Diabetic Peripheral Neuropathy in the Macrocirculatory and Microcirculatory Chronic Limb-Threatening Ischemia Puzzle: Does It Act as an Additional Factor for Vascular Damage?

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In 2019, approximately 9.3% of the global population was estimated to have type 1 or type 2 diabetes mellitus (DM), and about 4.2 million deaths were attributed to diabetes-related complications.[1] Among these complications, sensorimotor diabetic peripheral neuropathy (DPN), frequently accompanied by autonomic involvement, represents the most common neural disorder affecting the lower limbs.[2] Confirmed DPN prevalence ranges from 32% to 52%, depending on diabetes severity and duration, associated comorbidities, geographic variation, and diagnostic methodology.[3] DPN substantially reduces quality of life and is associated with increased all-cause and cardiovascular mortality among patients with diabetes.[3] Approximately 80% of patients with diabetic foot (DF) ulcers present varying degrees of DPN, while nearly 37% also demonstrate latent or clinically evident ischemic features.[4,5]

Historically, DPN has been closely associated with lower extremity arteriopathy[5] and severe infection of the foot.[4,6] This complex clinical entity was previously described as "multifactorial DF gangrene",[6] a concept initially proposed by Levy[6] in the pioneering *Textbook of Chiropody*, published in 1914.[6] The same work also introduced early recommendations for multidisciplinary management of neuroischemic wounds, an approach that has only gained widespread clinical validation in recent decades through improved outcomes and survival among patients with DM.[7]

Potential interactions[8,9] between DPN and chronic limb-threatening ischemia (CLTI) were initially suggested by observations of more extensive infrapopliteal arterial calcification,[7–9] aggressive below-the-knee (BTK) arterial occlusive disease,[8,9] and delayed wound healing despite technically satisfactory angiographic outcomes. These observations have been increasingly reported over the past 4 decades,[8] yet robust clinical evidence remains limited.[8–11]

The Global Vascular Guidelines (GVG)[12] document on the management of CLTI emphasizes the importance of a systematic multidisciplinary approach in the treatment of complex morphologic and functional CLTI lesions, particularly those encountered in patients with neuroischemic DF syndrome.[12]

This review examines the current evidence on macrovascular and microvascular interactions between CLTI and DPN and evaluates their implications for the contemporary management of the neuroischemic DF, with the goal of improving tissue preservation and limb salvage rates.[10,11] It is further hypothesized that progressive DPN may represent an additional risk factor in patients with diabetes who have peripheral arterial disease (PAD) or CLTI.[4,12] Such interactions may contribute to greater perioperative technical complexity, increased incidence of major adverse limb events, [4,12] and poorer postinterventional reflow outcomes.[2,4,8-10,12]

Accordingly, as previously postulated by the Wound, Ischemia and foot Infection (WIfI) risk stratification system in CLTI,[4] it appears important to systematically assess CLTI and parallel DPN neurovascular diagnostic interactions in routine DF wound care,[2,4,12] with the goal of reducing tissue loss and major limb amputation according to current clinical knowledge.[2,4,5,10-12]

Materials and Methods

Publication screening and data selection

This scoping review examined relevant studies of DPN and CLTI in patients with DM and neuroischemic inferior limbs, with emphasis on publications from the past 2 decades. A PubMed search supplemented by an unrestricted online literature search

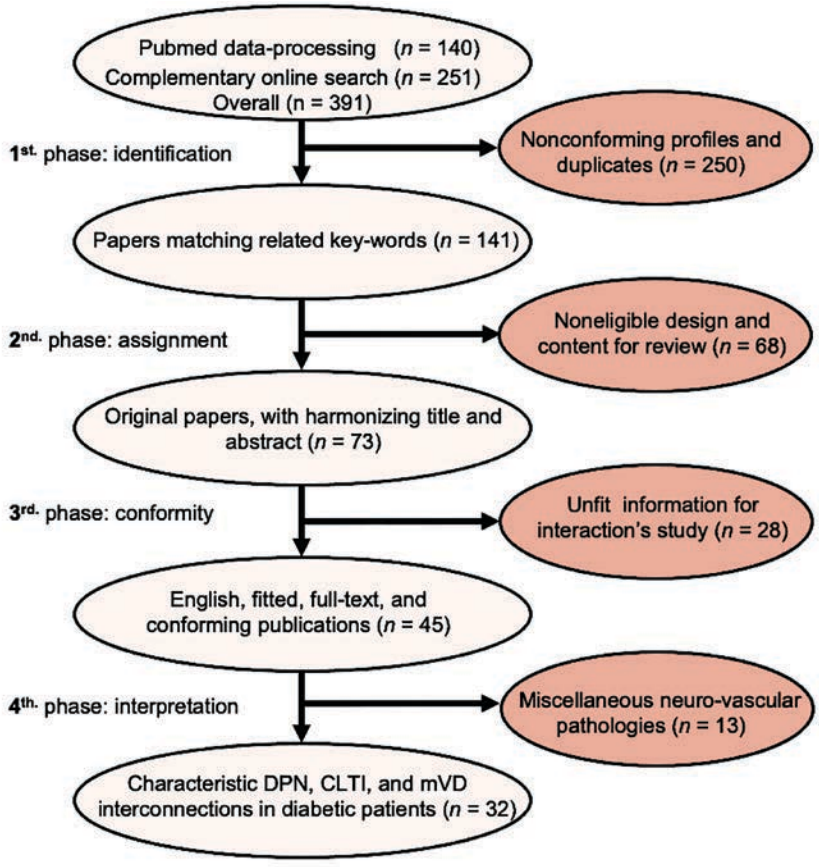

FIGURE 1. A schematized flowchart resuming the selection and study processes. First phase, eligible publication screening and identification; second phase, assignment of matching key words after withdrawal of papers with nonconforming design and content; third phase, checking for correspondent and original papers that harmonize by title and abstract with the goal of this review; and fourth phase, interpretation and analysis of relevant, full-text papers.
Abbreviations: CLTI, chronic limb-threatening ischemia; DPN, diabetic peripheral neuropathy; mVD, microvascular disease.

was performed (**Figure 1**), focusing on specific morphologic and pathophysiologic aspects that may link DPN and CLTI, including potential bilateral interactions. Fourteen words and terms were searched in the database, including "diabetic neuroischemic foot", "chronic hyperglycemia", "chronic limb-threatening ischemia", "diabetic peripheral neuropathy", "diabetic autonomic neuropathy", "diabetic microangiopathy", "diabetic microcirculation", "medial arterial calcification", "medial arterial sclerosis", "diabetic endothelial damage", "lower limb salvage", "below-the-knee arterial revascularization", "diabetic foot ulceration", and "systemic diabetic microangiopathy".

Design for data dispatching and analysis

Utilizing a 4-phase approach, the identification, assignment, conformity, and analytical processes are briefly illustrated in **Figure 1**.

Following data selection, distinct analysis of bilateral DPN/CLTI interplay in DF syndrome revealed little evidence-based information. Few publications matched the scope of this study and were further examined in a narrative review format.

Etiologic Aspects

From an etiologic perspective, persistent hyperglycemia contributes to the development of DPN in approximately half of adults with DM.[1-3] The pathogenesis of DPN is multifactorial and involves not only metabolic syndrome but also dyslipidemia, chronic inflammation, persistent hypoxia, and insulin resistance.[1-3,13] Although the complete pathophysiologic sequence remains incompletely understood, several interconnected mechanisms have been identified (**Figure 2**) and are summarized below.

Direct hyperglycemic cellular damage

DPN arises through multiple molecular pathways that exert direct tissue toxicity during chronic hyperglycemia.[14,15] Activation of the polyol (sorbitol) pathway and excessive formation of advanced glycation end products (AGEs) within neurons increase cellular oxidative stress and promote uncontrolled production of reactive oxygen species (ROS).[14-16] These processes result in progressive mitochondrial harm, local tissue hypoxia, acidosis, and systemic cellular injury (**Figure 2**), including the endothelial cells in regional arterioles and capillaries that are critical to the viability of the neuroischemic limb.[16,17]

Indirect hyperglycemic damage to lower limb innervation

AGEs can simultaneously damage the microcirculatory system by disrupting both the morphology and function of endothelial structures,[14,17] including the neural microvessels responsible for nerve perfusion, known as the vasa nervorum (VN).[5,14,17] Initially confined to endothelial injury, AGE-mediated endothelial damage progressively involves the entire microvascular wall (**Figure 2**) and produces indirect cellular harmful effects through chronic tissue hypoxia.[14,17]

Consequently, the severely impaired perfusion caused by hypoxic microvascular disease (mVD) promotes regional microthrombosis and sclerotic tissue growth.[16,17] This extensive and complex neurovascular microcirculatory impairment[13,14,17] may drive the clinical evolution of neural tissue, which is highly susceptible to hypoxia.[14,16]

Lipid imbalance and insulin resistance

Recent studies demonstrate that dyslipidemia further accelerates the progression of DPN (**Figure 2**) and exerts neurotoxic effects,[14,18,19] primarily mediated by free fatty acids and oxidized low-density lipoproteins.[18,19] Notably, an adverse lipid profile characterized by hypercholesterolemia has been identified as an independent negative predictor of healing in patients with diabetic neuroischemic ulcers and is associated with increased risk of limb loss.[18-20]

Additional etiologic factors frequently associated with DPN include insulin resistance (**Figure 2**), vitamin D deficiency,[21,22] and chronic inflammation.[15] These factors involve multiple inflammatory pathways and collectively contribute to the initiation and progression of DPN.[2,15,23]

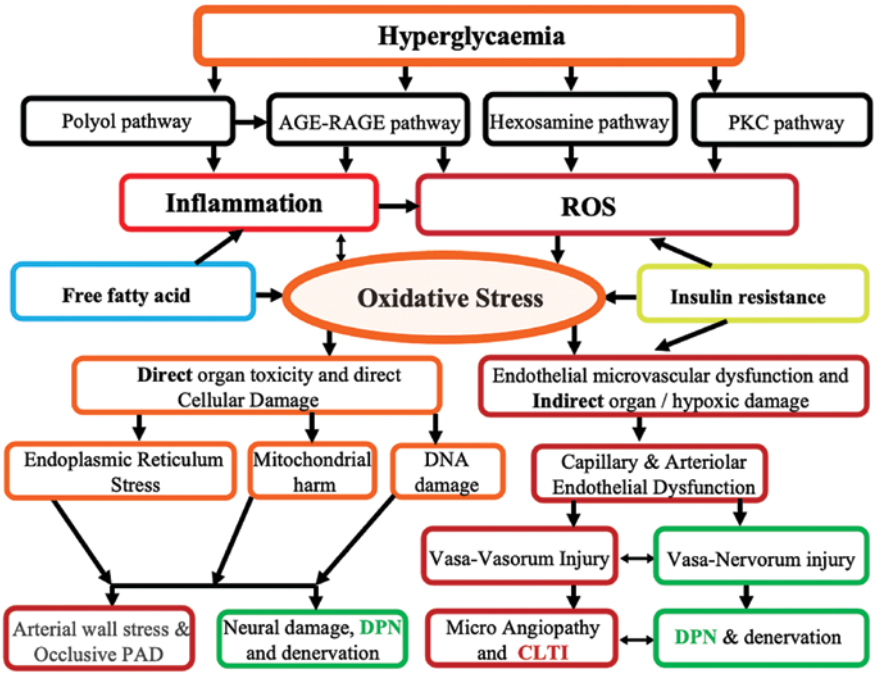

FIGURE 2. Main pathologic pathways triggered by chronic hyperglycemia. Although the entirety of the mechanisms underlying chronic hyperglycemic injury remain incompletely understood, major pathologic pathways include the polyol, advanced glycation end-product (AGE)–receptor for advanced glycation end-product (RAGE) adding hexosamine, and protein kinase C (PKC) pathways. These pathways promote chronic inflammation and increased production of reactive oxygen species (ROS), resulting in oxidative stress. Insulin resistance and free fatty acids may further increase oxidative stress. This oxidative stress can induce its harmful effect either by direct cellular injury (on all tissues) or by indirect hypoxic tissue damage (via the microvascular arteriolar and capillary endothelial dysfunction). As shown on the left, hyperglycemia can cause direct cellular injury to vascular and neural tissues, contributing to peripheral arterial disease (PAD), chronic limb-threatening ischemia (CLTI), diabetic peripheral neuropathy (DPN), and denervation. As shown on the right, hyperglycemia can also cause indirect hypoxic tissue injury through arteriolar and capillary endothelial dysfunction, including injury to the vasa vasorum and vasa nervorum. The resulting tissue hypoxia may compound direct hyperglycemic tissue injury.

Structural and Pathophysiologic Features

Morphologic changes in peripheral neural structures contribute to progressive sensory-motor and autonomic changes in lower limb peripheral nerves, revealing a bidirectional self-perpetuating neurovascular interaction. These interactions may operate during the early or subclinical stages of DPN.[14,17,24,25]

Progressive neural and perineural anatomical alterations

As in other tissues, the lower extremities contain reproducible neurovascular bundles that provide a consistent anatomic relationship between nerves and blood vessels.[26] First described by Taylor et al[26] in the early 1990s, this consistent topographic neurovascular arrangement is essential for normal tissue function and repair following injury.[26] It enabled the authors to better define the complex role of these bundles as specialized vascular pathways that facilitate regional tissue monitoring.[26] Pathologic remodeling originating from either the vascular or neural component of these bundles may result in harmful bilateral neurovascular interactions.[24-26]

However, these essential neurovascular bundles are not damaged solely by intrinsic neural or vascular dysfunction.[25,26] Surrounding tissues that envelop these multifunctional hubs frequently undergo harmful extrinsic transformation, creating a rigid peri-neurovascular sclerotic environment with entrapment features. This diffuse perineural fibrosis appears to result from concomitant musculoskeletal diabetic microangiopathy and contributes to limited joint and fascial mobility, chronic ligamentous hypertension, bone deformities and lysis, and foot compartment syndromes. These conditions generate additional anatomical constraints that worsen the DPN clinical picture.[15,17,24,27]

Together, these intrinsic and extrinsic neurovascular structural alterations promote the creation of a hostile neurovascular environment in DF, facilitating early DPN and mVD development within the complex diabetic neuroischemic foot syndrome.[4,12,13,15,24,25,27] Patients with diabetes experience combined multifactorial injury affecting arterial, venous, neural, and surrounding tissue structures.[3,4,15,17]

Conventionally, the peripheral arterial network is divided into macrocirculatory conduits, including arterial trunks and branches with diameters >100 μm and microcirculatory vessels with diameters <100 μm.[25,27,28]

Macrovascular arterial structural damage produces characteristic morphologic wall changes that lead to regional or global ischemia

in DF tissues, including specific forms of axonal neuropathy observed in neuroischemic feet with CLTI.[4,29] In addition, BTK and below-the-ankle (BTA) macrovascular occlusive disease affects arterial branches that may undergo medial arterial sclerosis (MAS) and medial arterial calcification (MAC).[11,25] These macrovascular changes promote severe arterial chronic total occlusions (CTOs) with common continuous wall calcifications that often correspond to GVG/Global Limb Anatomic Staging System (GLASS)[12] infrainguinal grades 3-4 severity lesions within the affected vessels.[9,12,30,31]

Although the mechanisms underlying MAS and MAC remain incompletely understood, Edmonds et al first reported a possible association between tibial and pedal artery calcification and autonomic DPN in 1982 (**Figure 3**).[8] This association was subsequently confirmed by Gilbery et al[9] and later investigations.[10,17] In most DF patients with complex thrombocalcific occlusions (GVG/GLASS grades 3-4),[12] tissue recovery attempts have been proposed through wound-oriented revascularization and regional foot reperfusion.[26,32] These approaches have been collectively described as intentionally targeted revascularization[30] and include the end-artery occlusive disease (EAOD) theory,[31] the anatomical and functional angiosome model for CLTI foot perfusion,[30] and the older concept of wound-related artery (inline flow),[32] more recently called the *woundosome concept*.[33] Despite encouraging wound-healing outcomes, robust evidence supporting their effectiveness remains limited,[12,17,30,32] and consistent evidence of DPN recovery has not been established.[25]

Microvascular structural impairment simultaneously contributes to DF complications related to chronic hyperglycemia affecting foot tissue, including peripheral nerves. mVD involves irreversible proximal arteriolar damage associated with MAS and MAC[9,11,17,28] and widespread capillary injury characterized by endothelial basement membrane thickening.[24,25,27,28] These changes adversely affect neural structures, including the vasa vasorum and VN, leading to hypoxic depletion and impairment of axon-mediated vasomotor microcirculation.[2,24,28]

The disappearance of capillary networks and small nerve branches also results from inhibited arteriogenesis and angiogenesis.[9,10,14,28] A characteristic bidirectional neurovascular ischemic injury occurs in limbs affected by DPN combined with CLTI.[2,4,25,28] This injury damages multiple neural structures and leads to demyelination, distal-to-proximal neural dysfunction in the lower limbs, and eventually tissue denervation.[28,29]

Myelin plays a crucial structural role in normal axonal conduction and interneural signalling.[14,19] Progressive demyelination contributes to DF regional denervation and indirectly exacerbates mVD.[14,27]

Functional amendments

Several pathophysiologic mechanisms associated with DPN contribute to progressive neural degeneration.[14,24]

- *Macrovascular functional disturbances.* Progressive stiffening of patent arterial branches leads to regional collateral alterations[30-33] in which normal pulsatile peripheral collateral flow gradually transforms into abnormal laminar and slow flow in rigid containers.[34,35] These hemodynamic changes, frequently observed in diabetic BTK arteries, generate higher stiffness and reduced wall shear stress, abnormal vascular remodeling, and diminished arteriogenesis. Collectively, these factors (**Figure 3**) increase the macrovascular propensity for regional vessel thrombosis.[14,17,28,30]

  This hostile acidotic and prothrombotic environment may be intensified by local sepsis,[4] tissue necrosis,[4] scar tissue retraction, and inflammatory edema. These conditions mechanically distort macrovascular blood flow and progressively intensify regional hypoxia.[5,14,17,25,28]

  Adjacent neural structures are particularly vulnerable to chronic hypoxia, and progressive oxygen deprivation contributes to additional DPN-related injury.[17,27-29]
- *Microvascular functional disturbances.* Similar to many pathophysiologic conditions, DPN arises from dysfunction involving both peripheral and central neural mechanisms. Myelin is present in most axons of lower limb nerves; it functions as a principal regulator of neural signal transmission, contributes to the formation of nodes of Ranvier, and ensures appropriate pacing of electrical conduction, thereby playing a crucial role in rapid nerve signal propagation.[14,24,27]

Schwann cells provide metabolic protection against cytotoxic agents such as AGEs and ROS.[27,36,37] However, myelin is highly sensitive to hypoxic injury, and its depletion leads to slow, discontinuous axonal signal conduction.[27,28]

Long axons of the lower limbs are supplied by extensive microvascular networks through the VN.[27,28] These axons are particularly sensitive to small hemodynamic variations and demonstrate increased vulnerability to multiple flow-dependent factors.[14,25,27]

Peripheral nerve injury frequently induces persistent structural and functional fiber disorders due to impaired autoregulation within the somatosensory system.[29,37] Following such injury, the critical connection between peripheral nerves and central neural units becomes disrupted, ultimately resulting in neural loss.[2,5,36,37] This theory aligns with current guidelines in DPN pathology and diagnostics.[2,14] mVD associated with CLTI further reduces arteriolar and capillary perfusion[28,30] and may compromise the VN (**Figure 4**). This process accelerates DPN progression and is directly linked to peripheral axonal degeneration.[13,14,27-29]

Peripheral nerve injury ultimately produces sympathetic denervation, increased local tissue hypoxia, and vasodilatation (**Figure 4**) along with microcirculatory arteriovenous shunting in cutaneous and muscular tissues.[14,25,27,28]

The DPN-related abnormal arteriovenous cutaneous steal phenomenon diverts oxygenated blood from the foot directly into the venous circulation, resulting in reduced microvascular perfusion of the skin, particularly in DPN-denervated

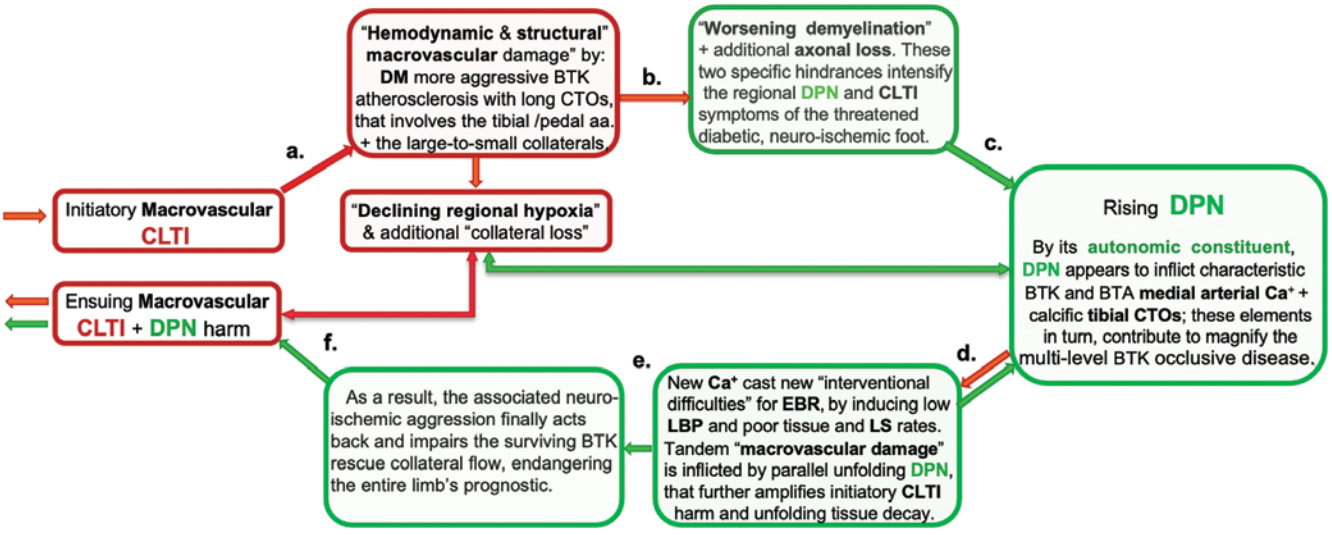

FIGURE 3. Circle of neurovascular interactions at the macrovascular level. A schematic representation of key bidirectional interactions between diabetic peripheral neuropathy (DPN) vs macrovascular chronic limb-threatening ischemia (CLTI). CLTI can inflict **(a)** primary axonal ischemic neuropathy, while rapidly expanding DPN appears to reciprocally assign a more aggressive, calcific below-the-knee (BTK) and below-the-ankle (BTA) atherosclerotic occlusive disease. The resulting increasing limb ischemia further engages worsening demyelination **(b)** and boosts rising DPN **(c)**. By its autonomic component, DPN increases medial artery sclerosis (MAS) and medical artery calcification (MAC) that in turn **(c, d)** contribute to magnifying the CLTI limb's multilevel BTK occlusive disease. The more extended the calcific occlusions, the harder to apply evidence-based revascularization (EBR), and the poorer the clinical resulting limb-based patency (LBP) and limb salvage (LS). This harmful interaction between progressive DPN and worsening macrovascular CLTI ultimately compromises the remaining collateral vessels and their already limited capacity to maintain limb perfusion **(e, f)**. As a result, the limb is at substantial risk of irreversible damage and eventual loss.
Abbreviations: DM, diabetes mellitus; CTO, chronic total occlusion.

territories.[10,27] Consequently, the progressive deterioration of foot perfusion caused by autonomic DPN (**Figure 4**) further intensifies CLTI-induced hypoxic microvascular injury.[24,25,27-30]

Discussion

Although the harmful effects of DPN in patients with CLTI require further investigation, systematic assessment of DPN in all patients presenting with neuroischemic DF is recommended.[4] This evaluation is incorporated into recent guidelines for vascular interventions, such as the WIfI classification,[4] which emphasize multidisciplinary DF care.[2,4,9,10,13,25,41]

Approximately 50% of patients with DPN are asymptomatic,[2,25,28] whereas symptomatic DPN develops in approximately 26% of patients with diabetes.[2,25] The coexistence of DPN and CLTI creates a distinctive clinical feature because each condition may function as either a cause or a consequence during different stages of this bidirectional pathophysiologic process.[25]

CLTI comprises heterogeneous combinations of macrovascular disease and mVD,[4,12,38] whereas DPN involves central and peripheral neural abnormalities.[36,39] These abnormalities may affect sensory, motor, and autonomic fibers in numerous interconnected patterns.[5,14,24,27,39] In this context, MAS, MAC, and mVD may represent progressive stages of a unified pathologic process that integrates macrovascular and microvascular arterial damang,[41] in the presence of DPN.

The basic epidemiologic,[42,43] anatomic, and functional observations described in this review[11,14,17,44] can be conceptually integrated into 2 representative circles of bilateral interactions (**Figures 3 and 4**) that link DPN and CLTI at both the macrovascular and microvascular levels.[5,24,27,28]

Practical clinical point: Before evaluating the bilateral interaction and treatment of CLTI and DPN, it is essential to review the history, type, characteristics, and duration of each documented neurovascular complication affecting patients with DM at specific macrovascular and microvascular levels.

Circle of neurovascular interactions at the macrovascular level

At the first level of interaction (**Figure 3a**), macrovascular CLTI may cause axonal ischemic neuropathy[29] in patients without previous evidence of neural dysfunction.[29] Conversely, progressive DPN interacts with the diabetic macrovascular arteriopathy commonly observed in these patients,[8,10,28,30] which typically manifests as a distal, rapidly evolving, and aggressive form of BTK atherosclerotic occlusive disease.[10,12,29-32]

This condition is potentially associated with long, calcified CTOs of the principal tibial and pedal arteries and extensive damage

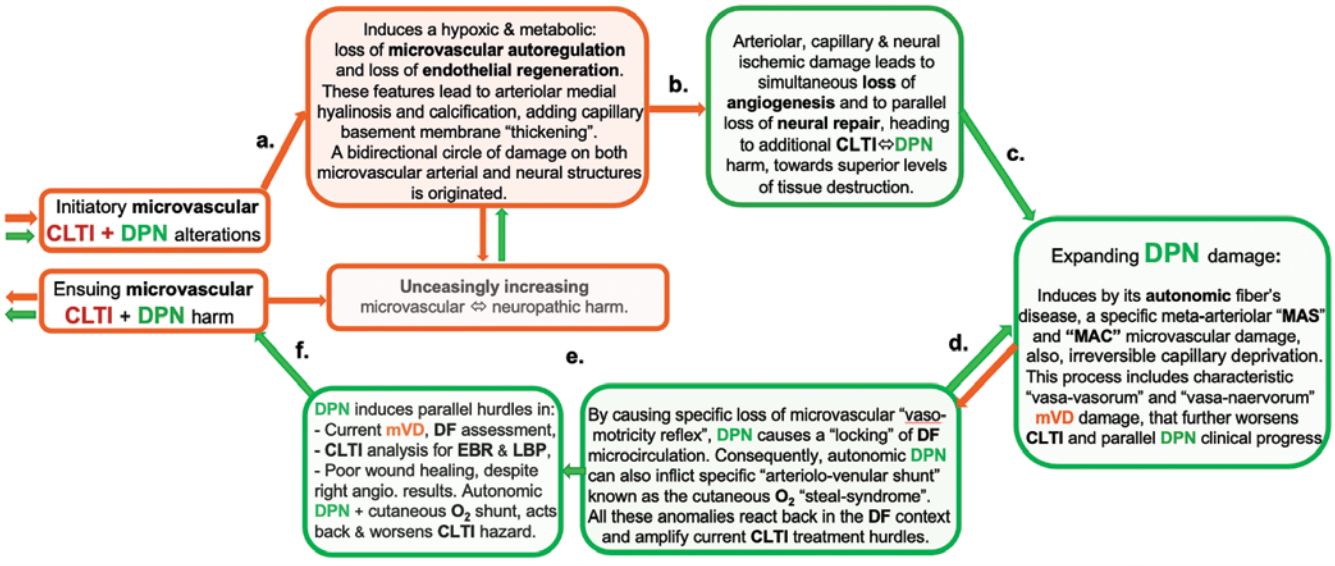

FIGURE 4. Circle of neurovascular interactions at microvascular level. Early microvascular changes associated with chronic limb-threatening ischemia (CLTI) occur alongside diabetic peripheral neuropathy (DPN) **(a)**, contributing to impaired microcirculatory autoregulation and endothelial regeneration. This initial neuroischemic damage promotes arteriolar medial hyalinosis and calcification, as well as capillary basement membrane thickening. A bidirectional, destructive cycle develops between adjacent microvascular and neural structures **(a, b)**, with impaired angiogenesis and diminished capillary and neural tissue repair **(b)**. Progressive DPN further aggravates medial arterial sclerosis (MAS), medial arterial calcification (MAC), and microvascular disease (mVD) involving the capillaries and arterioles **(c)**. Subsequent deterioration of the vasa vasorum and vasa nervorum may worsen CLTI as DPN severity increases **(d)**. Self-expanding DPN generates a loss of microvascular vaso-motricity reflex that causes a progressive locking of diabetic foot (DF) microcirculation **(d, e)**. Consequently, autonomic DPN may promote arteriovenous shunting, also described as cutaneous oxygen steal syndrome **(e)**. In advanced disease, these neurogenic abnormalities may further exacerbate CLTI **(e, f)**. These DPN-related disturbances may also complicate the assessment of mVD in the DF and affect analyses of evidence-based revascularization (EBR), limb-based patency (LBP), and limb salvage (LS) in current CLTI trials.

to large-to-small collateral networks.[10,12,30,32,33,45] Consequently, the extent of affected tissue may range from a few millimeters to the entire foot,[31] depending on whether perfusion is supplied by a single permeable arterial trunk or a group of collaterals nourishing flow,[31] as promoted by the EAOD theory.[31] Neural structures are similarly affected by this tissue-destructive process, resulting in progressive demyelination[14,29] and peripheral axonal loss (**Figure 3b**). The same mechanism may also accelerate pre-existing DPN that persists in subclinical forms.[10,29] Under such circumstances, progression of DPN may precipitate a transition to painful DPN (pDPN).[5,25,44] At this stage of progressive DPN in patients with CLTI (**Figure 3c**), affected limbs commonly exhibit notable macrovascular infrapopliteal MAS and MAC, together with markedly extended CTOs in BTK arteries (severe GLASS grade 3 and 4 lesions). In our interventional team's published experience, these findings were present in 79% of treated limbs.[10] These findings parallel a report by up Iida et al in a series of 440 patients with CLTI, in which 67% of limbs were classified as WIfI stage 4, 72% of patients had diabetes, and 49% had associated DPN.[32]

Once DPN reaches a critical "tipping point", it no longer represents only a consequence of the ischemic CLTI background. Instead, it may also contribute to additional ischemic burden in the neuroischemic CLTI foot by promoting a more aggressive, multilevel, and highly calcific pattern of BTK arterial occlusive disease.[8-10,25,41]

Although the precise pathogenic mechanisms underlying MAS and MAC, and their relationship with DPN, remain incompletely understood,[11,17] in 1982 Edmonds et al first proposed an association between pronounced tibial-pedal MAC and progressive autonomic DPN, particularly in patients with type 2 DM.[8]

This relationship (**Figure 3c**) has subsequently been reported with increasing frequency in patients with DM and autonomic DPN, and in those with renal disease (the Mönckeberg calcifications)[8-11,30,34,40] who present with macrovascular CLTI lesions. Current clinical evidence indicates that greater extension of BTK medial calcification is associated with increased risk of limb loss, major perioperative complications, and mortality.[10,11,34,40,41] These interactions complete the first specific cycle of macrovascular DPN–CLTI interplay (**Figure 3d**).

MAC, as a synchronous consequence and marker of progressive DPN and increasing CLTI severity,[8-12,34,40,41] further increases the original ischemic burden in the threatened lower limb and potentially amplifies the risk of tissue and limb loss (**Figures 3e, f**).

Circle of neurovascular interconnections at the microvascular level

The reported prevalence of DPN, considered a marker of systemic mVD, ranges from 6% to 51% among adults with DM,[4,5,42] with or without clinical manifestations. Similarly, findings from

the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial[43] demonstrated that 51% of patients with PAD and type 2 DM had a history of DPN or exhibited neuropathic signs and symptoms at baseline.[43]

Initial microvascular abnormalities associated with CLTI and DPN (**Figure 4a**) may induce loss of microcirculatory autoregulation and impaired endothelial regeneration.[24,28,36,46] These bilateral neurovascular disturbances lead to arteriolar medial hyalinosis, medial calcification, and thickening of the capillary basement membrane.[10,11,40,41,44] Consequently, a bidirectional cycle of damage develops between adjacent microvascular arterial and neural structures (**Figure 4b**), resulting in reduced angiogenesis and diminished repair of both capillary walls and peripheral nerves.[24,25,46] This early pathogenic cycle, which is often clinically silent, intensifies the reciprocal CLTI–DPN injury and does not necessarily parallel the macroscopic spread of macrovascular CLTI lesions.[30,41,44,47] Instead, it follows the complex regional cellular and conjunctive matrix progressive decay, being closely interconnected to mVD,[40,41,44] further exacerbating tissue hypoxia and ultimately promoting irreversible tissue destruction.[40,48]

Behroozian et al[44] evaluated reciprocal interactions between systemic mVD and PAD or CLTI in a cohort of 125,000 patients with diabetes. Systemic mVD was defined by the presence of neuropathy, retinopathy, or peripheral limb mVD. Using Cox hazard regression, the authors identified a 3.7-fold increase in amputation risk in patients presenting with lower limb mVD alone. This risk increased to 22.7-fold when PAD or CLTI coexisted with DPN or other systemic mVD manifestations such as retinopathy.[44]

Unlike the macrovascular interaction cycle, the microvascular interplay between DPN and CLTI may occur earlier and progress silently.[24,25,27] In many cases, this bilateral injury develops over months or years without overt clinical manifestations unless a significant clinical event occurs (**Figure 4c**), such as systemic metabolic or hemodynamic deterioration, progression from claudication to CLTI, extensive foot ulceration with spreading sepsis, onset of pDPN, or limb denervation.[5,14,30,31] These events compromise peripheral neurovascular integrity and may disrupt the fragile equilibrium maintained by the foot's collateral network. Progressive perfusion decline further impairs compensatory microvascular arteriolar and capillary flow.[30-32,33,41,45]

Progressive autonomic DPN injury (**Figure 4c, d**) is also associated with proximal metarteriolar MAS and MAC degeneration,[8-11,41] accompanied by further deterioration of the distal arteriolar and capillary microvasculature (mVD).[40,41]

The microvascular interaction cycle within the foot progresses through worsening stages of tissue ischemia and autonomic DPN.[24,25,27] Petropoulos et al[47] reported that retinal neurodegeneration correlates with the development of peripheral motor DPN. These findings suggest that systemic manifestations such as diabetic retinopathy may serve as indicators of DPN severity and aid clinical risk stratification.[48]

At the foot level, this progressive microvascular cascade manifests through 2 principal pathologic processes (**Figure 4d, e**).

The first involves loss of the peripheral microvascular vasomotor reflex.[41,46] Autonomic denervation caused by DPN prevents normal alternation between vasoconstriction and vasodilatation (**Figure 4d**) at the DF arteriolar level. This mechanism effectively "locks" the microcirculation of the affected limb.[24,28,41] As a consequence, the enclosed tissue territory becomes highly susceptible to local hypoxia, acidosis, and microvascular thrombosis caused by stagnation of capillary flow, thereby increasing the risk of tissue loss in the CLTI foot.[24,25,41,46]

A second microcirculatory abnormality induced by autonomic DPN is arteriolar-venular shunting (**Figure 4e, f**), also described as cutaneous oxygen steal syndrome.[5,25,41,46] This process further impairs would healing by diverting cutaneous blood flow, even when angiographic macrovascular results appear satisfactory (**Figure 4f**).[12,30-33,41]

These neuropathic microcirculatory abnormalities are receiving increased recognition in CLTI research.[4,17,25] The GVG[12] recommends perioperative macrovascular risk stratification using GLASS[12] evaluation and links evidence-based revascularization (EBR)[12] to postoperative evaluation of limb-based patency (LBP).[10,12] However, the need for systematic and independent microcirculatory neurovascular disease assessment and stratification is not clearly structured in the guidelines, specifically in this subset of diabetic neurovascular patients that associate CLTI to DPN and mVD[44,12,17,27,44] Similarly, rigorous GVG/Patient risk, Limb staging, and ANatomic patterns(PLAN) strategy[12] does not incorporate concomitant analysis and grading of mVD magnitude in this group of patients. As a result, successful restoration of macrovascular blood flow in large-diameter limb arteries (rigorously sustained by EBR and LBP)[10,12] may not translate into equivalent improvement in the capillary, arteriolar, and neural microcirculation surrounding the wound, which may remain dysfunctional. [24,30,33,41,44] Eventual heterogeneities in macrovascular blood flow patency follow-up[10,12,30,38] can be explained by the persistence of hostile downstream microcirculatory profiles that still operate in this patient population.[10,12,30,38,41]

Restoration of adequate angiographic blood flow appears crucial for tissue recovery in CLTI.[4,10,12,17,25,30] However, the presence of DPN-related loss of microvascular vasomotor reflex[2,25,28,29,41] and parallel arteriolar-venular cutaneous neuropathic shunting[5,25,41,46] may continue to impair tissue regeneration, complicating wound healing and limb salvage in this patient population.[2,10,25,28] The WIfI classification recommends systematic evaluation for DPN in patients with diabetes who are at risk for mVD; unfortunately, this goal is only seldom achieved in current studies of patients with CLTI and diabetes.[4,10,30,32,43] Consequently, reported treatment outcomes should be interpreted cautiously because the presence or absence of DPN may influence clinical measures of success.[4,10,25,30]

Through the combined effects of microcirculatory impairment and arteriolar-venular cutaneous oxygen steal syndrome, autonomic DPN ultimately exacerbates lower limb tissue ischemia (**Figure 4a**), completing a second cycle of neurovascular interaction (**Figure 4a, f**). As a result, the affected limb is exposed to increasing tissue hypoxia driven by progressive mVD of the foot and additional DPN-mediated risk for tissue and limb loss.[41,44] At this stage (**Figure 4f**), DPN acts as an additional risk contributor to limb microvascular hypoxia beyond the initial CLTI-related ischemic injury.[25]

Practical clinical point: The neuroischemic DF pathology presents a distinctive characteristic in which DPN and CLTI may alternately assume either a causal or resultant role at different stages of their bidirectional interaction. Although the precise mechanisms underlying the harmful interplay between DPN and CLTI remain incompletely defined, systematic assessment of mVD and DPN alongside contemporary vascular evaluation and treatment should be considered essential within an unremitting multidisciplinary DF approach.

Diagnostic Aspects

Synopsis of peripheral neurologic evaluation

Recent studies report from 35% to 63% symptomatic forms in patients with DM, including pDPN.[4,42,49] pDPN represents a severe form of DPN that has been associated with a 5-year mortality rate of up to 43%.[4,49] Several different types of DPN have been described, including distal symmetric bilateral polyneuropathy and sensory, motor, and autonomic neuropathies, as well as other forms of radiculoplexus neuropathies with or without associated pain.[2,5,14,36,37,46] It should be emphasized that for most common DPN and pDPN clinical presentations, no current diagnostic test serves as a universally accepted gold standard for the diagnosis of DPN or pDPN.[5,14,37,49] It is also important to note that for any neuropathic painful limb'presentation, a concomitant peripheral vascular examination is mandatory in order to exclude additional PAD.

For more clarity, several diagnostic evaluation levels[2,5,14] could be implemented in assessing this group of patients:

The First Level of diagnostic evaluation should focus on detailed anamnesis, doubled by rigorous initial clinical neurological exam (parallel to the vascular investigation) of the threatened limb.

Over the past 2 decades, several scoring scales and "patient-reported symptoms" questionnaires have been proposed to identify and stratify the progression and severity of DPN or pDPN, including those described by Tesfaye et al,[50] Scholz et al,[51] Young et al,[39] and Dyck et al.[52] Current practice guidelines recommend a careful neurologic evaluation at both the systemic and affected limb levels, ideally via multidisciplinary participation.[2,5,14,50]

The Second Level of diagnostic evaluation consists of complementary noninvasive exams that provide objective assessment of DPN.

These quantitative measures have been described as helpful for DPN recognition and stratification, using quantitative neural analysis exams.[14,37,49,50,51] Some of the current methods in use include:

- *Electrophysiologic assessment.*[50-54] Applied to sensory nerves, it is a highly sensitive key examination for quantitative evaluation of DPN.[50,53]
- *Point-of-care testing.*[47,51] Available devices include concomitant sural nerve conduction velocity analysis with plantar sweat analysis and assessment of sudomotor reflex function in the affected limbs.[47,48,51]

The Third Level of DPN assessment incorporates more performant, yet more expensive, diagnostic technologies that address targeted, complex neuropathic presentations, either in in isolation or in combination with CLTI.

Because concomitant systemic or peripheral mVD is common,[2,47-50] it should be considered in all patients presenting with a neuroischemic foot.[44,47-49] The use of these advanced diagnostic modalities should be individualized and guided by diabetic team consensus.[51-53,55] Representative diagnostic techniques include:

- *Skin biopsy.* Evaluation of intraepidermal nerve fiber density offers valuable information on lower limb DPN and systemic mVD involvement.[51-53]
- *Cornea confocal microscopy.* This noninvasive technique evaluates corneal nerve fiber damage.[55] Results require multidisciplinary team analysis.
- *Eleven neurology-related serum proteins.*[56] These demonstrate a significant correlation between specific serum inflammatory proteins and pDPN severity. This new DPN monitoring method still needs to be validated by additional clinical research, including evaluation of forthcoming DPN biomarkers.[56]

Synopsis of associated vascular assessment

According to the same step-by-step approach to vascular assessment, 2 main levels[2,5,14] can be acknowledged.

The First Level includes a comprehensive medical history and detailed examination of lower-extremity perfusion. Because most patients with diabetes and neurovascular disease have coexisting PAD or CLTI and varying degrees of DPN, concomitant screening for DPN is increasingly recommended in patients presenting with a neuroischemic foot.[2-5,10,49] These patients may exhibit atypical hypoxic signs and symptoms, even in the early stages of neurovascular interactions.[5,25,41,49] Affected feet may appear warm[2,5,41,49] with undistinguished cutaneous discoloration due to peripheral autonomic vasomotor reflex abolition.[25,49] This dysfunction results in capillary vasodilatation with or without associated cutaneous oxygen steal syndrome.[25,38]

The Second Level of vascular assessment includes mandatory paraclinical exams that should include:

(a) Macrovascular atherosclerotic occlusive disease evaluation. Assessment should document the presence of MAS and MAC.

Because of abnormal stiffness as a result of MAS and MAC, the segmental limb pressures and the ankle-brachial index (ABI) measurements often dwell without clinical pathological relevance.[12,30,38,49]

Contemporary approaches to standard macrovascular imaging were extensively reviewed in the last 3 decades concerning BTK arteriopathy in CLTI and are beyond the scope of this article.[4,12,49] Most neurovascular interactions can be assessed at the macrovascular level using several standardized methods (starting with noninvasive, moving toward more invasive technology),[12] including:

- *Extravascular ultrasound (EVUS).* A valuable noninvasive modality for evaluating MAS and MAC via direct visualization of the arterial wall,[12] it also provides indirect analysis of the pulsatility index,[34] pedal acceleration time,[35] and distal foot collateral resistance.[35,57]
- *Intravascular ultrasound (IVUS).* Used to accurately evaluate the extent and morphology of MAS and MAC,[58] its use is limited by the invasive nature of the procedure and reduced feasibility in occluded or severely stenotic arterial segments.[12,40,58]
- *Conventional plane radiography.* Particularly for MAC, it is recommended because it shows the characteristics and reproducible "railroad track" appearance.[40,58,59]
- *Computed tomography (CT).* It provides 70% sensitivity for MAC detection and correct quantitative arterial wall calcium analysis.[58,59,60]

(b) Current microvascular diagnostic methods. Targeting the arterial structures of <100-µm diameter (arterioles and capillaries), accurate mVD diagnosis can be done with several acknowledged methods in the absence of eventual arteriolovenular oxygen cutaneous shunting.[10,25,41] These include:

- *Transcutaneous pressure oxygen ($TcPO_2$) monitoring.* This can provide correct measurement of cutaneous oxygen levels in the foot.[12,17,49]
- *Laser Doppler skin perfusion pressure.* Combined with laser speckle flow imaging,[61,62] it enables real-time analysis of regional microcirculatory flow in the foot.
- *Near-infrared spectroscopy.* Used to provide noninvasive assessment of tissue oxygen in specific regions of the foot microcirculation,[63] but measurements may be affected by neuropathic influences.[10,25,29,41]
- *Hyperspectral imaging.* It provides reliable oxygen saturation data within targeted regions of the foot.[64]
- *Cutaneous videocapillaroscopy.* This method enables direct, high-resolution, noninvasive visualization of capillary morphology and function and functional skin capillary damange imaging.[65]
- *Spatial frequency domain imaging.* It combines assessment of cutaneous hemoglobin concentration with tissue oxygen saturation.[66]
- *Nuclear imaging.* Single-photon emission CT and positron emission tomography provide noninvasive quantification of intracellular mitochondrial ischemia.[67] These imaging methods are not affected by neuropathic cutaneous shunting and may complement digital subtraction angiography analysis, particularly for vessels <500-µm diameter, where visual acuity is diminished.[68]
- *Novel diagnostic techniques.* Thse techniques focus on endovascular endothelial cell biopsy and provide accurate diagnosis and stratification of early-stage mVD.[69] Independent from neuropathic interferences, this method has demonstrated a pooled technical success rate up to 91%.[69]
- *Distal foot videocapillaroscopy.* This method may aid differential diagnosis by distinguishing primary mVD (associated with CLTI) from secondary (DPN-induced) microvascular cutaneous arteriolovenular shunting.[17,41,65,70]

It is important to note that according to available guidelines, contemporary CLTI diagnostics should associate current macrovascular stratification (adding MAS/MAC evaluation)[40, 41,58,59] to at least one microcirculatory exploration[4,12,17,38,40,49,58] to rule out coupled mVD and its independently aggravating ischemic threat.

(c) Combined macrovascular and mVD diagnosis. This modern diagnostic technology can be successfully implemented (if it is available in reference DF centers) in association with other macro- and microvascular daily practice and above-mentioned exploration; It includes:

- *Indocyanine green angiography.* This technique provides accurate anatomic and functional imaging of macrocirculatory and microcirculatory foot perfusion.[71] It promotes targeted topographic foot revascularization to optimize tissue healing.[30,71]
- *Contrast-enhanced magnetic resonance imaging (MRI).* Encompassing arterial spin labeling and blood oxygenation level-dependent techniques, it enables a direct flow (morpho-functional) assessment of macrovascular and microvascular perfusion in small arterial branches, MAC, arterioles, and capillaries affected by mVD.[72]

Treatment Insights

Current management of the diabetic neuroischemic foot in patients with CLTI requires rapid diagnosis of both macrovascular disease and mVD, combined with multidisciplinary evaluation that includes assessment for DPN, and timely macrovascular revascularization performed in conjunction with wound debridement.[12,30,41,49]

However, no standardized treatment algorithms or consensus recommendations specifically address the management of diabetic MAS, MAC, and mVD.[17,40,41,49,59] Several studies have suggested that CLTI revascularization may provide clinical benefit, including potential improvement in DPN. However, the available evidence remains limited and inconsistent.[12,24,74-76]

Several studies have evaluated the effects of CLTI bypass revascularization on microvascular perfusion and DPN. In these investigations, $TcPO_2$ and laser flowmetry were used to assess microvascular perfusion, while peroneal nerve conduction velocity was analyzed for DPN evaluation in patients undergoing CLTI revascularization.[74-76] Some studies reported that reversal of limb hypoxia halted DPN progression,[74] whereas others demonstrated significant improvement in limb perfusion accompanied by parallel improvement in neuropathic symptoms.[75] In contrast, other investigators found no meaningful changes in DPN manifestations or nerve conduction parameters despite successful revascularization.[10,76]

Recently, Jujo et al[77] reported findings from a prospective series of patients with neuroischemic CLTI. Three months after endovascular revascularization, both the current perception threshold (used to assess DPN) and ABI (used to evaluate CLTI) improved significantly.[77] Patients who experienced improvement in DPN-related sensory symptoms also had a significantly higher 6-month survival rate.[77]

Based on the hypothesis that peripheral nerves in patients with diabetes are particularly vulnerable to compression at specific anatomical entrapment sites in the neuropathic foot, minimally invasive nerve decompression techniques have recently been proposed.[49,78] These interventions have been associated with improved pain scores; however, consistent resolution of symptoms within 3 months has not been reported.[78]

Limitations

A major limitation of this scoping review is the limited quality and quantity of available evidence, as few studies directly address the central topic. Despite a rigorous literature search, relatively few publications adequately described the relevant mechanisms. Much of the available information focuses on relatively novel pathologic entities, such as DF mVD, with or without concomitant MAS and MAC. Evidence regarding the bidirectional interactions between CLTI and DPN is particularly limited and is derived largely from observational studies and clinical interpretations. Consequently, these findings do not provide a comprehensive etiopathogenetic classification or a complete mechanistic understanding of these processes.

Another important limitation is the lack of systematic DPN screening and severity stratification in most clinical studies of diabetic neuroischemic CLTI. Detailed neuropathic assessment is rarely incorporated into CLTI revascularization studies and, when reported, is often limited to descriptive or anecdotal observations.

Conclusion

Limbs affected by DPN may coexist with CLTI and appear to form closely interconnected pathologic processes that interact continuously at both the macrovascular and microvascular levels. These complex interactions may accelerate tissue injury and increase the risk of tissue damage and limb loss. Current evidence supports a comprehensive vascular assessment that includes evaluation of both macrovascular disease and mVD, together with systematic screening for DPN as part of multidisciplinary management. Additional research is needed to clarify the underlying mechanisms of these neurovascular interactions and establish evidence-based diagnostic and therapeutic strategies.

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