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COMPREHENSIVE REVIEW OF CHRONIC LIMB-THREATENING ISCHEMIA: FROM PATHOPHYSIOLOGY TO INNOVATIVE TREATMENT APPROACHES

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ABSTRACT

Introduction: Chronic Limb-Threatening Ischemia (CLTI) represents the most advanced stage of peripheral artery disease (PAD) and is associated with a high risk of major amputation and mortality. Characterized by rest pain, non-healing ulcers, or gangrene, CLTI reflects severe systemic atherosclerosis with widespread cardiovascular involvement. The disease burden is increasing globally, particularly in aging populations with diabetes or hypertension.
Methods: A literature review of PubMed, Scopus, and Google Scholar summarized current evidence on the definition, pathophysiology, classification, diagnostic strategies, and management of CLTI. It also highlights emerging research directions, including novel endovascular and surgical revascularization techniques, biologic and cell-based therapies, and evolving approaches to patient-centered care.
Results: Advances in imaging modalities and revascularization strategies particularly endovascular, surgical, and hybrid techniques have significantly improved limb salvage and survival rates. Recent studies emphasize the importance of individualized therapy and multidisciplinary management. Concurrently, innovative therapies focusing on angiogenesis, gene therapy, and regenerative medicine show promise for "no-option" patients, although further randomized trials are needed to validate long-term efficacy and safety.
Conclusions: CLTI remains a complex and life-threatening condition requiring early diagnosis, comprehensive risk factor control, and personalized treatment planning. The integration of precision medicine, advanced imaging, and regenerative approaches holds the potential to redefine therapeutic strategies and improve patient outcomes. Future research should focus on optimizing patient selection, expanding access to limb-salvage interventions, and reducing global disease burden through preventive care.

KEYWORDS

Chronic Limb-Threatening Ischemia, Peripheral Artery Disease, Revascularization, Angiogenesis, Atherosclerosis, Vascular Surgery

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Introduction

Chronic Limb-Threatening Ischemia (CLTI) represents the most severe manifestation of peripheral artery disease (PAD), characterized by rest pain, non-healing ulcers, or gangrene in the lower extremities due to prolonged and critical impairment of blood flow. This advanced stage of PAD results in significant tissue ischemia, often leading to irreversible tissue damage and an increased risk of major limb loss. CLTI is not only a local vascular problem but also a systemic marker of severe atherosclerotic disease, as patients with CLTI frequently exhibit widespread cardiovascular comorbidities. Epidemiological studies estimate that CLTI affects approximately 1–2% of the general population, with higher prevalence observed in older adults and individuals with diabetes. In the United States, CLTI accounts for roughly 10–15% of PAD cases, and its incidence continues to rise in the context of aging populations and the global increase in metabolic disorders. [1]

Several risk factors contribute to the development and progression of CLTI. Advanced age is strongly associated with increased prevalence, reflecting the cumulative effect of atherosclerosis over time. Diabetes mellitus, particularly type 2 diabetes, markedly elevates the risk by promoting both macrovascular and microvascular dysfunction. Smoking remains one of the most potent modifiable risk factors, accelerating the atherosclerotic process and impairing endothelial function. Hypertension and hyperlipidemia further exacerbate vascular injury, promoting plaque formation and arterial narrowing. Chronic kidney disease also significantly increases the risk of CLTI, as renal impairment is associated with endothelial dysfunction, vascular calcification, and poor wound healing. [2]

Comorbid conditions in patients with CLTI substantially influence outcomes and prognosis. Heart failure is common among this population and contributes to higher rates of limb loss and mortality. Depression,

frequently underrecognized in vascular patients, has been associated with worse adherence to therapy, reduced physical activity, and poorer overall outcomes. Pulmonary diseases, including chronic obstructive pulmonary disease, may exacerbate systemic hypoxia and limit functional recovery. The coexistence of multiple comorbidities, particularly diabetes, renal disease, and cardiovascular disease, underscores the complexity of CLTI management and highlights the need for a multidisciplinary approach to optimize limb salvage and overall survival. [3]

Methodology

A literature review of PubMed, Scopus, and Google Scholar summarized current evidence on the definition, pathophysiology, classification, diagnostic strategies, and management of CLTI. It also highlights emerging research directions, including novel endovascular and surgical revascularization techniques, biologic and cell-based therapies, and evolving approaches to patient-centered care.

Pathophysiology

The pathophysiology of CLTI is multifactorial, involving complex interactions between hemodynamic, vascular, inflammatory, and metabolic factors.

The primary mechanism underlying CLTI is the progressive atherosclerosis of arterial vessels, leading to significant luminal narrowing and occlusion. This process begins with endothelial injury, promoting the accumulation of lipids and the formation of atherosclerotic plaques. These plaques can rupture, exposing their thrombogenic core and leading to the formation of thrombi that further obstruct blood flow. Studies have shown that patients with CLTI exhibit elevated levels of acute-phase reactants such as C-reactive protein and fibrinogen, alongside decreased levels of albumin and high-density lipoprotein cholesterol, indicating an active inflammatory state and altered lipid metabolism. [4]

In response to chronic ischemia, the body attempts to compensate by promoting angiogenesis the formation of new blood vessels. However, in CLTI, this compensatory mechanism is often insufficient. The newly formed vessels are frequently dysfunctional, exhibiting impaired endothelial function and reduced perfusion capacity. Additionally, there is evidence of microvascular rarefaction, where the number and density of small vessels decrease, further exacerbating tissue ischemia. [4]

Medial arterial calcification (MAC) is a common finding in patients with CLTI, particularly among those with diabetes and chronic kidney disease. MAC leads to the stiffening of arterial walls, reducing their ability to dilate and accommodate increased blood flow. This arterial rigidity contributes to the progression of ischemia and complicates revascularization efforts. Studies have highlighted the adverse impact of MAC on clinical outcomes, including increased risk of amputation and mortality. [5]

The presence of comorbid conditions such as diabetes mellitus, chronic kidney disease, and heart failure significantly influences the pathophysiology and progression of CLTI. Diabetes accelerates atherosclerosis and impairs wound healing, while chronic kidney disease contributes to vascular calcification and endothelial dysfunction. Heart failure exacerbates peripheral ischemia due to reduced cardiac output and peripheral perfusion. The interplay of these comorbidities complicates the clinical management of CLTI and worsens patient outcomes. [6]

Classifications of Chronic Limb-Threatening Ischemia

Accurate classification of Chronic Limb-Threatening Ischemia (CLTI) is essential for determining prognosis, guiding treatment decisions, and predicting outcomes. Two primary classification systems are widely utilized: the Wound, Ischemia, and Foot Infection (WIfI) staging system and the Global Limb Anatomic Staging System (GLASS). The Rutherford classification is a widely used clinical grading system for PAD and plays an essential role in the assessment of CLTI.

The WIfI classification system, developed by the Society for Vascular Surgery, evaluates three critical components: wound severity, ischemia, and foot infection. Each component is graded on a scale from 0 to 4, with higher scores indicating more severe conditions. The cumulative score determines the overall WIfI stage, which ranges from 0 (no threat) to 4 (severe threat). This system has been validated as a reliable predictor of major adverse limb events (MALE) and amputation-free survival (AFS) in CLTI patients. Studies have demonstrated that patients with higher WIfI stages experience worse outcomes, including increased rates of amputation and lower survival rates. For instance, a study by Cheun et al. (2024) found that patients with worsening WIfI stages had significantly higher rates of major amputation and lower AFS at five years compared to those whose WIfI stage improved or remained unchanged. [7]

The GLASS system assesses the anatomic complexity of arterial disease by evaluating the presence and severity of lesions in specific arterial segments. It categorizes patients into three stages: Stage I (low complexity), Stage II (moderate complexity), and Stage III (high complexity). This classification aids in determining the most appropriate revascularization strategy, whether endovascular or surgical. Research indicates that higher GLASS stages are associated with poorer outcomes, including lower limb salvage rates and wound healing. For example, a study by Morisaki et al. (2023) found that patients with GLASS Stage III had significantly lower limb salvage and wound healing rates compared to those with lower GLASS stages. [8]

The Rutherford scale categorizes patients based on clinical symptoms, ranging from asymptomatic disease to severe ischemia with tissue loss. The classification includes seven categories: Category 0 indicates asymptomatic PAD; Categories 1-3 describe varying degrees of intermittent claudication, from mild to severe; Category 4 corresponds to rest pain, representing a transition toward critical limb ischemia; Categories 5 and 6 denote minor and major tissue loss, respectively, including non-healing ulcers or gangrene. [9]

Clinical Diagnosis and Imaging in Chronic Limb-Threatening Ischemia

Accurate diagnosis of Chronic Limb-Threatening Ischemia (CLTI) is crucial for effective management and treatment planning. The diagnostic approach combines a thorough clinical assessment with advanced imaging techniques to evaluate the severity and extent of arterial insufficiency.

a) Clinical Assessment

The initial evaluation of a patient suspected of having CLTI involves a comprehensive clinical assessment, including a detailed medical history, physical examination, and assessment of symptoms. Key indicators include rest pain, non-healing ulcers, and gangrene. The Rutherford Classification system is commonly used to stage the severity of symptoms, ranging from mild claudication to severe ischemia with tissue loss. Higher Rutherford stages correlate with increased risk of adverse outcomes, including major amputation and mortality. [9]

b) Ankle-Brachial Index (ABI)

The Ankle-Brachial Index (ABI) is a non-invasive and widely used method to assess peripheral arterial disease. An ABI value of less than 0.90 is indicative of arterial insufficiency. However, in patients with heavily calcified arteries, particularly those with diabetes, ABI measurements may be falsely elevated, limiting its diagnostic accuracy. In such cases, alternative non-invasive tests are recommended. [10]

c) Ultrasound

Doppler ultrasound is a non-invasive imaging technique that allows for the evaluation of blood flow and the identification of stenotic or occluded vessels. It is often used as a first-line imaging modality due to its accessibility and cost-effectiveness. However, its effectiveness can be limited in patients with extensive calcification or obesity.

d) Computed Tomography Angiography (CTA)

CTA provides high-resolution images of the arterial tree, allowing for the assessment of the location and severity of stenoses or occlusions. It is particularly useful in planning revascularization procedures. Recent studies have highlighted the utility of CTA in evaluating coronary artery disease in CLTI patients, as many individuals with CLTI may have concomitant coronary artery disease that requires assessment. [11]

e) Magnetic Resonance Angiography (MRA)

MRA is an alternative to CTA, offering detailed images without the use of ionizing radiation. It is particularly beneficial in patients with renal insufficiency who are at risk of contrast-induced nephropathy. MRA can effectively delineate arterial anatomy and assess the extent of disease, aiding in the planning of surgical or endovascular interventions.

f) Digital Subtraction Angiography (DSA)

DSA remains the gold standard for evaluating the arterial system, providing real-time images during catheter-based procedures. It allows for precise localization of lesions and assessment of the vascular anatomy. However, DSA involves the use of contrast agents and ionizing radiation, which may limit its use in certain patient populations. [12]

Conservative Management of Chronic Limb-Threatening Ischemia

Conservative management of Chronic Limb-Threatening Ischemia (CLTI) is primarily aimed at alleviating symptoms, preventing disease progression, and improving limb salvage prospects in patients who are not candidates for revascularization. This approach encompasses medical optimization, wound care, and lifestyle modifications.

The cornerstone of conservative therapy involves the management of modifiable risk factors. Aggressive control of hyperlipidemia, hypertension, and diabetes mellitus is essential to slow the progression of atherosclerosis and improve overall vascular health. Antiplatelet therapy, typically with aspirin or clopidogrel, is commonly prescribed to reduce the risk of thrombotic events. Additionally, statins are utilized not only for lipid control but also for their pleiotropic effects, including anti-inflammatory properties that may benefit patients with CLTI.

Patients with CLTI often present with non-healing ulcers or gangrene. Effective wound care is paramount and includes regular debridement, infection control, and the use of advanced dressings to promote healing. In cases of infection, appropriate antibiotic therapy based on culture results is critical. For diabetic patients, offloading pressure from the affected limb using specialized footwear or devices can significantly aid in ulcer healing.

Smoking cessation is perhaps the most impactful lifestyle change for patients with CLTI. Smoking accelerates atherosclerosis and impairs wound healing, thus its cessation is strongly advised. Structured supervised exercise programs have also been shown to improve walking distance and quality of life in patients with intermittent claudication, a precursor to CLTI. [13,8]

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Management of CLTI requires a collaborative approach involving vascular surgeons, interventionalists, podiatrists, and other healthcare professionals. Regular monitoring and reassessment are necessary to evaluate the effectiveness of conservative measures and to determine if and when revascularization becomes appropriate. [14]

Revascularization Strategies in Chronic Limb-Threatening Ischemia

Revascularization remains the cornerstone of treatment for Chronic Limb-Threatening Ischemia (CLTI), aiming to restore adequate blood flow, alleviate symptoms, and prevent limb loss. The choice of revascularization technique: endovascular, surgical, or hybrid depends on factors such as lesion location, severity, patient comorbidities, and anatomical considerations.

a) Endovascular Interventions

Percutaneous Transluminal Angioplasty (PTA), often combined with stenting, has become the preferred initial approach for many patients with CLTI due to its minimally invasive nature and favorable outcomes in appropriately selected cases. PTA is particularly effective for lesions in the superficial femoral artery (SFA) and popliteal artery, especially when the lesions are short and the distal runoff is good. Recent studies have

demonstrated that endovascular interventions, including PTA and stenting, offer comparable outcomes to surgical bypass in terms of limb salvage and wound healing, with the added benefits of shorter recovery times and reduced perioperative morbidity. [15,16]

b) Surgical Revascularization

Lower extremity bypass (LEB) surgery remains the gold standard for patients with complex or long-segment arterial occlusions, particularly those with poor distal runoff or recurrent disease. Autologous great saphenous vein grafts are preferred due to their superior patency rates. However, synthetic grafts or alternative conduits may be used when autologous veins are unavailable. Studies have shown that LEB provides higher technical success rates and long-term patency compared to endovascular treatments in certain patient populations. [15]

c) Hybrid Approaches

Hybrid procedures, combining endovascular techniques with surgical bypass or endarterectomy, are increasingly utilized for complex CLTI cases. For instance, femoral endarterectomy combined with PTA or femoropopliteal bypass combined with tibial PTA have been reported to improve outcomes in patients with multi-segmental disease. These approaches aim to optimize blood flow restoration while minimizing surgical morbidity. [17]

Latest research

Contemporary research in Chronic Limb-Threatening Ischemia (CLTI) emphasizes both incremental improvements in revascularization technologies and paradigm-shifting regenerative and biologic therapies. Large randomized trials and comparative effectiveness studies (notably BEST-CLI) have refined patient selection for open bypass versus endovascular strategies and highlighted the importance of conduit quality and individualized decision-making. [18] Parallel device-focused research has explored drug-eluting and drug-coated platforms (including sirolimus-based technologies) and novel scaffolds for infrapopliteal and femoropopliteal disease, with accumulating real-world and trial data suggesting improved patency and limb outcomes in selected cohorts. [19,20] Minimally invasive bypass alternatives such as the DETOUR percutaneous bypass system are being evaluated in multicenter studies for complex long-segment occlusions, offering promising limb-salvage options for patients who are poor surgical candidates. [21] At the same time, a growing body of translational and clinical work focuses on therapeutic angiogenesis and cell-based approaches including gene therapy, mesenchymal and autologous bone-marrow or adipose-derived cell therapies aimed at restoring microvascular perfusion in “no-option” CLTI; early-phase trials demonstrate feasibility and safety but heterogeneous efficacy, underlining the need for larger, standardized randomized trials. [22,23] Finally, contemporary trials increasingly adopt broader, patient-centred endpoints and integrate advanced imaging, biomarkers, and health-services research to optimize limb functional outcomes and survival rather than angiographic success alone- a shift that is reshaping trial design and clinical practice in CLTI. [24]

Conclusions

Chronic Limb-Threatening Ischemia (CLTI) remains one of the most challenging entities in vascular surgery, representing the final and most severe stage of peripheral artery disease. Despite major advances in diagnostic imaging, revascularization techniques, and wound management, CLTI continues to carry high rates of morbidity, amputation, and mortality. The complexity of its pathophysiology involving macrovascular occlusions, microvascular dysfunction, inflammation, and calcification underscores the need for individualized and multidisciplinary care.

Recent research has expanded therapeutic possibilities beyond conventional revascularization, with growing interest in biologic, gene, and cell-based therapies for “no-option” patients. While early results are encouraging, large randomized controlled trials are still required to confirm efficacy and safety. Advances in drug-eluting technologies, percutaneous bypass systems, and hybrid approaches are progressively redefining the boundaries of limb salvage.

The future of CLTI management lies in integrating precision medicine, advanced imaging, and personalized risk stratification to guide therapy selection and optimize long-term outcomes. Emphasis should also be placed on preventive strategies, early diagnosis, and aggressive management of cardiovascular risk factors to reduce disease incidence. Ultimately, improving the survival and quality of life of patients with CLTI will depend on combining technological innovation with holistic, patient-centered care.

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