Distinguishing Painful Peripheral Neuropathies From Ischemic Limb Rest Pain in Patients With Diabetes

Vlad Adrian Alexandrescu, MD, PhD; Arnaud Kerzmann, MD; Vincent Tchana-Sato, MD

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The distribution of detectable diabetic peripheral neuropathy (DPN) is estimated to range from 10% within 1 year of diabetes mellitus (DM) diagnosis to up to 60% in patients with DM lasting for more than 25 years.[1] Given the increasing prevalence of DM from 425 million (8.6% of the general population) in 2019 to 9.8% of people worldwide, expected in 2045,[2,3] a soaring incidence (around 60% in newly diagnosed cases) is anticipated.[2,3] DPN is often accompanied by peripheral occlusive arterial disease as a parallel complication of DM, particularly in patients with long-lasting or poorly controlled hyperglycemia.[1-3] A contemporary review by Zaffar et al[1] revealed that 66% of type 1 and 59% of type 2 DM cases demonstrated evidence of DPN at comparable time intervals.[1] Painful DPN (pDPN) represents a frequent clinical subset of DPN, ranging from 35% to 65% of neuropathic patients (owing to specific individual systemic, geographical, and sociocultural influences).[1,3,6,7] Chronic limb-threatening ischemia (CLTI)[4] has been previously studied as a precarious critical limb ischemia (CLI) condition[4,5] associated with the most extreme and terminal type of lower limb occlusive arterial disease.[4,5] High amputation rates,[4,5] major cardiovascular events, and death (20% mortality within 6 months and 50% at 5 years) have been documented in these patients.[3-5] Distinguishing the true origin of pain is not always straightforward,[6-8] and the most motivated clinician may be confronted with unexpected hurdles to accurate diagnosis.

Definitions

For more clarity and a practical point of view, the current definitions of the main pathophysiological entities discussed in this paper are reproduced below, according to recent taxonomy publications and reviews.

Neuropathic pain (NP) is defined as "pain caused by a lesion or disease of the somatosensory nervous system".[6,8] A recognized diagnosis of NP requires the presence of underlying neurological lesions.[6,8]

The generic diabetic neuropathy embodies "the presence of neuropathic symptoms and/or signs of central or peripheral nerve dysfunction in persons with diabetes after ruling out other causes, which may range from hereditary, traumatic, compressive, metabolic, toxic, nutritional, infections, immune-mediated, neoplastic, and secondary to other systemic illness".[1]

Specific diabetic peripheral neuropathy (DPN) encompasses (according to the Toronto Neuropathy Expert Group meeting)[9] "a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and perineural microvessel alterations, as a result of chronic hyperglycemia exposure and cardiovascular risk covariates".[9]

Specific painful diabetic peripheral neuropathy (pDPN), following consensual definitions, represents a frequent subtype of peripheral NP that is correlated with DPN. It is defined as "neuropathic pain as a direct consequence of abnormalities in the peripheral somatosensory neural system in people with DM".[6,9]

In a parallel consensus,[4] chronic limb-threatening ischemia (CLTI) pain is usually described as "affecting unilaterally the ischemic inferior limb, more frequently the forefoot, getting worse at night, and requiring opiate analgesia for management".[4] A high probability of CLTI pain is associated with its presence for more than 2 weeks to specific hemodynamic proofs for severely damaged limb perfusion (eg, absolute ankle pressure (AP) <50 mm Hg and absolute toe pressure (TP) <30 mm Hg).[4] The ankle-brachial index (ABI) should be typically <0.4 for this condition, but it may be subject to inadequate analysis,[4,5] especially for patients with DM, those presenting with chronic kidney disease, or both subgroups that may exhibit incompressible, calcified crural arteries.[4,5]

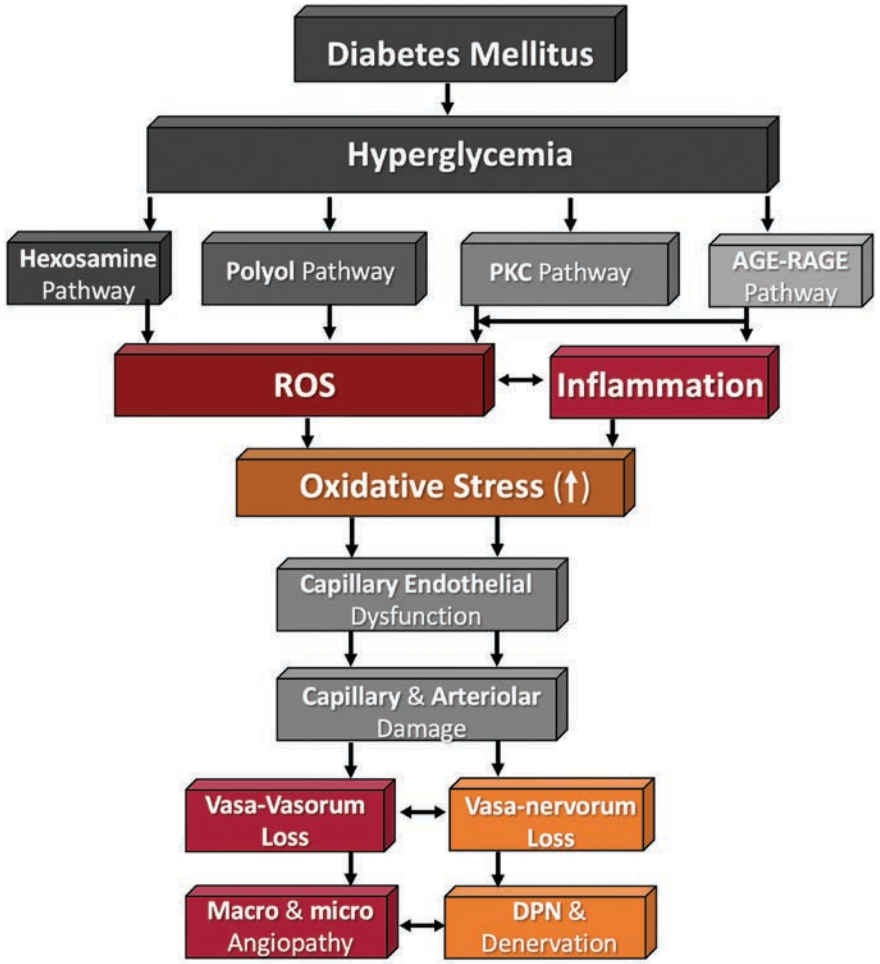

FIGURE 1. Differential pathways of hyperglycemic toxicity. The full extent of the deleterious effects of persistent hyperglycemia remains partially understood. However, several pathological metabolic pathways have been identified and are schematically depicted: the hexosamine pathway, polyol pathway, protein kinase C pathway, and the advanced glycation end product pathway, including its receptor for advanced glycation end products. These pathways converge to produce elevated levels of ROS, along with chronic inflammation, resulting in harmful oxidative stress to tissues. Consequently, hyperglycemic toxicity leads to DNA and mitochondrial damage, cellular dysfunction, and eventual cell loss. These interconnected pathogenic mechanisms involve microcirculatory capillary and arteriolar endothelial damage, specifically affecting the vasa vasorum (in arterial branches) and vasa nervorum (in peripheral nerves), causing their dysfunction and eventual loss. Pain should be carefully evaluated as a potential symptom indicating the onset of these metabolic disorders, such as chronic limb-threatening ischemia or pDPN. *Abbreviations: ROS, reactive oxygen species; DPN, diabetic peripheral neuropathy; pDPN, painful diabetic peripheral neuropathy.*

The Toronto Diabetic Neuropathy Expert Panel[10] proposes a mainstay diagnostic feasibility stratification that is applied in 4 grades (possible, probable, confirmed, and subclinical DPN). At the same time, a recent study by Scholz et al recommends a specific pDPN classification structured upon a 3-level clinical diagnostic scale[11] featuring NP as the first level, chronic DPN as the second level, and pDPN as the third clinical severity level.[11]

Regarding the individual types of fiber denervation[9] and related peripheral neuronal loss,[11,12] DPN (containing the pDPN variant) was further subdivided into sensory, motor, and autonomic varieties of limb denervation.[1,9,11,12] Reciprocally, considering the contingent nature of patients with a painful ischemic limb, their specific CLTI designation is justified by the presence of clinical signs and symptoms of severe ischemic lower limb tissue threat.[4,5] This partition is currently sustained in the literature by the Rutherford clinical stratification (ie, patient categories 4, 5, and 6),[4] adding the recent Global Limb Anatomic Staging System (GLASS) classification[4] and parallel to the Society of Vascular Surgery's Wound, Ischemia, and Foot Infection (WIfI) 3-variable inferior limb ischemia grading system to predict major tissue loss.[4]

Classification

Regarding patients having dominant neuropathic painful affectation, the UK screening test score for DPN represents a noninvasive and highly reproducible method for screening and grading diabetic lower limb chronic denervation.[10] Based on sensory and vibration perception thresholds, DPN can be easily detected and scored (0-10 points) as normal (0-1), mild (2-4), moderate (5-6), or severe (7-10).[7,10]

Etiology and Pathophysiology

Although the precise etiological and pathophysiological initiatory mechanisms remain partially unknown, the presence of chronic and persistent hyperglycemia (**Figure 1**) seems to represent a key element in the induction and development of DPN, pDPN, and CLTI, as well as other parallel microcirculatory dysfunctions at the systemic level.[1-3,9,11] Nevertheless, pDPN, as a pathogenic entity, seems to add a wide array of multifactorial interactions, such as genetic, biological, clinical, metabolic, and psychosocial individual risk factors.[6,8] **Figure 2** shows a schematic illustration of DPN classification (Toronto consensus)[9] associated with the "3-level" specific pDPN diagnostic scale (IASP).[11]

It was stipulated that NP may result from both central and peripheral nerve damage.[6,8,11] Characteristic neural lesions observed in pDPN can provoke persistent structural and functional maladaptive nerve responses in specific somatosensory locations.[6,11] Particularly concerning the DM environment, persistent hyperglycemia seems to directly inflict defective peripheral neurotropism and impaired axonal transport [1,8,12] by several deleterious pathways (**Figure 1**), such as a) the hexosamine pathway, b) the polyol pathway by c) protein kinase C, and d) the advanced glycation end products pathways.[1,12] Therefore, the persistent progression of all these deleterious hyperglycemic mechanisms may increase local reactive oxygen species (ROS) and secondary oxidative stress.[1,6,12] This process appears to involve further mitochondrial dysfunction, the endoplasmic reticulum injury, and leads to systemic microvascular endothelial cell affliction.[1,12] Interestingly, up to this point of pathogenic progress, both DPN and CLTI share a common microvascular pathogenic cascade, unveiling 1 common unfolding pathway from the basic molecular level until mitochondrial degradation.[1,6]

This initial pathogenic path divides itself into the microvascular vasa nervorum and separate vasa vasorum structural wall and endothelial damage (**Figure 1**); hence, this dichotomy may induce independent endothelial injuries for both vascular and neural microcirculatory nourishing networks.[1,6,12]

Parallel microvascular manifestations of abnormal capillary blood flow are equally documented in other territories of the human body, at the same level as pDPN (**Figure 2**) and neuroischemic CLTI foot syndrome.[2,3 6] Therefore, the brain, retina, and visceral afflictions, including kidney microvascular disease, may parallel the peripheric neural and arteriolar system microcirculatory decay, joining musculoskeletal structures and skin perfusion disorders, among others.[1,9,11,12] The knowledgeable clinician may anticipate these potential concomitant targets of a poorly controlled metabolic syndrome. The irreversible DPN changes may correlate to concomitant arterial microcirculatory damage (diabetic microangiopathy) in specific diabetic foot territories.[1,9,12]

Not surprisingly, abnormal oxidative stress also damages the normal angiogenesis and arteriogenesis processes and connects to muscular mass degradation and timely deconditioning of the whole neurovascular inferior limb.[11-13]

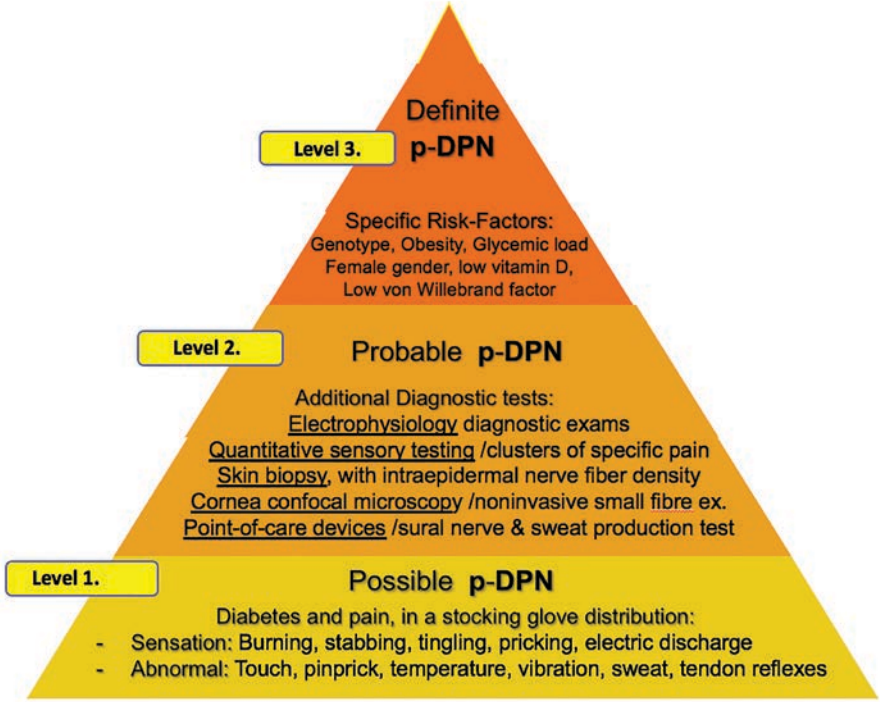

FIGURE 2. The accuracy of pDPN diagnosis. A synthetic representation of the currently described signs and symptoms of pDPN. The multivariable diagnostic approach to pDPN is schematically depicted in a 3-level diagram, categorizing cases as "possible," "probable," and "definite" limb pain potentially associated with DPN. Each level corresponds to specific types of individual denervation and is associated with characteristic neuropathic symptoms, relevant diagnostic tests, and the associated risk factors for pDPN. *Abbreviations: DPN, diabetic peripheral neuropathy; pDPN, painful diabetic peripheral neuropathy.*

Clinical Features and Appropriate Diagnostics

Several reviews have estimated that the prevalence of patients with DM with a proven DPN diagnosis ranges from 20% to approximately 35%, while pDPN has been documented in approximately 35% to 65% of patients with DM.[1,2,6,9,13] Particularly concerning pDPN (a severe form of DPN), this seems to be associated with increased mortality (42%) at 5 years,9 and (seemingly for DPN), there are no established current diagnostic gold standards to date.[9,13]

An important point in the clinical evaluation of patients with probable or definite pDPN (**Figure 2**) is the precocious recognition and of each evocative pDPN symptom.[11,13]

From a practical perspective, different types of peripheral nerve damage[12,13] and their clinical presentations have been described as potentially induced by DM, including distal symmetric polyneuropathy, autonomic neuropathy, radiculoplexopathy, and mononeuropathies, with or without irritative discomfort.[1,6,12,13]

For all these diabetes-related entities, several diagnostic challenges must be noted first, as the current gold standard diagnostic test for DPN and pDPN is still lacking.[1,13] Peripheral nerves are structured as large- and small-diameter fibers, and each group

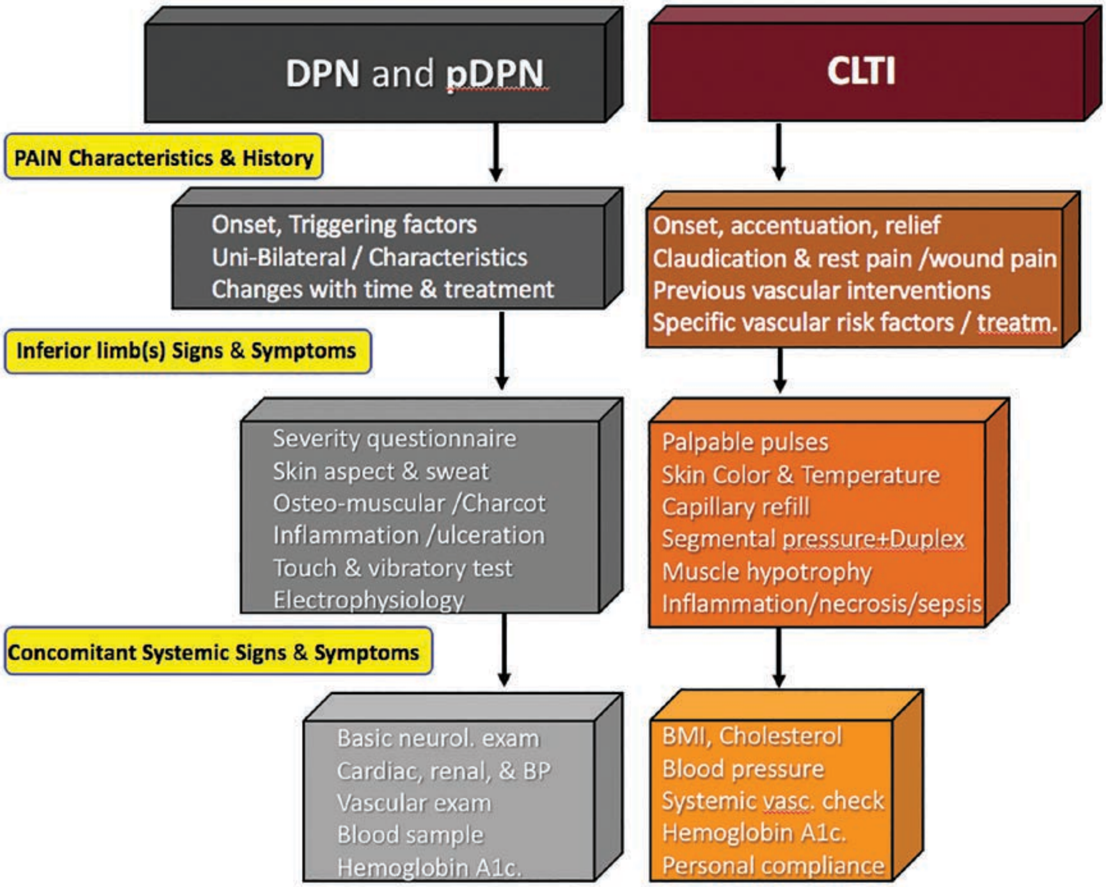

FIGURE 3. Main characteristic pain signs and symptoms of DPN vs CLTI. A schematic illustration of key clinical characteristics to consider in the differential diagnosis of pDPN vs severe CLTI pain. The optimal diagnostic approach remains challenging and relies on a thorough anamnesis, a skillful clinical examination, and the judicious application of recommended first-line noninvasive tests for CLTI and pDPN. The recommended diagnostic algorithm for every pain onset involves a three-pillar convergence of data, including: (a) a detailed assessment of pain characteristics and history; (b) identification of the most evocative symptoms and signs, judiciously connected to confirmatory diagnostic tests, with a diagnostic priority given to any suspicion of CLTI coexistence; and (c) a parallel systemic evaluation for potential multiorgan diabetic complications, useful in determining the patient's risk class for future treatment planning. *Abbreviations: DPN, diabetic peripheral neuropathy; pDPN, painful diabetic peripheral neuropathy; CLTI, chronic limb-threatening ischemia; BP, blood pressure; BMI, body mass index.*

exhibits specific symptoms (**Figure 3**). Large fiber dysfunction manifests as weakness, numbness, tingling, and loss of balance. In contrast, dysfunction related to small fiber destruction includes sporadic or continuous pain and local anesthesia.[1,8,13] Small fiber symptoms may prevail, particularly in the early stages of DPN, and in association with eventual autonomic denervation.[1,8,13]

Early pDPN symptoms appear to be exacerbated at night and usually include (**Figures 2** and **3**) bilateral and symmetrical foot pain (usually in a stocking-glove distribution)[1,3,8,15] associated with different forms of paresthesia, commonly presented as tingling, burning, prickling, or shooting pain, and the more unusual addition of cold sensations[1,13] (**Figure 2**).

Another challenge in current pDPN assessments is severity appraisal.[9,11,13] During the last decade, numerous severity scales and questionnaires were proposed to uncover DPN or pDPN progression.[9,11,13,14] A review conducted by Dyck et al[14] suggested a coordinated follow-up that progressively added new signs and symptoms related to individual clinical and electrophysiological irregularities (**Figure 2**). Alternatively, several analogous composite scores, including different scale questionnaires, have been proposed. However, clear evidence based on prospective and multicenter studies remains scarce.[1,3,8,13,14] The most common clinical form of DPN to be suspected is, by far, distal symmetrical polyneuropathy, currently adding pDPN symptoms.[1,9,12] Its presence and unfolding symptoms are related to the length of the involved nerves, so it may primarily affect the longest nerves in the feet.[1,13] A schematic representation of currently described pDPN signs and symptoms is presented in **Figure 2**.

Specific sensory features of DPN and pDPN

The accurate diagnosis of sensory pDPN characteristics may eventually prove to be demanding. Commonly, pain affectation shows (**Figures 2** and **3**) the same specific allocation as the sensory symptoms.[1,3,8,13]

It is also generally accepted that large-fiber evaluation should include the analysis of vibration sensation using a 128 Hz tuning fork and light touch perception by applying a 10-g monofilament on the dorsal aspect of the toes.[1,3,8,13-15] The results, however, seem to depend on each clinician's experience and daily practice.[3,13] A study conducted by Dyck et al[16] associated 24 patients with DM with and without DPN who were examined in a blind manner by 12 experienced physicians. Interestingly, the results showed that considerable and excessive variability among physician judgment of signs, symptoms, and diagnosis was noted.[16]

Motor specificities of DPN and pDPN

Motor neuropathy can also be suspected upon meticulous clinical examination;[1-3,13] information about muscle strength, tonus, or atrophy should be correlated with eventual bone deformations (Charcot foot) and vicious postures.[1,3,13] Global evaluation associates a parallel appraisal of nerve conduction (**Figures 2** and **3**). Although there is no uniform level of evidence, motor disabilities seem to appear much later than sensory decay in DPN (sometimes associated with pain onset) and gather a multifactorial neuromyopathic profile.[1,3,8,13,14]

Autonomic characteristics of DPN and pDPN

Autonomic denervation can occur in the early stages of DPN and is commonly associated with sensory, motor, and painful clinical manifestations.[1,8,13] Small neural fiber damage is associated with pain, anesthesia to a pinprick and temperature sensations, and autonomic dysfunction. Regarding diabetic distal symmetrical polyneuropathy, eventual autonomic involvement can be suspected if the patient has abnormalities in sweating and microcirculatory temperature reflexes.[1,3,13,15] Several generic tests have been proposed, such as the vagal baroreflex exam, thermoregulatory sweat testing, and skin vasomotor reflex monitoring (which incorporates the use of laser Doppler flowmetry) for evaluating the severity of autonomic fiber damage.[1,3,13,15]

Pain specificities associated with DPN

The association between small neural fiber involvement and common symmetric and pDPN has been described (**Figures 2** and **3**) as the current phenotype of distal DPN.[9,13,15] Small fiber injuries are usually revealed early in DPN onset and typically induce pain, anesthesia to a pinprick, and temperature changes.[1,13,15] In pDPN patients, various types of neuropathic pain have been described that can be assembled in distinct cluster-symptoms groups based on each patient's pain and sensory profile.[13,15] Hence, different clusters may address different pathophysiological pathways (**Figure 1**), according to the 4 distinct pathways of the hyperglycemic damage previously mentioned in **Figure 1**.

Complementary pDPN diagnostic exams

Hoping to improve individual DPN diagnostics and better outline pDPN singularities regarding other painful syndromes of the lower extremities (including CLTI), several quantitative diagnostic exams have been described in the last decade,[11-13,15] such as:

a) Electrophysiological assessment, with higher sensitivit,y has been applied to sensory nerves and is a key examination for quantitatively evaluating large nerve fiber function.
b) Skin biopsies that add intraepidermal neural fiber density appraisal.
c) Cornea confocal microscopy, which noninvasively estimates corneal small fiber alterations.
d) Point-of-care devices, which include simultaneous sural nerve conduction velocity analysis, adding plantar sweat evaluation, and parallel measurements of sudomotor reflex activity in both hands.
e) Eleven specific serum proteins, which were significantly correlated with pDPN severity, warranting further complementary investigation as eventual forthcoming biomarkers.[17]

Despite undeniable technological progress with better DPN and pDPN diagnostics, all the aforementioned methods still require clinical validation based on larger prospective and multicenter studies.[13,15]

Practical observation: The onset of predominantly bilateral lower limb pain symptoms in a stocking-glove distribution, often associated with abnormalities in light touch and vibration sensation tests (commonly seen in long-standing diabetic patients with poor glycemic control), may suggest a probable diagnosis of pDPN. A parallel duplex vascular examination is recommended to rule out complex or latent forms of diabetic arteriopathy. Confirmation of pDPN should include additional electrophysiological studies.

Noninvasive, Basic Diagnostics for CLTI

Diminished limb perfusion, tissue oxygenation, and nutrition may cause claudication or CLTI rest pain.[4,5] However, these typical symptoms of peripheral arterial disease can be altered or absent in certain patients with diabetes who exhibit peripheral denervation by concomitant DPN. Alternatively, CLTI may or may not mask atypical unilateral DPN pain symptoms in patients with neuroischemic diabetic lower limbs.[4,5]

More precisely, CLTI ischemic rest pain (**Figure 3**) is usually unilaterally located; it frequently involves the forefoot and worsens in a decline position[4] and may require opiate analgesia for management.[4] If this type of pain is present for more than 2 weeks and is combined with hemodynamic evidence of severely impaired arterial perfusion (AP <50 mmHg and TP <30 mmHg), it could represent a thorough argument for CLTI.[4]

Several first-line AP, TP, ABI, and TBI exams are currently mentioned in the CLTI dedicated literature. Other noninvasive tests for CLTI confirmation have been proposed in recent years (without detailed description in this paragraph), such as pedal (or plantar) acceleration time, transcutaneous oxygen pressure, laser Doppler flowmetry and laser speckle imaging, near-infrared spectroscopy, hyperspectral imaging, computed tomography (CT) angiography and color-coded CT perfusion, magnetic resonance imaging (MRI) angiography, arterial spin labeling MRI, diffuse speckle contrast analysis, skin micro-oxygen sensors, and nuclear medicine evaluation by single photon emission CT, among others.[3-5,18,19]

All these novel technologies have undeniable advantages and inherent limitations for the scrutiny of each flow type. Nevertheless, when associated with clinical observations, they afford a more accurate analysis of macro- and microvascular flow, capillary and tissue oxygenation levels, or potential intracellular hypoxia at the mitochondrial level.[4,5,18]

Practical observation: In a diabetic patient with pertinent cardiovascular risk factors, the presence of recent, predominantly unilateral, relentless foot pain that worsens in a decline position, and may not be accompanied by pallor and coldness (due to concurrent neuropathy and inflammation), should prompt consideration of CLTI. Expeditious multidisciplinary assessment and potential fast-track revascularization for limb preservation are recommended.

Discussion and Differential Diagnostics

The presence of chronic, disabling pain in the lower limbs, possibly associated with specific risk factors for DPN, pDPN, and CLTI, is always a priority for detailed investigation and treatment. Rapid and irreversible degradation of the exposed extremity leads to severe hypoxia, local tissue decay, bacterial proliferation, increased neuropathic effects, irreversible denervation, and diminished tissue regeneration capacities.[1-3,8,9,13-15] The hypothesis of a highly probable CLTI condition (with or without associated DPN)[18,19] should always be evoked in the first place (**Figure 3**).

In summary, any lower limb painful syndrome that lasts for more than 2 weeks[4] in a patient with DM with positive vascular risk factors needs to be first interpreted as ischemia-related unless additional diagnostic exams prove the contrary.[2,3 4,13,19] As an aphorism, any clinical suspicion of pDPN may paradoxically require, in the first place, a vascular, not neurological, preamble (ie, segmental pressures and duplex) for ruling out any eventual, more urgent vascular hidden pathology. The correct recognition of painful DPN vs severe CLTI pain relies on meticulous anamnesis, clinical examination, and recommended first-line noninvasive examinations.[1-4,15,18,19] In conjunction with a detailed clinical examination, the first-line diagnostic exclusion of PAD/CLTI using noninvasive AP, TP, ABI, TBI, and segmental pressure screening may be prone to interpretation errors or may be inapplicable in many patients with DM who exhibit characteristic BTK vascular calcifications and stiff tibial and pedal arteries.[4,5,20-22]

The vascular specialist may be confronted with unexpected diagnostic defiance in their daily practice because classic ischemic pain[4] can be distorted or excluded by concomitant diabetic limb neuropathy.[3-6,19] Moreover, palpable perimalleolar pulses can be misleading in certain distal (predominantly inframalleolar) forms of diabetic neuroischemic disease. These CLTI variants are characterized by BTA occlusive microangiopathy[20,23] and moderate upstream macrovascular stenotic lesions.[4,20] In such cases, more advanced transcutaneous "second line" noninvasive technologies, such as transcutaneous oxygen pressure, laser Doppler flowmetry, and laser speckle imaging, can be utilized—depending on the expertise of the team and the availability of equipment—to provide more accurate assessments of foot capillary oxygenation and flow analysis.[23] However, these diagnostic methods are not without limitations, which may be influenced by factors such as local skin inflammation, the depth of ischemic tissue, regional edema, and tissue capillary shunting caused by autonomic denervation.[7,20,23]

Any attempt to standardize the differential diagnosis and prognosis of pDPN vs CLTI rest pain becomes even more delicate because of their mutable appearance according to their divergent evolutions.[6,12,13]

Because pDPN and CLTI can display myriad clinical combinations (**Figures 2** and **3**) within the same ongoing metabolic syndrome (whether controlled or not), no gold standard examination for timely identification and differential diagnosis has been unanimously recognized.[9,11-13]

Practical observation: Painful diabetic foot syndrome does not always adhere to standardized CLTI criteria due to the numerous interactions among macrovascular and microvascular angiopathy, various forms of DPN, chronic inflammation, sepsis, direct hyperglycemic cellular toxicity, and other factors. Complex presentations involving overlapping DPN and CLTI are not uncommon, particularly in aging individuals with diabetes. Current recommendations emphasize the importance of a comprehensive clinical evaluation, close monitoring of symptoms (especially when the initial diagnosis is challenging), and prompt referral, if necessary, to specialized multidisciplinary centers, adhering to a diligent "time is tissue" approach.

Special Considerations

Finally, since some of the multifaceted appearances of pDPN may change over time and with each phenotype, and since no standard pDPN diagnostic has been proven reliable to date,[11-13] and since CLTI may appear heterogeneous (assembling many subgroups of population),[23,24] including "asymptomatic" patients (those with DPN denervation),[5] the specific segmental pressure[4,22] first-line hemodynamic assessment[4,5,20,23] can be completed by parallel second-line noninvasive BTK and BTA arteriolar and capillary flow exploration; a meticulous limb flow analysis down to the foot arches also appears mandatory.[3-5,20,23]

Over 20 years ago, a review of the effectiveness of DPN diagnostic was made by England et al,[25] who concluded that the DPN and pDPN formal diagnostics remain troublesome and depends on the examiner's skill for tying together symptoms, signs, and diagnostic test results.[25] Despite notable advances in CLTI and DPN diagnosis and limb salvage,[3,4,24] this assertion seems equally valid in current practice.[13,20]

Conclusions

The assessment of painful diabetic neuroischemic limbs invariably requires a multispecialty approach. The differential diagnosis of painful DPN relies on thoroughly analyzing each individual's medical history, clinical evaluation, and noninvasive screening test data. Concomitant ischemic participation should be systematically ruled out by focused arterial flow examination and diagnostic methodology in concordance with the available consensual CLTI vascular recommendations.

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From the Cardiovascular and Thoracic Surgery Department, CHU Sart-Tilman University Hospital Center, Liège, Belgium.

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Corresponding author: Vlad Adrian Alexandrescu, MD, Cardiovascular and Thoracic Surgery Dept, CHU Sart-Tilman Hospital, Avenue de l'Hôpital 1, 4000 Liège, Belgium. Email: v.alex@skynet.be