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Review

GLP-1 Receptor Agonists in Diabetic Lower Extremity Peripheral Artery Disease: From Mechanisms to Clinical Practice

Jie Pan[1], Chengnan Guo[1], Qiuwei Huang[2], Yikai Zhang[1], Yimin Shen[1,*], Caiyun Guo[3,*]

[1]Department of Endocrinology and Metabolism, The Second Affiliated Hospital, Zhejiang University School of Medicine, 310009 Hangzhou, Zhejiang, China
[2]School of Medicine, Zhejiang Chinese Medical University, 310053 Hangzhou, Zhejiang, China
[3]Department of Endocrinology, Ningbo University Affiliated Yangming Hospital, 315400 Ningbo, Zhejiang, China
*Correspondence: shen06@zju.edu.cn (Yimin Shen); guocaiyun9112@163.com (Caiyun Guo)
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Abstract

Diabetic lower extremity peripheral artery disease (PAD) is a complex and multifactorial complication of diabetes mellitus, characterized by extensive distal disease burden, accelerated progression, and a markedly elevated risk of major adverse limb events. Despite considerable advances in endovascular and surgical revascularization, limb salvage rates in this population remain suboptimal, largely due to the limited efficacy of current pharmacological options in improving microvascular perfusion, accelerating wound healing, or preventing re-occlusion. In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a transformative therapeutic class, demonstrating cardiovascular protective effects beyond glycemic control. Large-scale real-world studies have generated encouraging signals regarding their potential to reduce amputation risk and promote wound healing. However, the current evidence base remains limited, and the precise molecular mechanisms by which GLP-1 RAs may protect the diabetic lower extremity require further elucidation. This review systematically examines the epidemiology and pathophysiology of diabetic lower extremity PAD, elucidates the molecular mechanisms of GLP-1 RA-mediated vascular protection, critically evaluates clinical and real-world evidence, and discusses key challenges and future directions for optimizing therapeutic outcomes in this high risk population.

Keywords: glucagon-like peptide-1 receptor agonists; peripheral arterial disease; diabetes mellitus, type 2

1. Introduction

Diabetic lower extremity peripheral artery disease (PAD) is one of the most severe and resource-intensive complications of diabetes mellitus, encompassing a clinical spectrum that extends from asymptomatic peripheral artery disease to chronic limb-threatening ischemia (CLTI), and ultimately to lower extremity amputation (LEA) in severe cases [1]. As the global prevalence of type 2 diabetes mellitus (T2DM) continues to rise, the burden of PAD has become a major public health concern, profoundly affecting patient morbidity, mortality, and quality of life [2]. The pathophysiology of this condition is complex and stems from a combination of chronic hyperglycemia, insulin resistance, and dyslipidemia that collectively promote vascular inflammation, induce endothelial dysfunction, impair angiogenesis, and exacerbate atherosclerotic plaque instability in the peripheral circulation [3]. Despite ongoing advances in endovascular and surgical revascularization techniques, few pharmacological options remain to improve functional outcomes in diabetic lower extremity PAD.

In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a transformative therapeutic class, offering cardiovascular benefits that extend well beyond their glucose-lowering effects [4]. Agents such as liraglutide, semaglutide have exhibited the ability to effectively reduce the incidence of major adverse cardiovascular events (MACE) in patients with T2DM at high cardiovascular risk [5]. However, as these landmark trials were primarily designed to assess MACE occurrence and were not powered to evaluate limb-specific endpoints, the available evidence regarding lower extremity outcomes has largely been derived from post-hoc or subgroup analyses. In contrast with these general cardiovascular findings, large-scale real-world studies have suggested that GLP-1 RAs may confer specific advantages for patients with concomitant diabetes and PAD, including potential reductions in lower extremity amputation risk, improved wound healing, and enhanced peripheral perfusion [6].

Despite established therapeutic strategies, including risk factor modification, antiplatelet therapy, and advances in revascularization techniques, limb salvage rates in patients with both diabetes and PAD remain suboptimal. Specifically, current pharmacological options offer limited efficacy in directly improving microvascular perfusion, accelerating wound healing, or preventing the rapid neointimal hyperplasia that contributes to re-occlusion in diabetic patients. Furthermore, although large-scale real-world studies have generated encouraging signals regard-

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ing the ability of GLP-1 RAs to reduce amputation risk and promote wound healing [6,7], the current evidence base remains constrained. Most cardiovascular outcome trials were not designed with limb-specific endpoints as primary outcomes, contributing to a reliance on post-hoc analyses and observational data. Moreover, the precise molecular mechanisms by which GLP-1 RAs may protect the lower extremities in the context of diabetes, particularly with respect to distinct pathologies such as distal arterial calcification and microvascular rarefaction, require further elucidation.

This review aims to provide a comprehensive and up-to-date overview of the available evidence regarding the use of GLP-1 RAs in the context of diabetic lower extremity PAD, to elucidate the underlying pathophysiological mechanisms, to explore the molecular basis of GLP-1 RA-mediated vascular protection in the lower extremities, to evaluate the available clinical trial and real-world evidence, and to discuss the challenges and future directions for optimizing GLP-1 RA therapy in this high-risk patient population. Therefore, a systematic literature search was conducted across PubMed, Embase, Cochrane Library, and Web of Science from inception to July 2026, using terms related to GLP-1 RAs and diabetic lower extremity vascular outcomes. Additional records were obtained by manually screening the reference lists of retrieved articles.

2. Diabetic Lower Extremity Peripheral Artery Disease: A Clinical Overview

2.1 Disease Epidemiology

The global prevalence of lower extremity arterial disease has been steadily increasing such that it now represents a substantial public health issue worldwide. According to a landmark systematic review and analysis conducted by Song et al. [8], the estimated number of individuals aged 25 years and older affected by PAD increased from 164 million in 2000 to 202 million in 2010. A more recent literature showed that a total of 236 million people aged 25 years and older were living with PAD globally in 2015, among whom 72.91% were in low-income and middle-income countries (LMICs) [8]. Across all subgroups stratified by sex and country income level, the prevalence of PAD consistently rose with increasing age, with the highest rates observed in the oldest age groups (85–89 years and above) [9]. Women bear a slightly greater global burden of PAD than men, particularly in high-income countries (HIC) and in older age groups, challenging the traditional view of PAD as a predominantly male-dominated disease [8]. These demographic patterns are further reflected in the regional and national distribution of PAD. Although over 70% of the global disease burden is concentrated in LMICs [8], there is a disproportionately higher absolute number of affected individuals in the most populous nations, including China, India, and the United States. This is attributable at least in part to the large population bases of these countries, which inevitably contribute substantial case numbers despite differences in income levels and healthcare infrastructure. The Western Pacific region accounts for the largest share of overall PAD cases in the world, while at the national level, China, India, and the United States have the highest numbers of affected individuals [8,10]. These trends have profound implications for long-term PAD management, particularly given the ongoing and progressive aging of the global population.

2.2 Disease Pathophysiology

The pathophysiology of diabetic lower extremity PAD is based on the fundamental vascular complications of diabetes mellitus, which are driven by the sustained metabolic perturbations derived from chronic hyperglycemia [11]. As demonstrated by Paneni et al. [12], chronic hyperglycemia serves as a primary driver of endothelial dysfunction through multiple interconnected mechanisms. Hyperglycemia-induced oxidative stress, characterized by excessive reactive oxygen species (ROS) production together with diminished antioxidant capacity, compromises endothelial cell function and viability. In the context of hyperglycemia, multiple inflammatory pathways, including the protein kinase C (PKC), hexosamine, and polyol pathways, are activated [12]. These signaling axes stimulate vascular smooth muscle cell proliferation, matrix remodeling, and vulnerable plaque phenotype development. The PKC pathway, activated by diacylglycerol in the presence of hyperglycemia, leads to increased expression of pro-inflammatory cytokines, growth factors, and adhesion molecules [13], whereas the polyol pathway contributes to osmotic stress and oxidative injury through aldose reductase-mediated sorbitol accumulation [14,15]. The hexosamine pathway diverts glucose metabolites to generate UDP-N-acetylglucosamine, which modifies transcription factors and further amplifies inflammation-associated gene expression [16]. The accumulation of advanced glycation end products (AGEs) is another important pathway involved in diabetic vascular injury [17]. When faced with persistent hyperglycemia, the non-enzymatic glycation of proteins and lipids takes place, resulting in markedly enhanced AGE formation. Binding of AGEs to their receptor (RAGE) triggers pro-inflammatory signaling cascades, including the nuclear factor-κB (NF-κB) pathway, resulting in the upregulated expression of adhesion molecules, cytokines, and growth factors [18]. This downstream cascade, in turn, drives accelerated atherosclerosis, endothelial dysfunction, and compromised vascular repair. In addition to these effects, AGE accumulation promotes collagen cross-linking in the arterial wall, leading to increasingly severe arterial stiffness and decreased compliance, thereby further impairing peripheral perfusion [19].

The concept of metabolic memory encompasses vascular damage that exists despite appropriate glycemic control, with this deleterious process being driven by the en-

during effects of prior hyperglycemia on cellular function and gene expression, making it particularly relevant to distal vasculopathy in diabetic PAD [20]. The sustained accumulation of AGEs and ROS, epigenetic reprogramming, and persistent pro-inflammatory signaling give rise to this metabolic memory, which, in turn, selectively impairs the distal microvascular bed. In the lower extremities, this metabolic "imprint" actively suppresses hypoxia-induced compensatory angiogenesis and severely hinders the effective development of collateral circulation. Consequently, even after glucose levels have normalized, distal microvascular endothelial cells remain in a state of impaired repair capacity and heightened susceptibility to ischemic injury, accelerating progression towards CLTI and amputation [21,22,23]. These pathophysiological considerations emphasize the reason why glycemic control alone is insufficient to reverse established distal vascular damage. This mechanistic understanding provides a clear rationale for the use of glucose-lowering agents with pleiotropic vascular benefits, such as GLP-1 RAs, to counteract persistent hyperglycemic vascular injury [4]. GLP-1 RAs have been shown to intervene in key pathways of metabolic memory [24,25] and to promote angiogenic processes, thereby improving microcirculatory perfusion and wound healing in the ischemic distal limb. The vasculature of the lower extremities is particularly susceptible to diabetic complications. Angiographic studies have demonstrated that distal arterial segments, particularly the tibial and peroneal arteries, are preferentially affected in diabetic patients with PAD [26], leading to poor collateral circulation [27], heightened sensitivity to ischemic injury [28], and significantly increased barriers to revascularization [29]. Moreover, the pathophysiology of lower extremity PAD in T2DM encompasses a combination of macrovascular atherosclerosis as well as widespread microvascular dysfunction involving the capillaries, arterioles, and venules [30], together constituting a "double hit" that severely exacerbates tissue ischemia and promotes reperfusion injury [31]. The chronic complications of diabetes are frequently accompanied by peripheral neuropathy, impacting upwards of 50% of patients with long-standing diabetes. Peripheral neuropathy often has the effect of masking ischemic symptoms, contributing to delayed presentation and more advanced disease in T2DM patients with PAD [32].

Owing to these factors, affected patients tend to more frequently present with CLTI rather than intermittent claudication. The presence of comorbid diabetes, peripheral neuropathy, and PAD has the potential to further obscure foot infection incidence, as diminished protective sensation can allow for the undetected progression of minor injuries until they have become deeply ulcerated or gangrenous. This vulnerable patient population is characterized by delayed presentation and a markedly elevated risk of limb loss, underscoring the urgent need for heightened clinical vigilance and integrated therapeutic strategies.

2.3 Diabetes as a Major Risk Factor for PAD

Diabetes mellitus is one of the most critical risk factors for PAD progression [33]. Patients with diabetes have as much as 2–4 times greater risk of developing atherosclerosis [34]. In a large prospective cohort of 11,140 patients with T2DM followed for a median of 9.9 years, 516 (4.6%) exhibited baseline major PAD, defined as lower-extremity chronic ulceration or amputation secondary to vascular disease, or a history of peripheral revascularization [35]. Patients with major PAD demonstrated significantly higher rates of all-cause mortality and major macrovascular events [35]. These findings emphasize the poor prognosis associated with PAD in diabetic patient populations while also highlighting the urgent need for aggressive risk factor modification and multidisciplinary care.

Poor glycemic control in diabetic patients also exerts a profound impact on the distribution, severity, and natural history of PAD [36]. One study compared the severity and distribution of peripheral arterial disease between diabetic and non-diabetic patients referred for lower-extremity angiography [26], and revealed that diabetic patients had significantly greater severity of arterial disease in the profunda femoris and all infrapopliteal segments ($p < 0.02$). Specifically, diabetic patients exhibited markedly higher occlusion scores in the anterior tibial (median score 13 vs. 3, $p = 0.002$), peroneal (5 vs. 0, $p = 0.001$), and posterior tibial (15 vs. 4, $p = 0.001$) arteries [26]. The distal, multisegmental, and frequently diffuse nature of this disease limits collateral development, contributing to accelerated progression to critical limb ischemia and complicating clinical decision-making.

2.4 Long-Term Disease Outcomes

The co-occurrence of diabetes and PAD multiplies the risk of lower extremity amputation, which remains an extremely severe and potentially devastating complication of diabetic lower extremity PAD [37]. A comprehensive review of the epidemiology and risk of amputation in patients with diabetes and PAD revealed that nearly 100,000 major leg amputations are performed annually in the United States, with over half of these cases being attributable to the combined effect of diabetes and PAD [38]. Among patients with CLTI, the estimated prevalence of diabetes ranges from 27% to 76%, and this cohort faces an amputation rate four times higher than the national average. Importantly, there is a significant disparity in amputation risk across demographic and socioeconomic strata [38]. These disparities are strongly influenced by healthcare accessibility, quality of care, and social determinants of health, which collectively shape the clinical outcomes for affected patients.

Patient prognosis following amputation in individuals affected by diabetes and PAD remains poor. CLTI affects over 2 million Americans, and the associated mortality risk is estimated at 24% at 1-year post-diagnosis, increasing to

60% at 5 years [39]. For patients with CLTI who do not undergo amputation, the 5-year mortality rate is estimated at 55% to 65%, exceeding the 5-year mortality associated with female breast cancer (10%), colon cancer (35%), and even myeloma (50%) [38]. These statistics underscore the urgent need for prevention-focused strategies and effective disease management in patients with coexisting diabetes and PAD.

Lower extremity revascularization (LER) is essential when seeking to manage symptomatic PAD; however, the presence of diabetes substantially compromises both procedural success and long-term outcomes for affected individuals. Among 39,441 patients hospitalized for LER in the 2014 Nationwide Readmissions Database, 50.8% had diabetes mellitus. Relative to non-diabetic patients, those with diabetes were more likely to undergo major limb amputation and exhibited higher 6-month hospital readmission rates [40]. Notably, the presence of diabetes complications further amplified adverse outcomes. Among diabetic patients undergoing LER, 55.7% had complicated diabetes, defined by poor glycemic control or end-organ damage. This subgroup exhibited significantly higher risks of in-hospital major adverse cardiovascular and limb events (MACLE) and 6-month readmission relative to those affected by uncomplicated diabetes [40]. These findings underscore the critical importance of comprehensive diabetes management during the peri-revascularization period.

3. GLP-1 RAs and Vascular Protection: Mechanistic Insights

3.1 Effects on Atherosclerosis and Plaque Stability

Comprehensive reviews have identified the suppression of pro-inflammatory mediator release from activated leukocytes, inhibition of nuclear factor-κB (NF-κB) activation, attenuation of macrophage inflammation, and promotion of M2 polarization as core anti-atherosclerotic actions of incretin receptor agonists (IRAs) [41,42]. GLP-1 RAs reduce the risk of plaque rupture and subsequent thrombotic events that may precipitate acute limb ischemia by inhibiting the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin, thereby attenuating leukocyte recruitment, monocyte adhesion, and transendothelial migration during early atherogenesis [43,44]. In addition to modulating immune cell activity, GLP-1 RAs exert direct effects on the vascular wall. Specifically, GLP-1 RA treatment suppresses the proliferation and migration of vascular smooth muscle cells, reduces matrix metalloproteinase (MMP) expression, and promotes a quiescent, contractile phenotype, thereby stabilizing plaques and reducing vulnerability to rupture [45]. GLP-1 RAs have also been shown to reduce ROS production via the inhibition of NADPH oxidase activity, enhancement of antioxidant defenses through superoxide dismutase and catalase upregulation, and preservation of mitochondrial function, thereby protecting endothelial cells from hyperglycemia-mediated oxidative damage [24,25]. GLP-1 RA on endothelial cells stimulates nitric oxide (NO) production via endothelial NO synthase (eNOS) phosphorylation at Ser1177, improving vasodilation, reducing vascular resistance, and enhancing peripheral perfusion, with this effect being particularly pronounced in the diabetic state, where NO bioavailability is severely compromised [46]. Concurrently, GLP-1 RAs downregulate RAGE expression and inhibit AGE formation, thereby attenuating the AGE-RAGE-mediated inflammatory cascade that drives accelerated atherosclerosis and vascular stiffness in individuals with diabetes [47].

Consistently, GLP-1RA treatment has been shown to reduce plaque burden, improve plaque morphology, and decrease the frequency of plaque rupture events in animal models of atherosclerosis. Despite only limited direct evidence in human peripheral arteries, the consistency of these findings across different vascular beds suggests that similar benefits likely extend to the lower extremity circulation.

3.2 Beneficial Effects on Angiogenesis and Microcirculatory Function

In addition to their effects on macrovascular disease, GLP-1 RAs confer additional benefits to microvascular function and tissue repair, both of which are directly relevant to diabetic foot ulcer (DFU) management [48]. The STARDUST randomized clinical trial recently demonstrated that liraglutide significantly improved peripheral perfusion in patients with T2DM and PAD, as assessed by transcutaneous oxygen pressure measurements, suggesting that GLP-1 RAs may delay PAD clinical progression through microcirculatory enhancement [49]. GLP-1 RAs enhance peripheral perfusion via direct microvascular vasodilation, augmented capillary recruitment, and improved arteriolar responsiveness, thereby reinforcing the benefits of revascularization and optimizing tissue oxygenation at the microcirculatory level [50].

Moreover, GLP-1 RA-mediated improvements in endothelial function have been demonstrated in some preclinical models and human studies, as evidenced by enhanced flow-mediated dilation and reduced levels of circulating markers of endothelial dysfunction [51]. At the mechanistic level, GLP-1 has been shown to promote the mobilization of endothelial progenitor cells (EPCs) from the bone marrow, enhance their differentiation and functional capacity, and stimulate angiogenesis in ischemic tissues via the upregulation of vascular endothelial growth factor (VEGF) and other pro-angiogenic factors [52,53,54]. These eNOS- and VEGF-mediated mechanistic effects are explicitly captured in the integrative framework of incretin vascular biology recently outlined in a review, which identified enhanced eNOS activity and VEGF upregulation as key facets of the cardiovascular protective properties of GLP-1 RAs [44]. The role of GLP-1 RAs in promoting neovascularization and improving wound healing through VEGF up-

regulation has been further corroborated by evidence from diabetic animal models [48].

The above properties are particularly beneficial for patients with DFUs, given that impaired angiogenesis and disturbed microcirculatory perfusion are major contributors to poor wound healing and progression to gangrene in these cases [55].

3.3 Metabolic Effects Relevant to Vascular Protection

In addition to their vascular effects, GLP-1 RAs offer systemic metabolic advantages that are conducive to vascular protection in diabetic lower extremity PAD, encompassing multiple domains including glycemic control, modulation of weight and adipose metabolism, lipid regulation, and blood pressure management.

In terms of glycemic control, the glucose-dependent hypoglycemic effects of these drugs can minimize the risk of hypoglycemia, which is particularly relevant for patients with PAD [56].

With respect to effects on weight and adipose metabolism, in addition to inducing significant weight loss, GLP-1 RAs ameliorate inflammation within the adipose tissue compartment, enhance insulin sensitivity, and restore a favorable adipokine balance through simultaneous reductions in leptin and resistin levels together with increases in adiponectin. These effects are mediated by reductions in visceral adiposity, which serves as a critical determinant of metabolic health given its established role in the secretion of pro-atherogenic cytokines and free fatty acids [57].

GLP-1 RAs exert lipid-regulating effects through their ability to reduce levels of triglycerides and low-density lipoprotein cholesterol while modestly increasing high-density lipoprotein cholesterol through the enhancement of hepatic lipid metabolism together with reductions in intestinal lipid absorption [58]. The resulting improvement in overall lipid parameters complements the effects of statin therapy and may confer additional cardiovascular protection in patients with PAD, who frequently present with complex dyslipidemia.

GLP-1 RAs can additionally lower blood pressure through multiple mechanisms, including natriuresis, improved endothelial function, and weight loss, with typical reductions in systolic blood pressure ranging from 2–5 mmHg [59]. Although modest, these blood pressure reductions may add to the cardiovascular benefits achieved with other antihypertensive therapies.

Collectively, the cellular and molecular pathways discussed above, including eNOS phosphorylation, NF-κB inhibition, M2 macrophage polarization, suppression of vascular smooth muscle cell proliferation, and VEGF-mediated angiogenesis, are all closely related to the direct vascular protective effects of GLP-1 RAs and GIP-RAs. These convergent effects offer a clear biological rationale for GLP-1 RA-mediated vascular protection in the context of PAD (Fig. 1).

4. GLP-1 RAs in Diabetic Lower Extremity Peripheral Artery Disease: Evidence and Clinical Applications

4.1 Clinical Evidence for GLP-1 RAs in Lower Extremity Outcomes

Emerging evidence from large-scale real-world studies offers support for the ability of GLP-1 RAs to confer clinically meaningful benefits for lower extremity outcomes in patients affected by both diabetes and PAD. A landmark retrospective cohort study conducted in 2025 based on a U.S. electronic health records (EHR) database compared GLP-1 RAs, SGLT2 inhibitors, and DPP-4 inhibitors for lower extremity vascular complications and mortality in patients with PAD and T2DM, following 77,393 patients per cohort over a median interval of 1.7 years [60]. The results of this study suggested that, compared with SGLT2i therapy, GLP-1RA treatment was associated with a 21% reduction in the risk of major amputation, an 18% drop in the risk of lower extremity revascularization, and a 29% decrease in the risk of all-cause mortality. Comparable reductions were evident when GLP-1 RAs were compared with DPP-4 inhibitors. However, in light of the inherent limitations of EHR data, these findings should be interpreted as suggestive associations rather than definitive evidence of any causal effects. While these benefits were consistently observed in patients with symptomatic PAD and those with prior revascularisation, the extent to which they can be fully attributed to the drug effect versus unmeasured confounding will warrant careful consideration [60]. In a separate 2025 cohort study of 180,740 patients per group based on a federated EHR network, the initiation of GLP-1 RA treatment was associated with significantly better 3-year amputation-free survival than the use of SGLT2 inhibitors (99.69% vs. 99.64%, $p = 0.001$). That same analysis suggested that GLP-1 RAs reduced major amputation risk by 23% (HR 0.77, 95% CI 0.66–0.90), minor amputation risk by 27% (HR 0.73, 95% CI 0.63–0.84), and DFU risk by 8% (HR 0.92, 95% CI 0.87–0.96). The observed benefits were most pronounced in patients with established PAD (HR 0.68) or pre-existing foot ulcers (HR 0.70) [61]. These results prompted Goldenberg and Verma to characterize GLP-1 RAs as agents capable of helping to protect the legs [62].

Despite the compelling nature of this large-scale real-world evidence, these findings must be interpreted with explicit acknowledgment of the inherent methodological limitations associated therewith. EHR-based observational cohort studies are particularly susceptible to residual confounding. Notably, prescription bias is a major concern, as newer agents such as tirzepatide and semaglutide are more likely to be prescribed to patients with higher baseline metabolic needs or, conversely, to those with better insurance access and socioeconomic status, which are independently correlated with superior limb outcomes. Furthermore, selection bias may arise, as healthier patients are

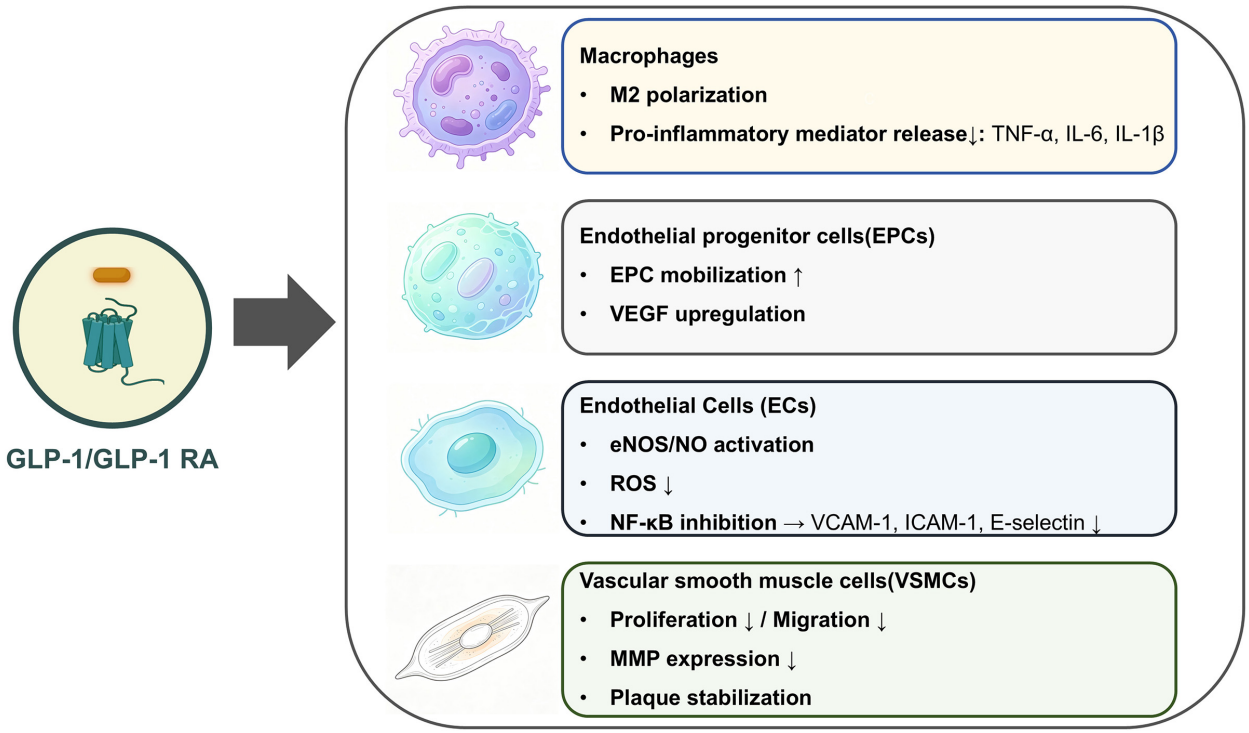


Fig. 1. GLP-1 RAs: vascular protection via cellular actions. This figure was created by the authors using Microsoft PowerPoint. GLP-1 RAs exert direct vascular protective effects across four key cell types. In endothelial cells, they enhance NO bioavailability via eNOS phosphorylation, reduce oxidative stress, and suppress inflammation through NF-κB inhibition, improving vasodilation and perfusion. In vascular smooth muscle cells, they inhibit proliferation, migration, and MMP expression while promoting a contractile phenotype, thereby stabilizing plaques. In macrophages, they attenuate pro-inflammatory cytokine release and promote M2 polarization. In endothelial progenitor cells, they mobilize EPCs and upregulate VEGF to stimulate angiogenesis and improve microcirculatory perfusion. Collectively, these cellular actions underpin the therapeutic potential of GLP-1 RAs in diabetic lower extremity vascular disease. GLP-1 RAs, glucagon-like peptide-1 receptor agonists; NO, nitric oxide; eNOS, endothelial NO synthase; MMP, matrix metalloproteinase; VEGF, vascular endothelial growth factor; NF-κB, nuclear factor-κB; EPCs, endothelial progenitor cells; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; ROS, reactive oxygen species; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1.

more likely to remain on therapy. Finally, inconsistent endpoint definitions across heterogeneous databases, such as variable ICD coding for minor amputations, DFUs, or intermittent claudication, can significantly skew effect estimates. Therefore, while the directionality of the benefit is highly suggestive, the precise magnitude of risk reduction reported for individual agents will require validation through prospective, adequately powered RCTs employing standardized, adjudicated limb endpoints.

4.2 Diabetic Foot Ulcer Outcomes and Amputation Prevention

The potential beneficial effects of GLP-1 RAs on DFU outcomes are of particular clinical interest. In the LEADER trial, treatment with liraglutide was associated with a significantly lower risk of DFU-related amputations compared with placebo (HR 0.65, 95% CI 0.45–0.95) [63], whereas the same was not true for other glucose-lowering agents. This 35% reduction in amputation risk is striking [63], given that some glucose-lowering agents, particularly SGLT2 inhibitors, have been associated with a greater risk of amputation [64]. The protective effect may stem from improved wound healing via enhanced angiogenesis, reduced local inflammation, better peripheral perfusion, and optimized glycemic control. The EXSCEL trial provided additional insights into GLP-1 RA effects in patients with PAD. Among the 2800 patients (19.0%) with documented PAD at baseline, those with PAD had higher rates of MACE (13.6% vs. 11.4%), all-cause mortality (10.0% vs. 6.8%), and amputations (5.0% vs. 0.9%) compared with those without PAD. Exenatide and placebo resulted in similar rates of amputations in those with PAD (5.0% vs. 4.9%), suggesting neutral effects on limb outcomes [65]. However, exenatide was associated with a significant reduction in all-cause mortality among patients with T2DM (HR: 0.86, 95% CI: 0.77–0.97) [66], indicating that cardiovascular mortality benefits may confer survival advantages even when limb-specific outcomes do not exhibit any direct

improvements. The STRIDE trial (NCT04560998) evaluated the effects of once-weekly semaglutide 1.0 mg versus placebo on walking ability among patients with T2DM and symptomatic PAD with intermittent claudication. Results from this trial revealed that semaglutide significantly improved maximum walking distance, symptoms, and quality of life, providing valuable insights into the functional benefits of GLP-1 RAs in patients with PAD [67]. However, it must be noted that a portion of the evidence supporting GLP-1 RA-mediated wound healing and microcirculatory benefits is derived from low-quality single-center studies and unpublished conference abstracts. Given the inherent limitations of these sources, including small sample sizes, lack of standardized outcome ascertainment, and susceptibility to selection bias, these findings should be interpreted with caution and considered hypothesis-generating until they have undergone validation through large-scale, multicenter RCTs.

4.3 Positioning GLP-1 RAs Relative to Other Glucose-Lowering Therapies

While the preceding sections have highlighted the limb-specific advantages of GLP-1 RAs, the selection of the most appropriate glucose-lowering therapy in diabetic lower extremity PAD must be guided by a balanced evaluation of cardiovascular, renal, and limb safety.

SGLT2 inhibitors have demonstrated consistent efficacy in reducing HF-associated hospitalization and slowing CKD progression [68]. However, the CANVAS program raised concerns regarding a potential increase in lower limb amputation risk with canagliflozin (HR: 1.97, 95% CI: 1.41–2.75) [64]. Although this signal was not replicated in subsequent trials with empagliflozin or dapagliflozin, caution remains warranted when prescribing SGLT2 inhibitors to patients with active foot ulcers, severe tissue ischemia, or a history of prior amputation [69]. By contrast, GLP-1 RAs have not been linked to any rise in amputation risk while also conferring specific anti-atherosclerotic and endothelial protective effects on both the peripheral macro- and microcirculation [63,65,70].

Given these complementary profiles, the concurrent use of GLP-1 RAs and SGLT2 inhibitors represents a synergistic therapeutic strategy that is often underutilized. This dual approach provides comprehensive metabolic control, combining the robust cardiorenal protection of SGLT2 inhibitors with the limb-specific, anti-inflammatory and plaque-stabilizing benefits of GLP-1 RAs. Furthermore, by improving microvascular perfusion and alleviating local tissue inflammation, GLP-1 RAs have the theoretical potential to mitigate or counterbalance the microvascular ischemic risk potentially associated with SGLT2 inhibitor-mediated volume shifts, thereby optimizing both limb salvage and systemic outcomes in the highest-risk patients.

We therefore posit that GLP-1 RAs and SGLT2 inhibitors should be viewed not as competing agents, but rather as complementary therapeutic options characterized by distinct yet non-overlapping primary vascular targets.

4.4 Clinical Guidelines and Treatment Recommendations

Growing consensus across multiple authoritative guidelines, including the 2023 European Society of Cardiology (ESC) Guidelines, the 2024 ACC/AHA Joint Guidelines on PAD Management, the 2025 ACC Scientific Statement on PAD in Diabetes, the IWGDF/ESVS/SVS 2023 Intersocietal Guidelines, and the ADA Standards of Care, has established the importance of prioritizing the use of glucose-lowering agents with proven cardiovascular benefit in patients with T2DM and ASCVD, while remaining particularly attentive to PAD-specific risk stratification [71,72,73]. However, there remains striking variability with respect to the extent to which these guidelines address limb-specific outcomes in detail, underscoring the need for a unified, stratified treatment algorithm tailored to distinct PAD patient phenotypes.

The 2023 ESC Guidelines recommend that patients with T2DM and ASCVD (including PAD) at very high cardiovascular risk receive an SGLT2 inhibitor and/or a GLP-1 RA (Class I recommendation), with preferential use of SGLT2 inhibitors in patients with severe target organ damage (including eGFR <45 mL/min/1.73 m^2) or prevalent HF, and GLP-1 RAs in those with a history of stroke [72]. The IWGDF/ESVS/SVS 2023 intersocietal guideline further specifies that, in treatment-naive patients with active foot ulcers, initiation of SGLT2 inhibitors is not recommended until ulcer healing, given the elevated risks of diabetic ketoacidosis and amputation (particularly with canagliflozin); in contrast, GLP-1 RAs are regarded as a safer option in the context of foot complications such that their use may be preferred [1]. The 2025 ACC Scientific Statement emphasizes that no trial to date has demonstrated the ability of SGLT2 inhibitors to reduce MALE incidence or improve functional outcomes in PAD, whereas GLP-1 RAs have been linked to MACE reductions and are favored in patients with active foot ulcers [68].

To address the clinical uncertainty when seeking to select among or combine these different classes of drugs, and to overcome the limitations associated with reliance on a single guideline source, we propose a stratified clinical decision algorithm based on an integrated synthesis of the above evidence, tailored to three core patient phenotypes:

• Subgroup 1: PAD with Active DFUs, Prior Amputation, or CLTI. For patients with confirmed PAD presenting with active DFUs, prior minor/major amputation, or CLTI, GLP-1 RAs (preferentially semaglutide or tirzepatide) are recommended as the primary glucose-lowering therapy, in line with the IWGDF/ESVS/SVS 2023 recommendation prioritizing the use of GLP-1 RAs when faced with foot complications [1]. In treatment-naïve patients, SGLT2 inhibitors should be withheld or used with extreme caution until ulcer healing, owing to the potential risks of volume

depletion, diabetic ketoacidosis, and amputation (especially when using canagliflozin) [1,64]. Temporary discontinuation should be considered in individuals already using these drugs until the affected foot has healed. Glycemic targets should be established on an individualized basis, with a target HbA1c of <8% (rather than <7%) to minimize the risk of hypoglycemia in this high-risk population, particularly when working with elderly patients [1]. Dual GLP-1 RA/SGLT2i therapy is not routinely recommended in this subgroup until ulcer healing is complete and infections have resolved.

• Subgroup 2: PAD with Concomitant HF or CKD. In patients presenting with PAD and concomitant HF (HFrEF, HFmrEF, or HFpEF) or CKD (eGFR <45 mL/min/1.73 m^2 or albuminuria), SGLT2 inhibitors remain the first-line agents of choice, consistent with their Class I recommendation under the 2023 ESC Guidelines for patients with severe target organ damage or prevalent HF, together with their proven renal and reverse-remodelling benefits [72]. If glycemic targets are not achieved or if there is a high burden of atherosclerotic disease, as in cases of prior MI, stroke, or polyvascular disease, a GLP-1 RA should be added as a second-line agent to provide complementary limb-specific, anti-atherosclerotic, and plaque-stabilizing protection. This dual approach can provide synergistic cardiorenal and limb protection, with GLP-1 RAs potentially mitigating the microvascular ischemic risk associated with SGLT2 inhibitor-mediated volume shifts. GLP-1 RA selection should prioritize those agents with an established ability to reduce MACE incidence (semaglutide, liraglutide, dulaglutide) or superior metabolic efficacy (tirzepatide), while recognizing that limb-specific comparative data remain hypothesis-generating.

• Subgroup 3: Stable Asymptomatic or Symptomatic PAD without Active Ulcers or Cardiorenal Complications. For patients with established but stable PAD (asymptomatic or intermittent claudication) without active ulcers, HF, or severe CKD, either a GLP-1 RA or an SGLT2 inhibitor can be used as a recommended first-line therapy (Class I recommendation, Level A evidence per the 2024 ACC/AHA Guidelines) [73]. The choice should be guided by individual patient-specific factors: GLP-1 RAs, for instance, may be preferred when seeking to prioritize weight management, anti-atherosclerotic benefit, or plaque stabilization, or when there is a history of stroke (per 2023 ESC recommendations for patients with established ASCVD including cerebrovascular disease) [72]. SGLT2 inhibitors, in contrast, may be preferred when a modest reduction in blood pressure, uric acid lowering, or additional renal protection is desired, provided there are no active foot lesions. Dual therapy can be considered in cases where monotherapy fails to achieve adequate metabolic control or if the patient has polyvascular disease with high residual cardiovascular risk.

This stratified approach acknowledges the complementary nature of GLP-1 RAs and SGLT2 inhibitors, rather than treating them as competing therapies, emphasizing their distinct primary vascular targets, the anti-atherosclerotic and endothelial-protective effects of GLP-1 RAs, as well as the cardiorenal protection afforded by SGLT2 inhibitors. This strategy also underscores the need for individualized selection based on limb risk, cardiorenal comorbidities, and patient preferences, as such an approach is essential for optimizing outcomes in this high-risk population.

5. Future Challenges and Directions

Despite the promise of GLP-1 RAs as tools capable of improving outcomes in diabetic lower extremity PAD, several barriers continue to hamper their integration into routine clinical practice for PAD management. These range from high costs and injection requirements, which persist even with the advent of oral semaglutide [74], to gastrointestinal side effects that can affect adherence, as well as limited knowledge among PAD-focused specialists regarding the potential vascular benefits of GLP-1 RAs.

A critical limitation of the current evidence is the lack of RCTs focused on specifically evaluating GLP-1 RAs in diabetic lower extremity PAD patients. The available data are largely derived from post-hoc and subgroup analyses of CVOTs designed primarily to assess cardiovascular safety and efficacy in T2DM patient populations. These trials have generally enrolled relatively small proportions of patients with established PAD, and were not specifically powered to evaluate limb-specific endpoints such as amputation, wound healing, walking distance, or functional improvement. Moreover, compelling and highly suggestive real-world EHR-derived evidence is nonetheless subject to inherent limitations, including the potential for residual confounding, selection bias, and variable data quality. These limitations underscore the importance of the STRIDE trial (NCT04560998), which is a phase 3b, double-blind, randomized, placebo-controlled trial that evaluated the effect of once-weekly semaglutide 1.0 mg on walking ability in 792 patients with T2DM and symptomatic PAD with intermittent claudication. The trial represents a critical step towards generating higher-quality evidence in this population [67].

Similarly, the SOUL trial (NCT03914326) has evaluated the effects of oral semaglutide on MACE and MALE in patients with T2DM and chronic kidney disease or cardiovascular disease, including those with symptomatic PAD [75]. Additional trials specifically targeting patients with CLTI and active diabetic foot ulcers are needed to define the role of GLP-1 RAs in those highest-risk populations. Future research should focus on dedicated randomized trials aimed at specifically examining the role of GLP-1 RAs in improving clinically relevant limb outcomes in patients with DLEVD. These trials should go beyond traditional cardiovascular endpoints, such as MACE incidence and mortality, to include patient-centered outcomes, including walk-

ing distance, quality of life, wound healing, amputation-free survival, and functional recovery. An optimally designed trial would include patients with established PAD, regardless of DFU status, randomizing them to GLP-1 RA therapy versus placebo or active comparator groups and incorporating a follow-up period of at least 2–3 years to capture clinically meaningful outcomes.

The diabetic lower extremity PAD treatment landscape is undergoing rapid changes, with multiple emerging options that may extend the reach of GLP-1 RA therapy. Tirzepatide, a dual GIP/GLP-1 agonist, has already demonstrated superior glycemic and weight outcomes [76], such that it has the hypothetical potential to afford greater protective effects on the cardiovascular and limb systems, though this requires rigorous prospective validation. Triple hormone receptor agonists targeting GLP-1, GIP, and glucagon receptors are in the early stages of development but have the potential to provide further metabolic and vascular advantages. Novel delivery systems, such as oral, implantable, or gene-based therapies, may be conducive to better patient acceptance and adherence. Additionally, in combination with anti-inflammatory drugs, advanced wound care, or regenerative approaches like stem cells and tissue engineering, GLP-1 RAs may be able to achieve synergistic benefits for patients with diabetic lower extremity PAD.

6. Conclusion

Diabetic lower extremity PAD is a debilitating complication of T2DM characterized by aggressive distal atherosclerosis and high rates of both amputation and mortality. This review highlights the therapeutic potential of GLP-1 RAs in this setting. Mechanistically, GLP-1 RAs exert pleiotropic vascular effects that directly counteract the pathophysiology of PAD, including reductions in oxidative stress and inflammation, improvements in endothelial function, and the induction of angiogenesis. Clinically, emerging evidence indicates that GLP-1 RAs are associated with significant reductions in lower extremity amputations, revascularization procedures, and all-cause mortality compared with other glucose-lowering agents, without the concomitant increase in amputation risk observed with some SGLT2 inhibitors.

These findings have important clinical implications, as they suggest that GLP-1 RAs should be strongly considered as a preferred therapeutic option for patients with T2DM and PAD, particularly in those individuals with active foot ulcers or a history of limb-threatening ischemia. Future research will be essential to further explore the potential of emerging multi-agonist therapies and to optimize combination strategies capable of reducing the burden of PAD in this high-risk population.

Key Points

• This review systematically synthesizes the epidemiology, pathophysiological features, and clinical burden of diabetic lower extremity PAD, with particular emphasis on the aggressive distal vascular phenotype driven by the coexistence of type 2 diabetes and peripheral artery disease.

• The review finds that current glucose-lowering pharmacotherapy offers limited limb-specific benefit, but glucagon-like peptide-1 receptor agonists (GLP-1 RAs) demonstrate multiple atheroprotective mechanisms, including improved endothelial function, reduced inflammation and oxidative stress, and stabilization of atherosclerotic plaques.

• Critically, large-scale real-world evidence reviewed reveals that GLP-1 RA use is associated with significantly lower risks of lower extremity amputation, and revascularization compared with other antidiabetic agents, particularly in high-risk patients with established PAD, suggesting a promising adjunctive role for limb salvage in diabetic lower extremity PAD.

Availability of Data and Materials

Not applicable.

Author Contributions

YMS and CYG conceived the review article. JP carried out the literature searches. CNG participated in the analysis and interpretation of the literature. QWH and YKZ made contributions to the conception and design of the study. JP and CNG wrote the original manuscript. All authors participated in critically revising the manuscript for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, ChatGPT-5.3 was used to assist with language refinement and to improve the clarity and readability of certain sections. After

using this tool, the authors carefully reviewed and revised the content as necessary and took full responsibility for the final published version.

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