REVIEW ARTICLE

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Botulinum toxin type A as an adjunctive strategy for diabetes-related lower limb complications – a review of microcirculatory, analgesic and biomechanical perspectives

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Abstract

Introduction and Objective. Diabetes-related lower limb complications, including diabetic foot ulcers, peripheral artery disease, critical limb ischaemia, and neuropathic pain, are public- and occupational-health concerns, as chronic wounds, impaired mobility, and amputation risk, reduce independence and work capacity. Despite advances in revascularization and wound care, options for advanced ischaemia, particularly 'no-option' critical limb ischaemia, remain limited. The aim of the review is to evaluate botulinum toxin type A (BoNT-A) as an adjunctive strategy targetting microcirculatory dysfunction, pain, and biomechanical overload.

Review Methods. A narrative review was conducted using PubMed, Scopus, and Google Scholar. The search included 'botulinum toxin', 'diabetes', 'diabetic foot', 'ischaemia, 'PAD', 'angiopathy', and 'sympathectomy', with emphasis on peer-reviewed clinical and experimental studies.

Brief description of the state of knowledge. Evidence suggests that BoNT-A may improve local perfusion through reversible chemical sympathectomy and norepinephrine-release inhibition, promoting vasodilation and microcirculatory flow. It may also reduce neuropathic and ischaemic pain by modulating substance P and CGRP release, and decrease plantar overload through muscle relaxation. These mechanisms are relevant to diabetic foot ulcers, painful diabetic neuropathy, and critical limb ischaemia. However, available data remain heterogeneous and limited by small cohorts, non-standardized protocols, and lack of randomized trials.

Summary. BoNT-A should not be regarded as a replacement for established diabetic foot care, revascularization, infection control, or offloading. Nevertheless, it may represent a promising adjunctive approach for selected high-risk patients when conventional options are limited. Randomized studies are needed before broader clinical implementation can be recommended.

Key words

occupational health, public health, wound healing, botulinum toxin type A, diabetic neuropathy, peripheral artery disease, microcirculation, critical limb ischaemia, diabetic foot

INTRODUCTION

Diabetes mellitus comprises a heterogeneous group of metabolic disorders characterized by persistent hyperglycaemia resulting from absolute or relative insulin deficiency, impaired insulin action, or a combination of both mechanisms. Prolonged exposure to elevated glucose levels leads to systemic metabolic disturbances and endothelial dysfunction, promoting accelerated atherogenesis in large-calibre vessels and the development of microangiopathic complications. These consequences manifest as vascular bed injury affecting the cardiovascular system, central nervous system, kidneys, and peripheral circulation [1]. Vascular tissues are particularly susceptible to injury in the setting of metabolic insulin resistance, and growing evidence indicates that insulin resistance at the vascular wall level may substantially contribute to the excess risk of cardiovascular disease (CVD) observed in this population. Metabolic insulin resistance promotes CVD, among other mechanisms, by intensifying selected factors (Fig. 1).

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Figure 1. Impact of Metabolic Insulin Resistance on Cardiovascular Disease Risk

At the same time, by inducing a compensatory increase in circulating insulin levels, metabolic insulin resistance may directly affect vascular cells through insulin-dependent signalling pathways. Therefore, the impact of metabolic insulin resistance on vascular function should be considered a key component of diabetic vascular pathology. By analogy with metabolic insulin resistance, vascular insulin resistance can be defined as a quantitatively reduced functional response of the vascular system to insulin compared with the response observed in healthy individuals [2].

Chronically sustained hyperglycaemia also creates a biological environment that promotes oxidative stress and inflammation, both of which are central mechanisms in the development of diabetic complications. Excessive production of reactive oxygen species (ROS), resulting from the activation of multiple hyperglycaemia-dependent metabolic pathways, leads to cellular injury and endothelial dysfunction, thereby sustaining the progression of vascular complications [3]. These mechanisms are of particular clinical importance because they contribute to the development of peripheral artery disease, diabetic foot syndrome, and critical limb ischemia. In patients with diabetes, peripheral artery disease is more frequent, more diffuse, and more likely to involve distal vessels below the knee. At the same time, sensory and autonomic neuropathy disrupts physiological vascular regulation and abolishes protective pain mechanisms, which promotes delayed recognition of ischaemia and the development of chronic ulcers. Consequently, diabetic foot syndrome remains one of the leading causes of non-traumatic lower limb amputation [4].

Despite substantial progress in revascularization techniques and conservative treatment, a significant proportion of patients develop advanced forms of ischaemia in which conventional therapeutic options are limited. A particular challenge is posed by patients with 'no-option critical limb ischaemia', in whom there are no technical possibilities for effective revascularization. In this group, even partial improvement in tissue perfusion or pain reduction may be clinically meaningful and may contribute to reducing the risk of amputation [5, 6].

In recent years, increasing attention has been given to the potential use of botulinum toxin type A (BoNT-A) in selected diabetic vascular complications. Beyond its well-established neuromuscular effects, BoNT-A can modulate sympathetic activity, improve microcirculation, and reduce neurogenic inflammation and pain. These mechanisms may potentially affect several key components of the pathogenesis of critical limb ischaemia and diabetic foot syndrome. Experimental and clinical data to date suggest that BoNT-A may improve tissue perfusion, support the healing of chronic ulcers, and reduce ischaemic and neuropathic pain; however, this therapy remains off-label and requires further clinical evaluation [7].

The main objective of this review is to critically analyse the established and theoretical role of botulinum toxin in mitigating diabetic vascular pathology and its clinical consequences. The review summarizes current evidence on the efficacy, mechanisms of action, and safety profile of this therapy, as well as to indicating future research directions and the potential place of this approach in clinical practice.

MATERIALS AND METHOD

A narrative literature review was conducted using the PubMed, Scopus, and Google Scholar databases. The search strategy included the following keywords and their combinations: 'botulinum toxin', 'diabetes', 'diabetic foot', 'ischaemia', 'PAD', 'angiopathy', 'neuropathic pain' and 'sympathectomy'. The review primarily included peer-reviewed articles addressing the efficacy, safety, mechanisms of action, and potential clinical applications of botulinum toxin in diabetes-related vascular and neuropathic complications, with particular emphasis on clinical outcomes, tissue perfusion, pain reduction, and ulcer healing. Both landmark publications and recent studies were considered in order to provide a balanced overview of the biological rationale and current clinical evidence. Publications from the last five years accounted for 68% of the cited literature, supporting the contemporary relevance of the evidence discussed. Because of the narrative character of the review, no formal meta-analysis or quantitative synthesis was performed.

STATE OF KNOWLEDGE

Botulinum toxin – pharmacological properties and mechanism of action. Botulinum neurotoxins (BoNTs) are a group of highly potent proteins produced by Clostridium botulinum which, despite their marked toxicity, have become widely used therapeutic agents with diverse clinical applications. Seven neurotoxin serotypes have been identified (A–G); however, in routine clinical practice, serotypes A (BoNT-A) and B (BoNT-B) are used most commonly. Owing to its longer duration of action and more sustained clinical effect, BoNT-A is the most extensively studied serotype in off-label vascular applications [8, 9]. BoNT acts as a zinc-dependent endopeptidase. Its light chain enters the presynaptic terminal and cleaves specific proteins of the SNARE complex (Soluble N-ethylmaleimide-sensitive factor Attachment Protein Receptor). The two serotypes act through distinct molecular targets: BoNT-A cleaves SNAP-25 (Synaptosomal-Associated Protein 25), whereas BoNT-B cleaves VAMP, also known as synaptobrevin [10]. This process prevents docking and fusion of neurotransmitter vesicles with the cell membrane, thereby blocking exocytosis of key neurotransmitters, including acetylcholine (ACh) at the neuromuscular junction and norepinephrine (NE) at sympathetic nerve endings [11]. The therapeutic potential of BoNT in vascular disorders is multifactorial: it induces functional chemical sympathectomy by inhibiting norepinephrine release from perivascular sympathetic neurons, leading to local vasodilation and improved cutaneous perfusion, while also modulating neurogenic inflammation and pain by blocking sensory neuropeptides such as substance P and CGRP [12].

A growing body of experimental and clinical evidence suggests that botulinum toxin may represent a novel therapeutic strategy targetting the neurogenic and microcirculatory components of ischaemia in diabetes. By modulating sympathetic activity, influencing tissue perfusion, and exerting analgesic effects, BoNT may potentially affect several key mechanisms involved in the development of critical limb ischaemia and diabetic foot syndrome. The mechanism of action and biological effects of botulinum toxin are presented in Figure 2.

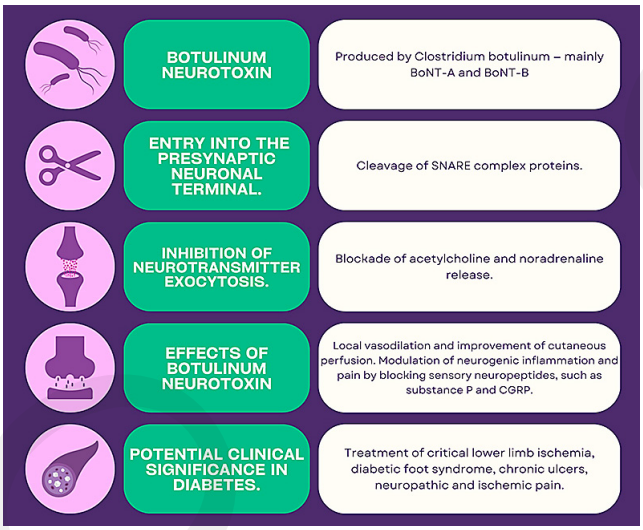

Figure 2. Mechanism of Action and Biological Effects of Botulinum Toxin. BoNT-A – Botulinum toxin type A; BoNT-B – Botulinum toxin type B; SNARE – Soluble N-ethylmaleimide-sensitive factor Attachment Protein Receptor; CGRP – Calcitonin gene-related peptide.

Pathophysiological mechanisms of diabetic vascular complications. Diabetic vascular complications may involve both large blood vessels, leading to diabetic macroangiopathy and microcirculation, resulting in diabetic microangiopathy. These mechanisms co-exist and mutually reinforce one another. The underlying processes primarily include non-enzymatic protein glycation, disturbances in cellular redox homeostasis, increased oxidative stress, and chronic inflammation. Prolonged exposure to elevated glucose levels induces a range of biochemical, structural, and functional changes in endothelial cells and vascular smooth muscle cells (VSMCs), leading to activation of alternative metabolic pathways associated with hyperglycaemia and oxidative stress. These processes result in increased production of extracellular matrix (ECM) components, such as collagen and fibronectin, activation of matrix metalloproteinases (MMPs), and increased synthesis of von Willebrand factor (vWF), thereby promoting a pro-inflammatory and pro-thrombotic vascular environment. These changes account for multiple pathological processes observed in diabetic microangiopathy, including endothelial dysfunction, increased vascular permeability, impaired angiogenesis, abnormal cellular proliferation and apoptosis, basement membrane thickening, ECM remodelling, disturbances in fatty acid metabolism, mitochondrial dysfunction, and altered activity of numerous enzymes and transcription factors.

The microcirculatory environment is particularly vulnerable to chronic hyperglycaemia, and microvascular functional impairment may develop even before overt hyperglycaemia and structural vascular changes become apparent. Microvascular injury may also occur through hyperosmolarity driven by hyperglycaemia and the highly osmotic sorbitol pathway. One of the earliest abnormalities is impaired endothelium-dependent vasodilation, resulting from reduced nitric oxide (NO) production and increased release of vasoconstrictive factors such as endothelin-1 (ET-1). As the disease progresses, abnormalities in cellular proliferation and migration, ischaemia, and pathological neoangiogenesis are also observed. Consequently, diabetic microvascular disease is characterized by abnormal remodelling and increased permeability of the microcirculation across multiple organ systems [13, 14].

The main manifestation of diabetic macrovascular disease is the development of atherosclerotic lesions affecting the aorta and the coronary, renal, basilar, and peripheral arteries, which may lead to vascular stenosis or occlusion, as well as increased calcification of the vessel wall. Consequently, diabetic macroangiopathy substantially increases the risk of major cardiovascular events, including stroke, myocardial infarction, heart failure, and limb amputation, and remains one of the leading causes of mortality and permanent disability in patients with diabetes [15]. Tissues characterized by high contractile activity, including the myocardium, are particularly susceptible to macrovascular complications, because even physiological narrowing of vessels such as the coronary arteries may lead to significant perfusion impairment, which is further aggravated in the presence of pathological vascular occlusion. The metabolic, humoral, and haemodynamic mechanisms involved in the pathogenesis of diabetic vasculopathy are closely interrelated and mutually reinforcing. For example, hyperglycaemia-induced oxidative stress promotes both increased formation of advanced glycation end products (AGEs) and activation of protein kinase C (PKC), both of which play important roles in the progression of vascular injury [16]. An important clinical problem is that glycaemic control alone cannot completely prevent or reverse the changes associated with diabetic macroangiopathy. Current therapeutic management is based mainly on combining glucose-lowering agents with cardiovascular-protective therapy; however, the effectiveness of this approach remains limited. Therefore, further elucidation of the molecular mechanisms underlying diabetic macroangiopathy is of particular importance, especially with regard to identifying new potential therapeutic targets that may contribute to more effective prevention and treatment of this group of complications [17].

Major clinical manifestations of diabetic microangiopathy. Peripheral neuropathy (PN) is one of the most common microvascular complications of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), occurring more frequently than diabetic nephropathy or retinopathy. It also remains one of the leading causes of lower limb amputation in developed countries. Diabetic neuropathy has an important vascular component, as chronic hyperglycaemia and impaired oxygen delivery through the vasa nervorum may induce inflammatory injury and disrupt nerve fibre function. The pathogenesis of this complication also involves dysfunction of the blood–nerve barrier, increased permeability of endoneurial vessels, oedema, and narrowing of the vascular lumen, ultimately leading to ischemic nerve injury [18].

Another clinical manifestation is diabetic retinopathy (DR). It is a chronic microvascular complication of diabetes resulting from long-standing metabolic disturbances. Progressive retinal vascular damage may lead to vision-threatening lesions and, in advanced cases, blindness. Its progression is promoted by poor glycaemic control, hypertension, dyslipidaemia, nephropathy, male gender, and obesity. Typical findings include microaneurysms, hard exudates, diabetic macular oedema, and neovascularization in proliferative DR. Treatment is based on systemic disease control, intravitreal therapy, and laser photocoagulation, while early diagnosis helps preserve visual acuity [19].

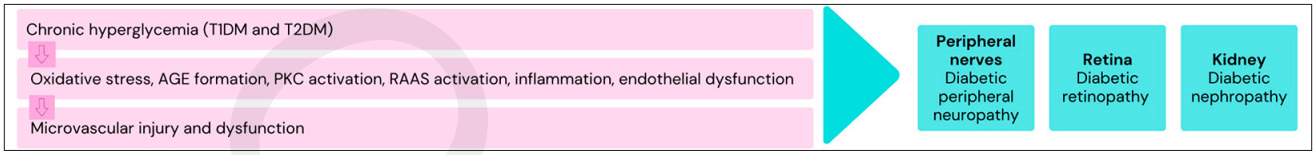

Figure 3. Major clinical manifestations of diabetic microangiopathy. AGE – advanced glycation end products; PKC – protein kinase C; RAAS – renin–angiotensin–aldosterone system; T1DM – type 1 diabetes mellitus; T2DM – type 2 diabetes mellitus

Diabetic nephropathy (DN) is a common and severe complication of diabetes, contributing substantially to morbidity and mortality. Chronic hyperglycaemia drives its pathogenesis through oxidative stress, advanced glycation end product formation, activation of protein kinase C and the renin–angiotensin–aldosterone system, leading to glomerular cell injury, filtration barrier disruption, proteinuria, and renal fibrosis. Additional mechanisms include inflammation, NF-κB and JAK-STAT activation, glomerular hypertension, hypoxia, and impaired autophagy. Consequently, renal function gradually deteriorates, accompanied by albuminuria and a decline in estimated glomerular filtration rate (eGFR) [20, 21]. The key clinical manifestations of diabetic microangiopathy are presented in Figure 3.

Potential therapeutic applications of botulinum toxin in diabetes-related vascular complications. The growing interest in the use of BoNT in diabetic vascular complications results from its multifactorial mechanism of action, which includes modulation of the sympathetic nervous system, improvement of microcirculation, analgesic effects, and influence on inflammatory processes. Available literature suggests that the vascular effects of botulinum toxin are dose-dependent and may exert a bidirectional influence on the vascular system. At higher doses, it may enhance vasodilation and improve tissue perfusion, whereas at lower concentrations it may limit excessive activity of cholinergic vasodilatory mechanisms and reduce neurogenic inflammation. These properties indicate that botulinum toxin may have potential applications in ischemic and vasospastic disorders, as well as in diseases with an inflammatory background. Overall, botulinum toxin demonstrates broad and diverse vascular effects, ranging from support of vascular regeneration and angiogenesis to modulation of excessive vascular responses [22].

The strongest clinical evidence for the use of BoNT-A in vascular disorders comes from its documented efficacy in Raynaud's phenomenon (RP) [23] and in digital ischemia secondary to systemic sclerosis or trauma. Injections into the neurovascular bundles of the fingers provide sustained reduction in vasospasm, pain relief, and ulcer healing lasting for 6–12 months [24, 25]. These observations provide a physiological rationale for extrapolating this approach to diabetic vascular complications, as both conditions involve excessive sympathetic activity contributing to distal ischemia, while BoNT-A acts on the dynamic neurogenic component that coexists with fixed vascular changes in diabetes [26].

The treatment of diabetic foot ulcers (DFUs) remains a major clinical challenge because of the co-existence of impaired tissue perfusion, chronic mechanical overload, and persistent inflammation. Perilesional intradermal or subcutaneous administration of botulinum toxin type A may improve microcirculation by reducing excessive local norepinephrine release within chronic wounds. Studies using laser Doppler flowmetry have shown increased local blood flow, accompanied by accelerated granulation tissue formation and reduction in ulcer area [27]. Chronic plantar forefoot ulcers in patients with diabetes and peripheral neuropathy are closely associated with increased forefoot pressure and limited ankle joint mobility. Surgical lengthening of the Achilles tendon is an established method for reducing forefoot overload and lowering the risk of ulcer recurrence, thereby confirming the importance of mechanical offloading in this region. In this context, administration of BoNT-A into the gastrocnemius and soleus muscles may be regarded as an attempt to achieve transient pharmacological weakening of the plantar flexors, and consequently to reduce excessive forefoot pressure without the need for surgical intervention. The results of a pilot study indicate that this strategy is technically feasible and well tolerated, although the optimal dosage and its actual impact on ulcer healing require further clinical evaluation [28]. In addition, intradermal administration of BoNT-A effectively reduces neuropathic pain and neurogenic inflammation by inhibiting the release of pro-nociceptive and pro-inflammatory mediators from C fibres, thereby limiting sympathetically mediated vasoconstriction that may aggravate ischaemia. Moreover, studies in mouse models have shown that intradermal injection of BTX-A into one limb reduced allodynia in both limbs, which may suggest the presence of a central analgesic mechanism of botulinum toxin [29].

The use of BoNT-A in lower limb ischaemia is based on achieving reversible chemical lumbar sympathectomy. Under computed tomography guidance, toxin injections have been administered into the lumbar sympathetic trunk, usually at the L2–L4 levels, and have been successfully used in severe, refractory vascular pain syndromes, such as complex regional pain syndrome. This supports the concept that blocking sympathetically mediated vasoconstriction may improve perfusion [30]. In studies focusing on severe Raynaud's phenomenon refractory to standard treatment, including cases complicated by digital ulceration and finger ischemia, local administration of BoNT-A was associated with clinical improvement, pain reduction, and enhanced healing of ulcerative lesions. Some studies also reported beneficial effects on perfusion parameters and an increase in finger temperature. These findings suggest the potential usefulness of this therapeutic approach, although they require confirmation in further clinical studies [31]. Compared with surgical sympathectomy or neurolytic agents such as phenol or alcohol, BoNT-A offers reversibility of effect, lower invasiveness, and a reduced risk of complications, including post-sympathectomy neuralgia [32].

The mechanisms of action and potential clinical effects of BoNT-A in diabetic vascular complications are presented in Table 1.

Safety and clinical relevance of botulinum toxin therapy. According to current guidelines issued by major scientific

Table 1. Mechanisms of action and potential clinical effects of BoNT-A in diabetic vascular complications

Clinical problem	Proposed mechanism of BoNT-A	Potential clinical effect	References
Diabetic foot ulcers	*Improved microcirculation and reduction of sympathetic vasoconstriction*	Enhanced wound healing	[27]
Neuropathic pain	*Inhibition of substance P and CGRP release*	Pain reduction	[29]
Critical limb ischemia	*Chemical sympathectomy and vasodilation*	Improved tissue perfusion	[30, 31, 32]
Plantar overload	*Muscle relaxation*	Reduced plantar pressure	[28]
Neurogenic inflammation	*Modulation of inflammatory mediators*	Decreased local inflammation	[12]
Raynaud-like ischemic symptoms	*Peripheral vasodilation*	Reduction of ischemic episodes	[23, 30, 31]

societies, including the American Diabetes Association, the European Society for Vascular Surgery, and the International Working Group on the Diabetic Foot, BoNT-A remains an off-label therapy. It is not yet recommended as a first- or second-line treatment because of insufficient high-quality evidence [27]. At the same time, when administered by experienced specialists at therapeutic doses, the overall safety profile of BoNT-A is very favourable. Adverse events are usually local and transient, most commonly including pain or bruising at the injection site. Systemic spread of the toxin causing botulism-like symptoms is exceptionally rare with low-dose, local injections used for vascular indications [33]. Patients with diabetes are at increased risk of soft-tissue infections. Injections must be strictly avoided in areas of damaged tissue, active infection, or deep cellulitis in order to prevent iatrogenic abscess formation or sepsis. Strict adherence to aseptic technique is essential in this high-risk population [34].

Based on the currently available evidence and biological plausibility, botulinum toxin type A may be considered as a specialized therapeutic option for the palliative treatment of severe ischemic rest pain in patients with 'no-option' CLI, as an adjunctive limb-salvage strategy aimed at improving local perfusion to optimize the wound bed or enable a more distal level of amputation, and as a biomechanical offloading approach for refractory plantar forefoot ulcers associated with fixed equinus deformity when surgical tendon lengthening is contraindicated [35].

Particular caution is required when considering BoNT therapy in patients with neuromuscular disorders, especially myasthenia gravis. Botulinum toxin inhibits neuromuscular transmission and may therefore aggravate pre-existing synaptic transmission disorders or unmask previously undiagnosed subclinical myasthenia. For this reason, neuromuscular disorders should be regarded as an important risk factor for adverse events, requiring individualized assessment of the benefit–risk ratio and close monitoring after administration [36].

In addition, the literature increasingly discusses the potential use of botulinum toxin in dermatology and vascular medicine beyond currently approved indications. Despite the established role of BoNT in selected clinical applications, such as the treatment of hyperhidrosis, chronic migraine, and aesthetic medicine procedures, some potential indications – including Raynaud's phenomenon, rosacea, and hidradenitis suppurativa – remain under investigation as off-label therapies. Therefore, their routine clinical use requires further validation in well-designed studies evaluating efficacy, safety, and optimal administration protocols [37].

The available scientific reports are characterized by substantial methodological heterogeneity, primarily due to the lack of standardized therapeutic protocols. This limits direct comparison of outcomes and their generalizability to broader patient populations. An additional limitation is that most available studies are retrospective or uncontrolled, while the doses, injection techniques, and therapeutic schedules differ considerably between studies [38]. Moreover, current IWGDF guidelines on diabetic foot disease emphasize that the cornerstone of ulcer treatment remains comprehensive management, including offloading, infection control, assessment and treatment of ischaemia, wound debridement, and multidisciplinary care, whereas botulinum toxin does not currently have an established role as a standard diabetological or angiological therapy in this patient group. With appropriate patient selection, dosing, and injection technique, BoNT is generally well tolerated; however, it should be regarded primarily as a potential adjunctive therapy the clinical use of which requires further evaluation. This applies particularly to chronic ulcers, neuropathic pain, and microcirculatory disturbances, in which potential therapeutic benefits may result from inhibition of neurotransmitter release, modulation of neurogenic inflammation, analgesic effects, and possible improvement of local perfusion.

CONCLUSIONS

Botulinum toxin type A demonstrates a distinctive therapeutic potential in the management of selected diabetes-related lower limb complications, particularly in patients with advanced ischaemia, chronic ulcers, neuropathic or ischemic pain, and limited conventional treatment options. Its potential clinical value results from a combination of mechanisms that are relevant to diabetic vascular pathology: reversible chemical sympathectomy, modulation of microcirculatory flow, analgesic activity, attenuation of neurogenic inflammation, and biomechanical offloading through targeted muscle relaxation. These effects may be particularly important in high-risk patients in whom impaired perfusion, persistent pain, chronic wounds, and plantar overload jointly contribute to loss of mobility, reduced independence, decreased work capacity, and increased amputation risk.

Current evidence suggests that BoNT-A should not be regarded as a replacement for established diabetic foot care, revascularization, infection control, wound debridement, or offloading strategies. Rather, it may represent a biologically plausible adjunctive approach for carefully selected patients, especially when standard therapeutic options are insufficient or technically unavailable. This position is consistent with the current state of evidence: available that experimental and clinical data are promising, but remain limited by small study populations, heterogeneous protocols, and insufficient randomized controlled trials. Therefore, before broader clinical implementation can be recommended, further well-designed, standardized studies are required to define the efficacy, safety, optimal dose, injection technique, duration of effect, patient-selection criteria, and clinically meaningful

outcomes of BoNT-A therapy. Particular attention should be paid to endpoints relevant not only to wound healing and perfusion, but also to pain reduction, limb preservation, functional mobility, quality of life, and return to occupational activity. Such an approach may help determine the future place of BoNT-A within the multidisciplinary care for diabetes-related lower limb complications.

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