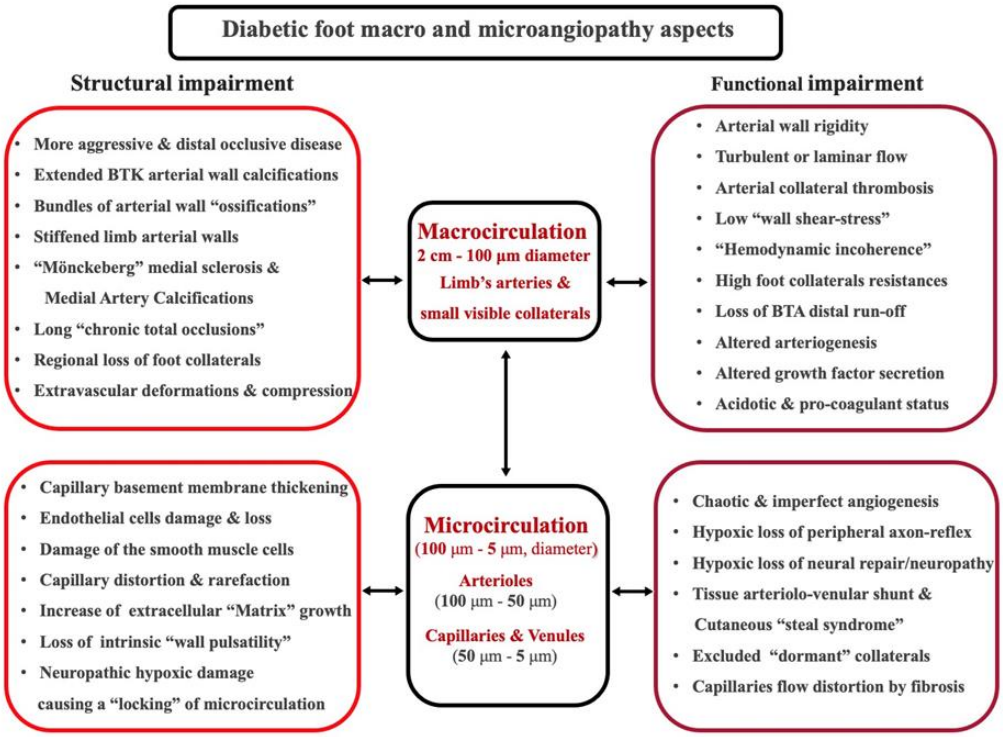

Figure 3. Structural and functional damage in diabetic macro and microangiopathy.

A brief illustration of main structural and functional vascular impairment encountered in diabetic macro and microangiopathy in the context of medial artery sclerosis, calcification, an microvascular disease, independently from atherosclerotic affliction.

Abbreviations: BTA, below-the-ankle; BTK, below-the-knee

Interestingly, the same AGE cellular aggression equally enhances extravascular interstitial, muscular, and connective tissue fibrosis [10, 15] by damaging matrix proteins such as elastin, laminin, and type IV collagen.

In other words, mVD capillaries and arterioles must confront a dual mechanical adversity represented by: (i) intrinsic wall stiffening, and (ii) extrinsic perivascular conjunctive matrix "freezing". These structural transformations induce functional alterations such as increased tissue hypoxia, local acidosis, inflammation, and loss of normal organ function. [12, 15]

Kintrup et al., in a nailfold capillaroscopy study of hypoxic limbs, [16] described severe rarefaction and distortions in capillary morphology that lead to uncontrolled microvascular vasomotor reactions and linked fluid extravasation with additional mVD wall thickening. [16] As a result, a decrease in normal blood flow parallel to increased microvascular resistance was also reported. [2, 9-11]

In a convergent study by Neubauer-Geryk et al. [17] it was observed that microvascular irregularities increase in parallel with the duration of diabetes and levels of haemoglobin A1c, and that specific endothelial cell injury and basement membrane thickening may vary in different organs with different anatomical and functional characteristics (e.g., differing processes described in the retina, peripheral nerves, myocardium, and musculoskeletal microvasculature). [10, 17]

Among the various systemic localisations of diabetic mVD, several organs have been extensively studied in the literature, [10] such as: the well-documented retinopathy and nephropathy, [11, 12] the microvascular heart damage (rest angina, myocardial stiffness, systolic-diastolic dysfunction, etc.), the lung microangiopathy (alveolar wall fibrosis, pulmonary hypertension, etc.), the brain microangiopathy (lacunar stroke, global cognitive decline and dementia), and the peripheral nerve hypoxic neuropathy (vasa nervorum depletion, parallel demyelination and axonal destruction, the neuropathic cutaneous "oxygen steal syndrome", the loss of peripheral vasomotricity, and the concomitant "locking" of the microcirculation). [9, 18, 19]

Focusing on the macro- and microvascular peripheral disease in CLTI, this latter essentially involves the loss of the vasavasorum and synchronous capillary distortion and rarefaction in the affected foot. [17, 19] This complex process, only partially understood, leads to independent lower-limb arteriolar medial sclerosis with the formation of calcification hubs, and very likely contributes to the loss of microvascular wall autoregeneration. [3, 11, 19]

Notably, microangiopathic CLTI does not encompass only specific endothelial and medial layer microvascular changes but also additional constraints from a characteristic perivascular rigid, sclerotic, and further calcified environment, represented by concomitant musculoskeletal microangiopathy (diffuse fibrosis, limited joint and fascial mobility, ligamentous hypertension, and secondary neuro-ischaemic foot compartmental syndromes). [3, 10]

Interestingly, through reciprocal interaction, the presence of peripheral neuropathy appears correlated with a significant decrease in both the morphology and number of the foot's nailfold capillaries (as a microangiopathic manifestation in diabetic neuropathic limbs). [3, 11, 17] Conversely, the progression of CLTI with advancing capillary hypoxia triggers inhibition of regional angiogenesis and vascular progenitor cell production; these hindrances in turn reinforce the local hypoxic, acidotic, and pro-coagulant milieu. [9-11, 19]

While part of the mVD clinical manifestations may be reversible (temporary regional loss of perfusion with compensation through "dormant" microvessels), [11, 19] other types of microvascular damage prove to be irreversible, as described by O'Neal et al. in their "end-artery occlusive disease" (EAOD) theory. [20]

Taking these circumstances into account, the role of wound- and flow-oriented foot reperfusion for better tissue healing has been amply discussed in the last decade's literature [21] and seems to support the hypothesis of improved tissue recovery [21, 22] when applying, whenever technically feasible, the angiosome, EAOD, and woundosome theories. [21-23]

Applied clinical comments: Since macro- and microvascular damage in diabetic neuro-ischaemic CLTI limbs can express a myriad of clinical appearances, an intentional topographic revascularisation could be considered in these patients. This goal can be achieved by careful evaluation of the local vascular anatomy, the foot's remaining patent arterial collaterals, the wound characteristics, and by taking into account the individual MAC, MAS, and mVD interrelated features as part of a unitary disease, according to each patient's peri-operative risk class.

Clinical Aspects

In most of the cases, the diabetic neuro-ischaemic foot's mVD develops silently (during months or years) until a notable clinical event (the passage from claudication to CLTI, extended foot wounds and sepsis, painful DPN, other hyperglycaemic systemic organ disorders, or sudden macrovascular atherosclerotic events) can disrupt the fragile perfusion balance created by regional arteriolar and capillary collateral compensation.

A parallel interplay (not fully understood) between CLTI, the severity of tibial and pedal arterial medial calcifications, and the presence of severe diabetic peripheral neuropathy (DPN) was already observed and emphasised since 1982 by Edmonds et al. [24] This concomitant microangiopathic interaction was recalled in contemporary CLTI and diabetic neuro-ischaemic foot literature, [25, 26] while its intimate molecular mechanisms still await to be decrypted. Nevertheless, below-the-knee (BTK) medial arterial calcifications in CLTI were found to represent an independent risk factor for MALE and major amputation, with or without manifest neuropathic affliction. [26, 27]

Stratification and related morbimortality

The diabetic neuro-ischaemic foot's microangiopathy reunites arterioles and capillaries whose diameter varies between 100 μm and 5 μm (Fig. 2). Equally assimilated as mVD, [10-12, 18] this morbid entity does not at present benefit from a specific BTK or below-the-ankle (BTA) arteriolar and capillary consensual severity classification. [3, 9, 10, 12] The presence of "latent" foot microangiopathy [28] and the duration of diabetes [29] may represent independent severity factors for mVD, leading to higher morbidity and amputation [3, 9-12, 28].

Currently, MAS and MAC (apprehended as a unitary systemic pathology) comprise characteristic arterial tunica media lesions in vessels that naturally possess this layer (in other words, all the macro- and part of the microvascular arterial structures, excepting the vast capillary network) [3, 10-12]. This degenerative process is commonly encountered in patients with diabetes mellitus, renal insufficiency, and various chronic inflammatory systemic diseases; it is also coupled to ageing. [2-5] As stated hypothesis of this review, MAS and MAC may represent essential interrelated pathological components (probably expressing an evolutive link) [2-5] and may integrate a larger systemic macro- and mVD picture. [2-4] Several staging scores based on the MAC radiological morphology, extent, size, and distribution have been proposed in recent years to correlate and compare individual CLTI characteristics and prognostic outcomes [2, 4, 27, 28, 30-32].

Amputation risk in patients with CLTI exhibiting MAS and MAC

A conspicuous and updated analysis by Lanzer et al. [2] evaluated MAS and MAC as an independent, unitary systemic vascular pathological process, different from atherosclerosis, that comprises both sclerosis and calcification phenomenon at different evolving stages. Multiplane X-ray radiography allows differentiation between medial ("rail-tracking") and intimal layer calcifications. [2, 4, 5] Thin-slice CT imaging and peripheral Duplex ultrasound studies may add information to support specific stratification in these patients. [2] The authors documented that the presence and the extent of MAC located in BTK arteries significantly associate with a major risk of developing CLTI, tissue and limb loss, together with high mortality rates [2]. Patients with MAC were also subject to low patency rates and higher revascularisation failure following interventions [4, 5].

Kim et al., in a 116-patient study exhibiting symptomatic PAD, [4] recently confirmed that high lower-limb MAC scores correspond with aggravating limb ischaemia; this correlation persisted even after adjustment for individual cardiovascular risk factors and the severity of occlusive disease. [4] In this study, MAC also appeared to directly correlate with higher rates of major amputation and mortality. [4]

A recently published prospective study involving 979 patients with diabetic foot ulcers, conducted over a nine-year period by Chen et al. [30] reported PAD in 53% and MAC in 8% of patients. Patients with PAD together with pedal MAC showed a significantly higher risk of amputation after adjusting for gender, age, albumin, haemoglobin, and diabetic retinopathy status. [30] Interestingly, although the presence of concomitant foot microangiopathy was not systematically evaluated, the presence of retinopathy was consistently recorded in the study protocol. [30]

An analogous paper by Liu et al. [31] examined a retrospective 250-patient cohort with CLTI over an eight-year period. The MAC score was applied for pedal artery evaluation using a minimum of two plain foot radiographic views. A higher score was significantly correlated with an increased risk of major amputation. [31]

In another distinct and convergent analysis dedicated to small artery disease (SAD) in association with MAC, a retrospective review was conducted on 223 patients with CLTI by Ferraresi et al. [32] The authors used a three-level imaging score based on angiographic findings for SAD and foot plain radiographs for MAC. They concluded that SAD and MAC represent manifestations of the same pathological process, in which the combined severity scores proved to be powerful predictors of amputation risk and MALE in patients with CLTI. It should be noted that this study is one of the few that associates radiographic MAC diagnosis with angiographic SAD (for the macrocirculation) and parallel $TcPO_2$ (for complementary microcirculatory assessment). [32]

Amputation risk in patients with CLTI adding specific foot's mVD

Similar findings to those stipulating the deleterious MAC influence on limb preservation and mortality have been independently described with regard to the parallel presence of diabetic foot mVD. [3, 9, 11, 12] This represents a common, yet poorly diagnosed and monitored, dreadful diabetic complication. [3, 11, 12] It is known that among the microcirculatory structures, the vast capillary network does not exhibit an individualised medial layer capable of harbouring "potential" MAC deposits. [2-4, 11] Thus, focused microvascular assessment in CLTI, for studying these ubiquitous vessels (with <100 μm diameter), requires a complementary and specific microvascular approach to be used alongside macrovascular plain X-ray or CT exploration, although the latter are very useful for MAC evaluation [3, 12, 25, 31, 32].

A vast 125,000-patient diabetic cohort was followed longitudinally over a mean nine-year period by Behroozian et al., [12]. The authors assessed the reciprocal relationship between predominant microvascular diseases (retinopathy, neuropathy, and/or nephropathy) and peripheral limb microangiopathy, either in isolation or in association with PAD or CLTI [12]. Using Cox hazard regression, they demonstrated a 3.7-fold increase in amputation risk in the presence of lower-limb mVD alone. This risk expanded up to 22.7-fold with the additional presence of PAD or CLTI [12]. Interestingly, one in six major amputations occurred in the context of diabetic foot microangiopathy alone [12].

These observations were confirmed in a recent review by Biscetti et al., [33] who analogously found that the presence of diabetes in PAD and CLTI can increase the risk of major amputation tenfold through complex vascular interactions including systemic and local foot mVD [33].

Another recent and expressive mVD analysis was conducted by Jett et al. [34] in a 153-patient cohort with PAD. All patients underwent transcutaneous microcirculatory assessment by spatial frequency domain imaging (SFDI). [34] This technology combines structured illumination at multiple wavelengths in the visible and near-infrared light spectrum. The patients with PAD were divided into four groups of severity:

1.without diabetes,

2.with uncomplicated diabetes,

3.with diabetes + neuropathy,

4.with diabetes + neuropathy + retinopathy (severe systemic complications).

Following logistic regression analysis, the authors documented those patients with PAD associated with any form of mVD located at one or multiple sites exhibited a significant and progressive risk for wound development and for MALE evolution towards limb loss [34].

Our diabetic team's research on the same topic developed an original four-grade (A–D) severity scale for the concomitant assessment of infra-malleolar macro/microvascular disease in CLTI feet [35]. In this retrospective study, the macrocirculatory angiographic features (pedal arteries, foot arches, and collaterals), combined with a dichotomic calcification evaluation, were complemented by parallel microcirculatory analysis using $TcPO_2$ and SPECT-scan imaging [35]. The results

confirmed a significant difference in limb salvage rates observed in progressive severity from A to D grades, with the poorest outcomes recorded in grade D, which were distinctly analysed in patients with and without diabetes. [35]

All these observations concerning the significance of mVD for tissue and limb loss (parallel to its MAS and MAC interconnections) correspond with analogous results from contemporary CLTI publications. [3, 4, 9, 12, 27, 36] Notably, in patients with technically impossible or failed arterial revascularization, that associate severe mVD, MAS and MAC disease in the foot, the performance of inferior limb deep veins arterialisation could be considered as extreme indication for limb salvage. [3]

Applied clinical comments: MAC and MAS (analysed as interconnected entities), together with mVD (as a distinct pathology or accompanying both MAC and MAS), have a clearly significant and harmful influence on the diabetic foot, promoting tissue and limb loss. It also appears that mVD (vessels <100 μm), when studied alone, can increase the amputation risk up to 23-fold in diabetic patients presenting CLTI. All these macro/microvascular pathological entities (different from atherosclerosis) should be acknowledged as interrelated pieces of same systemic disease, and carefully assessed by stringent diabetic team-work, in parallel with mandatory macrovascular revascularisation.

Diagnostic Techniques

Patients exhibiting mVD, MAS and MAC may initially lack ischemic signs and symptoms; this can be explained by the absence of hemodynamically severe arterial narrowing in early stages of disease. Due to the stiffness of peripheral arteries vessels, the ankle-brachial index (ABI) is often without clinical relevance. [2, 4, 11, 36-38]

MAC and MAS diagnostic methods currently gathers:

- Conventional radiography showing for MAC the classical "railroad track" images [4, 5].

- Computed Tomography, that can display MAC with 70% sensitivity [5].

- Pedal acceleration time [39] and arterial pulsatility index, [40] use extravascular ultrasound technology and can provide specific BTK 'vascular resistance' and 'collateral reserve' information [39, 40].

- Intravascular ultrasound (IVUS) can correctly describe MAS and MAC morphology; it remains however an invasive exam [4, 5].

- Extravascular ultrasound (EVUS) proves equally useful in MAS and MAC non-invasive exploration by direct wall analysis also by indirect pulsatility index assessment [38, 40].

- Optical coherence tomography offers high imaging resolution and affords a clear delineation of MAC and MAS, including the transition zone towards microcirculation and mVD [5].

Preferential mVD diagnostic (<100 μm-diameter vessels) can be achieved by:

- Transcutaneous Pressure Oxygen monitoring (TcPO2) that measures the skin oxygen levels (using indirect capillary flow appraisal), [3, 12, 38]

- Near-Infrared Spectroscopy (NIRS) provides non-invasive, continuous tissue oxygen distribution data in specific foot regions [42].

- Laser Doppler flowmetry and skin perfusion pressure [41] adding Laser speckle [43] imaging display effective, non-invasive, and real-time analysis of territorial capillary flow in the foot [41, 43].

- Hyperspectral imaging can afford reliable monitoring of the foot microcirculatory oxygen saturation in deliberately targeted territories [44].

- Cutaneous video-capillaroscopy [16, 17] enables direct, high-resolution, morphological and functional capillary damage analysis

- Spatial Frequency Domain Imaging associates structural skin papillary haemoglobin evaluation, to functional tissue oxygen saturation data [34].

- Nuclear medicine: SPECT and PET scan technologies can provide direct intracellular, mitochondrial hypoxic tissue information [45]. Its diagnostic is not conditioned by the damaged flow in arterioles and capillaries in the CLTI foot. Available imaging can complete DSA information particularly for < 500 μm-diameter vessels (Fig. 2), where visual acuity is notably diminished [46].

- Novel Endovascular endothelial cell biopsy can be achieved by various techniques [47]. It displays with high accuracy a precocious diagnostic about the presence, the severity, and the prognostic of mVD endothelial damage in diabetic CLTI feet, owing 91% pooled technical success rate. [47] This modern technology can be associated to distal foot video-capillaroscopy and may add important information in distinguishing independent mVD either from upstream "macrovascular-induced" flow alteration, or from eventual parallel neuropathic cutaneous arteriolo-venular shunting [3, 12, 14, 19, 47].

Combined MAC and MAS information associating mVD diagnostic

- Indocyanine green angiography enables detailed anatomical and haemodynamic macro- and microcirculatory imaging of regional foot perfusion, facilitating eventual targeted revascularisation [48].

- Contrast-enhanced magnetic resonance is represented by arterial spin labelling (ASL) and blood oxygenation level-dependent (BOLD) techniques; it allows a direct study of microvascular flow in capillaries associated with an indirect appraisal of tissue oxygen saturation [49].

Applied clinical comments: The diabetic neuro-ischaemic foot's microangiopathy may also exhibit various insidious clinical forms, particularly in patients with chronic, multifactorial, hypoxic foot ulcers. These patients may have palpable peripheral pulses and apparently acceptable macrocirculatory Duplex waveforms in BTK arteries, and are not necessarily suspected of being at high risk of limb loss. Careful systemic double-checking in search of other parallel systemic microangiopathic locations, together with at least two consecutive microcirculatory foot examinations ($TcPO_2$, NIRS, laser flowmetry, skin capillaroscopy etc.,), may help the experienced clinician to unveil these atypical CLTI forms presenting predominantly as mVD.

Treatment Options

Macrovascular revascularisation (by open surgery or endovascular techniques) in patients exhibiting PAD and CLTI remains the gold standard in current practice. However, this paradigm cannot constantly predict accurate target tissue regeneration, [37, 38] particularly in diabetic neuro-ischaemic limbs, [4, 5] which may present poor collateral reserve and an exhausted macro- and microvascular foot run-off. [4, 12, 20, 38]

From a contemporary perspective, MAC, MAS, and mVD can be perceived as stages of the same degenerative systemic vascular disease, observed at different unfolding grades, vascular wall architectures, and timelines. [3] This process may act independently and in parallel with atherosclerotic damage and its specific risk factors. [3, 10, 12, 32]

At present, there is no consensual therapy specifically dedicated to diabetic MAC and microangiopathy. [3, 5]

Several studies have evaluated a hypothetical benefit from using monitored aerobic exercise, phosphodiesterase-3 inhibitors (with vasodilatory effects), [15] additional vitamin K preparations, [5, 50] specific betaine supplementation in the diet (expecting reduction of "oxygen reactive species"), [3, 11] acetazolamide and aldosterone periodic treatment, [5, 19] etc. The clinical results have remained disappointing.

Applied clinical comments: The CLTI diabetic foot requires prompt macro- and microvascular diagnostic evaluation followed by expeditious macrovascular revascularisation and best multidisciplinary diabetic team treatment. Although accessibility in daily practice may vary, microcirculatory diagnostic assessment should form part of any CLTI evaluation. Systematic surveillance through a regular diabetic foot multidisciplinary team appears mandatory.

Limitations

- One major limitation of this review is represented by the difficulty of drawing synthetic information from the vast "diabetic microangiopathy" field, which is far from being conspicuously acknowledged. Other technical impediments are mentioned in the literature and concern:

- A precise distinction between medial and intimal calcifications in small arterial branches, [4] particularly at the arteriolar microcirculatory junction, using plain X-rays and current CT imaging, appears challenging for some practitioners. [4]

- Unlike the cardiological assessment, regarding peripheral MAC, various methodological protocols are currently in use, which may contribute to a less uniform qualitative and quantitative calcific appraisal. [4, 19]

Perspectives

Recent research has shown that genes associated with type 2 diabetes are also linked to retinopathy and neuropathy involvement [51] as microvascular-related pathologies, requiring further clinical investigation. [51]

Parallel research shows that the anti-aging gene Sirtuin 1 is critical to the prevention of diabetes, cardiovascular disease, ischemia and systemic inflammation. [52] The role of Sirtuin 1 activators vs. inhibitors is critical to the treatment and prevention of diabetic microangiopathy. The early activation of Sirtuin 1 may improve microangiopathic disease in diabetic neuro-ischaemic feet with relevance to tissue and limb loss. [52] The systematic mVD screening at systemic, and at the foot level appears as essential strategy, reiterated by the recent American Diabetes Association on retinopathy, neuropathy, and foot standards of care in Diabetes-2026. [53]

Conclusion

A high calcific MAC score appears significantly associated with increased major adverse limb events, amputation risk, and mortality in patients with PAD and CLTI. The presence of microangiopathic disease in diabetic neuro-ischaemic feet has likewise proven a deleterious influence on tissue and limb loss, which worsens when parallel systemic localisations are present. Diabetic microvascular disease seems correlated with the medial arterial sclerosis and calcification processes, as interrelated stages of a systemic, macro- and microcirculatory, non-atherosclerotic pathology, carrying an independent and adverse prognostic significance for limb loss.

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Author contribution

Conceptualization and design: VA and AK; research and data curation: VA; methodology of presentation: VA and KD; administrative tasks: VA; visualization and chapter integration: VA, and KD; writing, editing and critically reviewing: all author's contribution; supervision: VA; validation: by all authors. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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