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Microangiopathic disease in the diabetic neuro-ischemic feet: A threatening, often understated contributor, for tissue and limb loss

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ABSTRACT

Conventionally, vessels exhibiting diameters between 100 µm and 5 µm are related to the ubiquitarian *microcirculatory* realm that gathers the arterioles, the capillaries and the venules. This important network represents a fundamental anatomical and functional unit involved in all vital processes of human tissues. The microcirculatory system secures and regulates the microvascular flow and intraluminal pressure within specific organs (including the lower extremities). These purposes are achieved by harmonising the luminal diameter of regional microvessels to the changing metabolic needs, oxygen demand, neurologic signals, and eventual pathological surrounding conditions. Particularly in patients with diabetes mellitus, hyperglycaemia can generate characteristic microcirculatory damage through molecular, biochemical, structural, and functional alterations, which add reactional, self-unfolding, hypoxic and pro-coagulant local tissue conditions. Among various localisations of diabetic microvascular disease (retinopathy, nephropathy, peripheral neuropathy, etc.), diabetic foot microangiopathy essentially produces aberrant arteriolar wall remodelling, coupled with progressive thickening and stiffness of the concerned microvessels, which can lead to increased regional blood flow occlusions and increasing local tissue ischemia. Progressive structural and functional impairment of endothelial cells in arterioles and capillaries is well known in diabetes mellitus and mirrors the gradual loss of microvascular repair ability. Recent video-capillaroscopy research specifically conducted in patients with diabetes documented that the duration of diabetes and the severity of chronic hyperglycaemic levels, significantly influenced the spread and gravity of peripheral diabetic microangiopathy. This latest combined with peripheral macrovascular arterial disease manifested a 12-fold higher risk for major amputation, while suboptimal glycaemic control during and post-revascularization showed a significantly higher propensity for major adverse limb events in patients with chronic arterial disease and diabetic microangiopathy. This review equally avails a succinct overview of current diagnostic and treatment methods applied to diabetic microangiopathy concomitantly to prompt macrovascular revascularization, owing systematic surveillance by a multidisciplinary diabetic foot team. Significant clinical implications of inferior limb microangiopathy isolated, versus associated to diabetic arteriopathy and neuropathy, or to other parallel systemic microvascular manifestations are developed in distinct paragraphs, following referred recommendations, for better clinical knowledge and applicability.

Keywords: *chronic limb-threatening ischemia, hyperglycaemia, diabetic microangiopathy, microcirculation, diabetic peripheral neuropathy, diabetic foot syndrome, arterial calcification, capillary disease, peripheral angioplasty, inferior limb salvage.*

Introduction

Persistent hyperglycaemia is an important triggering factor for macrovascular (cardiac, cerebral, and peripheral) complications as well as microvascular (retinopathy, nephropathy, and peripheral neuropathy) hindrances in type 1 and 2 diabetes mellitus[1,2].

Despite increasing dedicated clinical research, particularly for inferior limbs suffering from chronic ischaemia, high glycaemic levels are reputed to initiate or aggravate diabetic macroangiopathy and microangiopathy at the local and systemic levels. This may lead to increased cardiovascular morbidity, lower limb amputations of all types, and high mortality (up to 50% at five years) in these patients[1,2]. Contemporary reports show that approximately 15% of diabetic patients develop foot ulcers during their lifetime and that, unfortunately, 14%–43% of them will end with inferior limb amputations[3]. The presence of lower limb microvascular disease appears to significantly increases the risk of amputation in patients with evidence of peripheral artery disease (PAD) and chronic limb-threatening ischaemia (CLTI)[1,4]. This latest, represents the most severe form of PAD and an important risk factor for high-level vascular morbimortality and socioeconomic burden, even after patent macrovascular revascularization[3-5]. The microcirculatory system can be pictured as a paired structure to any organ or tissue region in the body, with which is linked through oxygen and nutrient supply, tissue regeneration activity, metabolic, hormonal, genetic and epigenetic signalling[1,2,5]. Among all these systemic interactions, the threatened diabetic, neuro-ischemic inferior limb is also included.[1,3,5-7] The complex and independently unfolding diabetic peripheral microvascular hurdle shows equal importance in CLTI prevention and treatment as the macrovascular occlusive damage, generally more deeply analysed in the literature, for tissue and inferior limb preservation. Diabetic foot microangiopathy gained an increasing interest for limb salvage in the last decades (parallel to diabetic retinopathy, nephropathy, cardiomyopathy, or neuropathy knowledge), that continues to grow[1-3,5-7].

This autonomous piece of the wider metabolic syndrome puzzle embodies nowadays a characteristic and undeniable threat for major amputation in patients with, or without associated macrovascular occlusive CLTI[1,4,5-7].

The aim of this review was to update novel research focusing on diabetic peripheral microangiopathy in CLTI neuro-ischemic limbs, by integrating current aetiologic, structural, pathophysiologic, diagnostic, and therapeutic observations.

This paper also endeavours to highlight the importance of correct multidisciplinary assessment, adapted treatment and follow-up, for every concomitant macro- and microcirculatory presentation in CLTI diabetic patients; we believe that this scope may prove useful for every knowledgeable clinician and interventionist in their current practice.

Material and Methods

PUBLICATION SCREENING

A parallel MEDLINE database analysis associated with unrestricted online exploration was conducted for all publications related to diabetic foot microangiopathy (**Fig. 1**). A preferential data collection from the last decade publications was employed, that involved 16 keywords, including 'hyperglycaemia', 'chronic limb-threatening ischemia', 'macro- and microcirculation', 'diabetic neuro-ischemic foot', 'microangiopathy', 'arterial calcification', 'chronic limb-threatening limb ischemia', among others, without restriction on paper language.

DATA ASSEMBLING AND SELECTION

Marked inhomogeneity in paper designs, research protocols, and pathological process analysis was observed. The article identification, matching criteria, and selection process are illustrated in **Fig. 1.**

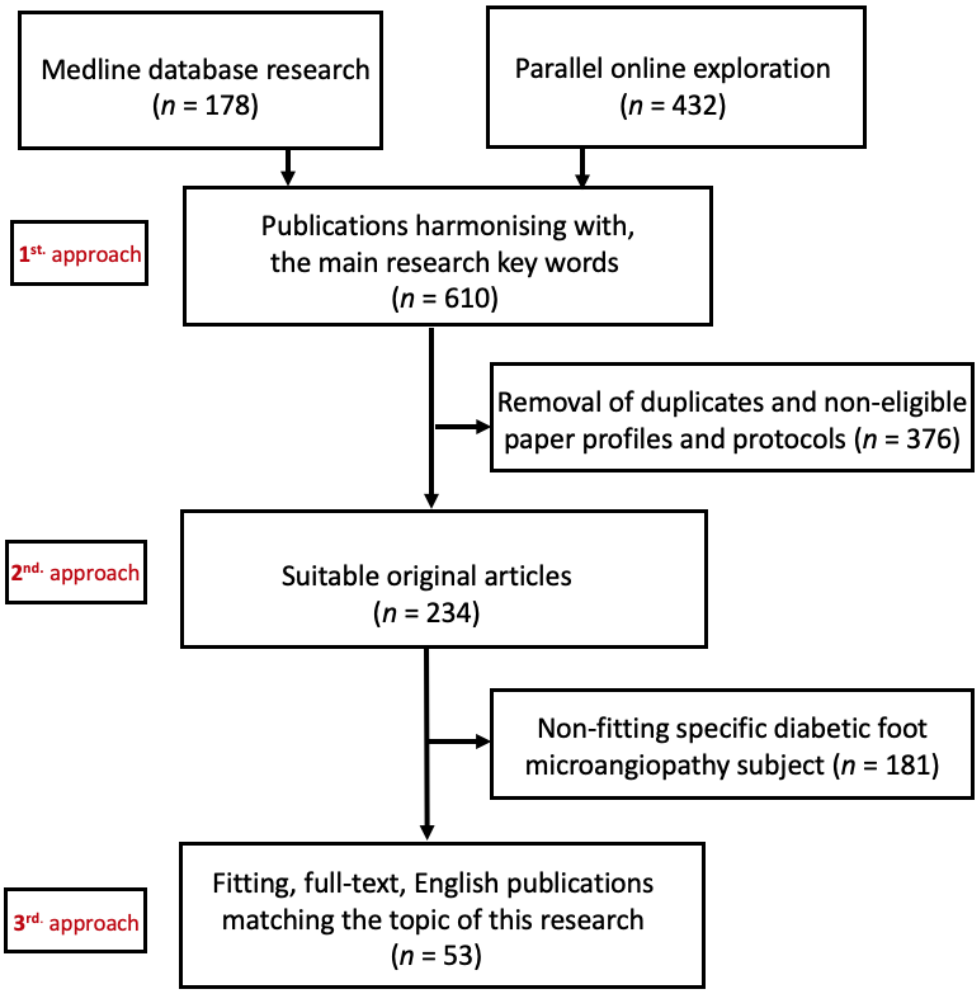

Figure 1: A simplified flow-chart representation of the study selection process:
1st. Approach: Identification of publications fitting the key words of this research.
2nd. Approach: Following duplicates and non-eligible papers retrieval, a rearrangement of unique, suitable articles was completed.
3rd. Approach: Complementary withdrawal of non-fitting papers with the diabetic foot pathology enabled the final selection of articles harmonising this research.

Structural and physiological microcirculatory aspects

The human body vasculature gathers a wide-variety diameter perfusion structures, ranging from 2 cm to 5 µm. Conventionally, vessels with > 100 µm diameter are referred to the *macrocirculation*, while vessels exhibiting diameters between 5 µm and 100 µm are related to the ubiquitarian *microcirculatory* realm that gathers the arterioles, the capillaries and venules[1].

From a structural perspective, one contemporary publication underscoring on this topic, proposes a simplified "six-level" scale arrangement concerning the inferior limb arterial segmentation (Fig. 2), mainly based on characteristic branching levels and on structural histologic criteria[6]. This model differentiates the arterial macrocirculatory levels (1–4) starting from the iliac arteries to the foot arches and their collaterals (all featuring a reproducible five-layer wall structure), followed by the microcirculatory levels (5 and 6) represented by the proximal and distal arterioles and capillaries. These tiny microcirculatory structures afford a specific wall configuration that is fully adapted to each organ or tissue region, owing to five or fewer wall structural layers (with variable thickness)[6].

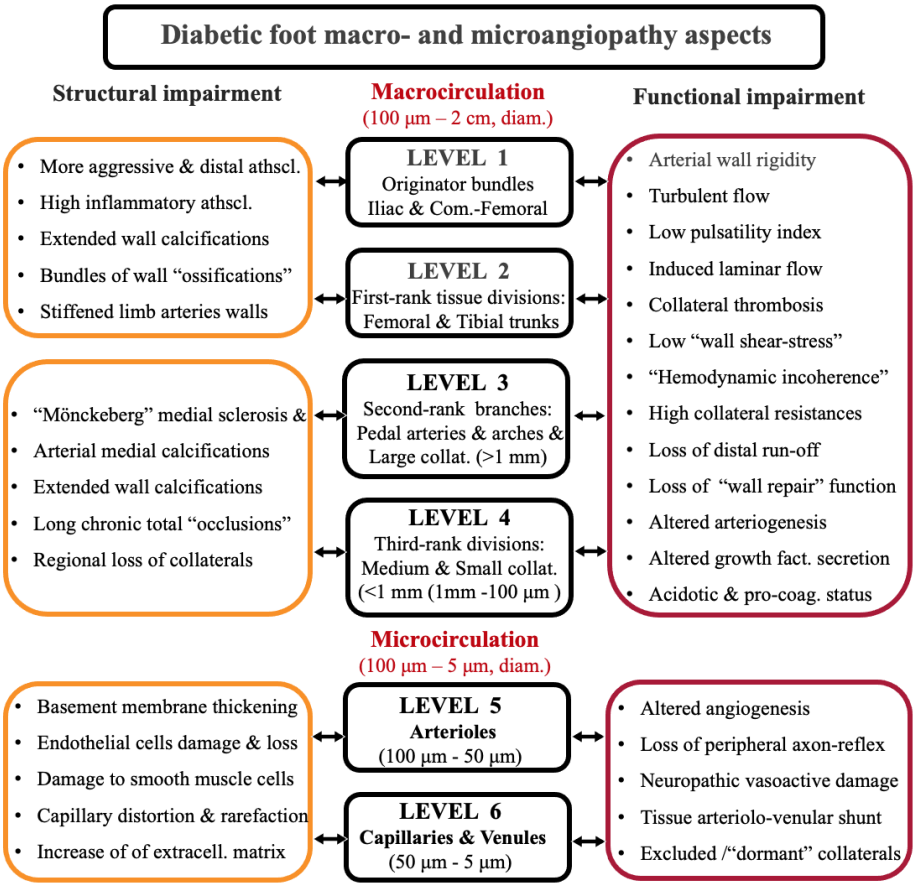

Figure 2: A schematic illustration of main macro- and microcirculatory arterial wall alterations encountered in the complex neuro-ischemic diabetic foot pathology
The left column: Leading structural impairments of the arterial macro- and microcirculatory framework.
The right column: Predominant functional changes with regard to same arterial macro- and microcirculatory diabetic foot model.

The capillaries wall structure is reinforced by a basement membrane that longitudinally sustains a kilometre pavement of endothelial cells surrounded by pericytes[1,7].

The arterioles exhibit a thin layer of smooth muscle cells (adapted to each host organ) and are connected to smaller-diameter meta-arterioles which dispose of the precapillary sphincters[6,7]. These act as important peripheral flow resistance-coordinating conduits that harmonise regional blood flow towards specific tissue territories.[1,7] Hence, any specific organ microperfusion pathology (including the foot) can be assessed as a unique '*anatomo-functional unit*' that associates countless of microvascular pathways to various target tissue-flow distribution[6,7].

From a functional perspective, the integrity of the capillary wall ensures a bidirectional passive and active permeability function, which influences the macrocirculatory haemodynamic parameters. All of these bilateral interchanges need to be conceived in an indissoluble circle of interactions[1,7].

This bilateral unceasing interplay between the macro- and microcirculation is known as 'hemodynamic coherence'[8].

Muscular and skin microcirculatory flow regulation of the normal foot is governed by both a *central neural-mediated* flow balance (vasoconstriction vs. vasodilatation) and the veno-arteriolar axon reflex, a *local neural-mediated* reflex[9]. These functions are essential for controlling harmful variations in foot capillary pressure[9]. Displaying grim consequences since abolished by peripheral neuropathy and by diabetic foot microangiopathy[4,9].

Etiological and pathophysiological pathways for diabetic foot microangiopathy

ACUTE AND CHRONIC PRESENTATIONS

Microcirculatory manifestations can be classified into acute and chronic clinical presentations.

Among the *acute forms*, various types of abrupt microvascular occlusions can be identified,

including those associated with acute limb ischemia, cardiogenic or septic shock, massive distal limb microembolism, vasospastic diseases, critical vasoconstrictive medications, and local septic thrombosis of collateral vessels in the context of diabetic foot syndrome.

The *chronic forms* of microangiopathy are often associated with systemic pathologies, such as hypertension, diabetes mellitus, vasculitis, chronic kidney disease, various medications and drug abuse, and peripheral arterial chronic occlusion at the macro- and microcirculatory levels[9].

The *severity* of the diabetic foot microvascular disease appears to be significantly related to the concomitant presence and gravity of other microangiopathic manifestations, such as retinopathy, nephropathy, and neuropathy, as linked markers of diabetic complications in same individuals[1,9,11].

CAPILLARY DAMAGE

Persistent hyperglycaemia induces both direct systemic cellular toxicity and indirect targeted organ hypoxia by damaging the ubiquitin-dependent capillary network and endothelial cells[12].

Progressive structural and functional impairment of endothelial cells is well known in diabetes mellitus and mirrors the gradual loss of microvascular repair ability[1,7]. More specifically, hyperglycaemia affects the mitochondria of the endothelial cells that consequently generate excessive amounts of 'reactive oxygen species' with recognised tissue toxicity[1]. Parallel and deleterious metabolic pathways are involved, such as the polyol, hexosamine, and protein kinase pathways. A specific increase in the glycation process leads to an excessive load of irreversible advanced glycation end products (AGE), resulting in a parallel increase in their receptors for AGE[1,12]. Thus, further activation of macrophages and microvascular smooth muscle cells, together with stressed endothelial capillary cells, is observed[1,13]. A primordial participation of AGE interactions in the genesis of the complex diabetic peripheral microvascular disease was also postulated[8,13]. AGEs can also directly alter the neuro-ischemic limb's regional arteriolar and capillary endothelial cells and their extracellular matrix proteins including type IV collagen and laminin[13]. Through this detrimental effect, AGEs simultaneously impair the structural integrity and function of the normal microvessel walls by promoting sclerotic tissue accumulation, while concurrently enhancing muscular and connective tissue fibrosis in the diabetic neuroischemic limb[13].

In a recent study using nailfold videocapillaroscopy by Kintrup et al., the authors performed direct capillary quantification in patients with a critical haemodynamic status (20% of diabetic limbs)[14]. The authors observed significant changes in capillary morphology including severe rarefaction, distortions, 'brushy and small loops formation', that inflict a brake-down of the normal capillary shape[3,14]. Parallel functional changes lead to 1) microvascular uncontrolled vasoconstriction (by nitric oxide and prostacyclin decline, following any endothelial injury), 2) to increased local coagulation, and to 3) fluid extravasation and supplementary wall thickening. The abovementioned structural functional damage inflicts a significant increase in microvascular resistance, which decreases the normal blood flow distribution in specific foot territories[1,6,12].

Similar capillaroscopy research by Neubauer-Geryk et al.[15] specifically conducted in patients with diabetes suggested that the duration of diabetes significantly influences the spread and severity of peripheral diabetic microangiopathy[15]. The authors described characteristic hyperglycaemic capillary irregularities, which first included a specific basement membrane thickening that may vary in different types of microvascular beds. For example, the retina, myocardium, peripheral nerves, skin, and muscles may exhibit different types of capillary distortions[1,15,16]. Additional pathological changes in capillaries include (Fig. 2) glycocalyx degeneration, progressive loss of endothelial cells and pericytes, subsequent decline and migration of smooth muscle cells, and dysregulation of vasodilation and vasoconstriction driven by persistent oxidative stress and newly circulating 'vasoactive agents'[1,7,14]. Moreover, the loss of pericytes induces disorganised local angiogenesis represented by acellular capillaries which inflict complementary impaired perfusion in tissues[16]. The presence of peripheral neuropathy appears to be directly correlated to a reduction in toe nailfold capillaries perfusion (as microangiopathic issue)[9], and with higher morbidity and risk for limb loss following revascularization[4,7], in diabetic microangiopathic feet. Hyperglycaemia appears to independently inhibit the growth of vascular progenitor cells, making capillary wall repair impossible[9,16].

ARTERIOLAR IMPAIRMENT

At rest, approximately 25% of the arteriolar network is actively perfused[17].

Unlike capillaries, arterioles feature an extremely thin vascular smooth muscle tunica media that triggers specific pathological transformations[7,11,15,17]. Madonna et al.[16] synthetized the main microcirculatory (arteriolar and capillary) structural and functional damages, inflicted by hyperglycaemia as: 1) *biochemical changes* (by increasing AGE and subsequent oxidative stress); 2) *structural changes* (extracellular, medial layer, excessive storage of matrix proteins, collagen, and fibronectin), and 3) *functional changes* (impaired endothelial cell regeneration, abnormal growth and migration of vascular smooth muscle cells, reduced angiogenesis, neuropathic affliction and loss of local vascular reactivity, ultimately resulting in 'cutaneous shunt' phenomenon)[7,11,12,16]. These changes (Fig. 2) promote an independent, chronic, procoagulant, and ischemic state within the microcirculation[16].

Previous publications documented a thickening process that develops at the level of capillaries and arterioles[7,18,19] initially designed as a progressive 'basement membrane condensing' phenomenon[11,18]. The resulting lumen narrowing was identified as a key *structural change* responsible for reduced blood flow and diminished delivery of oxygenated haemoglobin to the target foot tissues, leading to impaired tissue healing and an increased risk of septic complications[7,12,19].

Diabetic foot microangiopathy enhances aberrant arteriolar wall remodelling[7,16]. This process involves initial wall oedema, damage to smooth muscle cells, and their subsequent replacement through the accumulation of extracellular connective matrix and calcifications (Fig. 2), including lack of regenerative stem cell activation[1,11,16,18]. The resulting medial layer extracellular matrix (altered by chronic hyperglycaemia) may transform into specific local sclerosis, increased wall stiffness, and initiation of medial layer focal calcification hubs[20,21]. These characteristic infragenicular arterial and arteriolar wall calcifications were previously described as 'medial layer degenerative sclerosis' that can associate the 'Mönckeberg calcifications', particularly encountered in diabetic neuro-ischaemic limbs[22-24], also in renal patients.

Regarding *functional arteriolar changes*, beyond the above-mentioned 'cutaneous shunting phenomenon', a consecutive increase in the peripheral vascular resistance leads to a decline in the mean diastolic arterial pressure[20,25].

REVERSIBLE AND NON-REVERSIBLE MICROVASCULAR EFFECT

Microangiopathic manifestations of diabetic foot can harbour both *reversible* and, more frequently, *non-reversible* forms of occlusive disease[7,12]. For the former, transient hyper-pressure in specific foot regions can give rise to non-circulating (yet non-occluded) 'dormant' small collaterals or temporarily shunted arteriolo-capillary territories, which may play a critical role following macrovascular revascularization[6,25]. The *irreversible* modifications assemble all structural and functional wall alterations in collaterals, arterioles, and capillaries inflicted by hyperglycaemia. This state was synthetized by O'Neal et al.[26] as follows: 'In diabetic limbs, areas ranging from a few millimetres of skin to the entire foot may rely on a single end-territory vessel, in accordance with the 'end-artery occlusive disease' (EAOD) theory'[26].

Diabetic foot microangiopathy and major adverse limb events

Patients with diabetes exhibit a more aggressive and distally situated below-the-knee and below-the-ankle atherosclerotic occlusive disease[26], expressed by peripheral arterial disease (PAD) and by CLTI, as an extreme form of inferior limb chronic flow deprivation[10,26,27]. It has been estimated that patients with diabetes with PAD have a 10-fold higher risk of major amputation than patients who are non-diabetic[28,29]. Seemingly, in a vast cohort of 933,597 individuals in a study by Kris et al.[30], they found that diabetic microvascular disease combined with PAD manifested a 12-fold higher risk for major amputation, throughout a seven-year study period[30]. The severity of PAD or CLTI (stratified by macro- and microvascular analyses) was significantly influenced by the duration of diabetes and levels of uncontrolled hyperglycaemia[31].

In another large cohort of patients, Behroozian et al.[7] 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. The authors found an increase in the amputation risk of 3.7-fold, in the presence of lower-limb microvascular disease only; this risk increased to 22.7-fold with the additional presence of PAD[7]. One in six below-the-knee amputations occurred in the background of microangiopathy only[7].

Similarly, previous research by our team revealed that diabetic peripheral neuropathy is an independent and influential factor for poor clinical outcomes of below-the-knee endovascular revascularization[4,12].

According to a recent multicentre retrospective study by Cha et al.[32] on diabetic limb revascularization, perioperative suboptimal glycaemic control showed a significantly higher propensity for *major adverse limb events* (through macro- and microvascular diagnostics) and proved to be an independent predictor for re-interventions after endovascular therapy in patients with diabetes with PAD[32]. Parallel research based on a 979-patient prospective cohort study by Chen et al.[33] recently demonstrated that the presence of medial arterial (Mönckeberg) calcifications in the foot arteries was significantly associated with higher amputation and mortality rates in patients with diabetic foot syndrome. Interestingly, in this cohort, the same type of medial calcifications was analysed, which added a characteristically unfavourable predictive value to limb preservation other than PAD[33]. In a corresponding publication by Ferraresi et al., the authors scored the medial arterial calcification and the small artery disease in a retrospective, 259-inferior limb CLTI analysis[34]. The authors found that these two pathological entities represent manifestations of the same underlying occlusive disease and have powerful prognostic value for major adverse limb events in patients with CLTI[34].

Our group's related research on the same topic[35] developed an original four-grade (A–D) severity scale for occlusive infra-malleolar macrovascular and microangiopathic disease in CLTI-affected feet[35]. In this study, microcirculation was specifically analysed using $TcPO_2$ and SPECT scan imaging. The results confirmed a significant difference in the limb salvage rates observed in crescendo severity grades A, B, C, and D, which were distinctively considered for patients with diabetes and no diabetes[35].

All the aforementioned studies appear to match other parallel contemporary publications on microcirculatory disease implications[9,36,37], including consensual recommendations for CLTI treatment[27,37-40].

Practical point: Patients with diabetes and particularly those with PAD need to be timely evaluated for eventual microangiopathy manifestations, such as retinopathy, neuropathy, and nephropathy. Concomitant microvascular disease should be suspected in the threatened diabetic foot, as it can increase the risk of amputation by up to 23-fold if coordinated management by a diabetic foot team is not implemented.

Diagnostic methods and stratification

Regarding diabetic foot microangiopathy, no uniform consensus is currently available regarding the best diagnostic methodology. *Common clinical findings* associate a worm limb (by arteriolo-venular cutaneous shunting), to chronically inflammatory oedema, and variable degrees of pain, or sensory deficit (by associated neuropathy or denervation)[10-12]. Distal pulses may be present (although more difficult to assess in the presence of oedema), while the capillary filling appears significantly hindered. Variable degrees of tissue loss and local sepsis may be present. Beyond *morphological* stratification by cutaneous video capillaroscopy (discussed above)[14-15], other methods are currently in use (owing to their advantages and inherent drawbacks), such as the following:

- Pedal acceleration time[41] and arterial pulsatility index[42], both based on ultrasound technology, can provide *functional* foot vascular resistance evaluation and parallel foot collateral reserve estimation.

- Transcutaneous pressure oxygen monitoring ($TcPO_2$) measures skin oxygen levels (through indirect microcirculatory blood flow appraisal)[43],

- Near-infrared spectroscopy (NIRS) provides continuous tissue oxygen distribution (StO_2) values in specific skin and muscle regions[44].

- Hyperspectral imaging[45)] can monitor the tissue microcirculatory oxygen saturation in targeted territories (by indirect flow measurements).

- Laser Doppler flowmetry and laser speckle imaging[46] provide non-invasive, direct, and real-time assessments of territorial capillary flow.

- Indocyanine green angiography provides a detailed *anatomical* and *hemodynamic* imaging of

regional foot perfusion enabling targeted revascularization[47].

- Contrast-enhanced magnetic resonance is associated with arterial spin labelling (ASL) and to blood oxygenation level-dependent (BOLD) techniques[48]; both methods enable precise, non-invasive tissue micro-vessel flow measurement and synchronous blood and tissue oxygenation appraisal[48].

- Spatial frequency domain imaging associates structural skin papillary haemoglobin, to tissue oxygen saturation (StO_2) measurements[14],

- SPECT and PET scan technologies[49] that provide direct intracellular and mitochondrial hypoxic tissue information[49]. This aspect may be particularly important for microcirculatory diagnostics[50,51], as angiographic visualization alone of very small collaterals (<500 µm) can be challenging or scarce, owing to the limitations of human eye acuity[6,50,51].

Practical point: *The purpose of precise microcirculatory assessment is to detect specific foot regions with surviving small-vessel blood supply (run-off) for suitable revascularization, prompt wound healing, and reduced amputations.*

Current treatment approaches

During the last few decades, the established paradigm for PAD and CLTI treatment has required *macrovascular* valuation and revascularization[7,10,27,38-40] that remains the gold standard in today's practice. However, specific methods for treating *microvascular* occlusive disease in diabetic neuroischemic feet are scarce despite their equal importance in limb salvage and currently involve systemic control of hyperglycaemic harm[7]. Macrovascular flow restoration (by surgery or endovascular techniques), even by providing successful intentional direct wound revascularization[50], cannot constantly and utterly predict flawless tissue regeneration and limb preservation in all patients, which is particularly true in limbs exhibiting poor collateral and microvascular foot run-off[36-40]. Diabetic microangiopathy should be associated with the systematic implications of a multidisciplinary diabetic foot team[10,27,39] Parallel therapies (without standardized application) directed to *microcirculation improvement* were also proposed[7,16] such as the following: 1) controlled aerobic exercise; 2) use of antiplatelet agents and lipid-lowering and glucose-lowering medications[7,10,27,39]; 3) use of 'phosphodiesterase-3 inhibitors' that add antiplatelet and vasodilatory properties[13 4];) specific "Betain" supplementation in patient's daily diet (owing to decreased hypothesized diminution of 'reactive oxygen species')[16 5];) use of pro-angiogenetic factors[13-39], among others. Unlike macrovascular diseases, diabetic microangiopathy does not provide homogeneous recommendations for treatment to date. All the above-mentioned therapeutic observations are important, yet remain under clinical investigation owing to a lack of uniform evidence presently.

One specific **limitation** of this review is related to the vastness of diabetic microangiopathic disease (not entirely acknowledged), and to inherent difficulty to detail most of interrelated topics that it covers. Future publications, specifically focusing on preclinical, or clinical aspects, may afford much extensive introspection for selected subjects in this extensive research ground.

Practical point: *The diabetic microangiopathy requires a prompt macro- and microvascular diagnostic followed by punctual macrovascular revascularization. Although with variable accessibility in daily practice, the microcirculatory diagnostic should integrate any CLTI basic assessment. A systematic surveillance by a regular diabetic foot multidisciplinary team appears mandatory.*

Perspectives

Recent research by Lyssenko et al.[52] documented that genes associated with type 2 diabetes are also linked to retinopathy and neuropathy as microvascular-related pathologies, which require future targets for clinical investigation[52]. Until novel, or improved diagnostic technology (e.g. 'laser speckle'[53], 'implantable micro-oxygen sensors'[54], or 'peripheral fractional flow reserve'[55]), adding specific biomarkers, and standardised methods for micro-flow restoration become available, stringent preventive surveillance of all feet at risk of microcirculatory compromise by a multidisciplinary team appears essential to avoid amputation[7,10-12,27,40].

Conclusion

The presence of diabetic lower limb microangiopathy requires clinicians' awareness and understanding that microvascular disease always represents a multiorgan disorder with a myriad systemic

presentations. Its association with peripheral arterial disease and neuro-ischemic diabetic foot syndrome indicates a potentially high cardiovascular morbidity, mortality, and amputation risk, which necessitates close surveillance of patients with prompt referral to specialised centres for expeditious revascularization and multidisciplinary monitoring.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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