

# New Modalities in the Chronic Ischemic Diabetic Foot Management

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## KEYWORDS

• Critical limb ischemia • Diabetic foot • Therapy • Future perspectives

## KEY POINTS

- Stem cell therapy is safe and effective in chronic ischemic diabetic foot (CIDF) management, especially for patients without options for revascularization.
- Processed lipoaspirate cells autologous transplantation is a feasible new modality in CIDF with high patient tolerance.
- Lipo-prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) works by improvement of peripheral circulation in CIDF and provides a longer duration of action and fewer side effects.
- Granulocyte colony-stimulating factor (G-CSF) induces terminal differentiation and release and improves the function of neutrophils from the bone marrow. It can reduce the need for surgical interventions, especially amputations.
- Heberprot-P is a novel perilesional and intralesional injection drug that gives promising results when injected deep in the ulcer matrix of the CIDF.
- De Marco formula (DMF) is a combination of procaine hydrochloride and polyvinylpyrrolidone. It reduces the lesion area and contributes to a reduction of amputations rate in CIDF trials.
- Low-dose urokinase improves microvascular blood flow in the CIDF via decreasing plasma fibrinogen levels.
- Heparin-induced extracorporeal low-density lipoprotein precipitation (HELP) directly removes fibrinogen levels from the cardiovascular system and improves microvascular circulation.

## INTRODUCTION

Since the 1980s, the diabetic population has increased worldwide, with a tripling in the United States from 5.6 million to 20.9 million.<sup>1</sup> In 2006, there were 65,700

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nontraumatic lower limb amputations, of which more than 60% occurred in the diabetic population.<sup>2</sup> In general, the “rule of 15” is applicable in patients with diabetes: approximately 15% of all diabetic patients develop a foot or leg ulcer during their lifetime, 15% of ulcers develop osteomyelitis, and 15% of ulcers result in amputation.<sup>3</sup> Lower limb amputations for diabetic ulceration contribute up to 85% of total cases.<sup>4</sup> The staggering number of nontraumatic lower limb amputations in the diabetic population emphasizes the vulnerability of their immunologic, wound healing, and tissue perfusion capacity to overcome the various external or internal factors causing ulcers.

The pathophysiology of diabetic ulceration is multifactorial and complex but the major underlying causes are peripheral neuropathy and ischemia from peripheral arterial disease (PAD).<sup>5</sup> The enigma of developing limb-threatening foot ulcers in patients with mild symptoms of arterial insufficiency occurs because the blood supply needed to allow healing of an ulcer, once one is present, is greater than that needed to maintain intact skin. The ulcer progresses to a chronic wound or gangrene unless the blood supply is improved.<sup>6</sup> PAD is common in the diabetic population because patients with diabetes ages 60 years or older are 2 to 3 times more likely to report an inability to walk one-quarter mile, climb stairs, or do housework compared with individuals without diabetes in the same age group.<sup>2</sup> Atherosclerosis has a higher incidence at a younger age in individuals with diabetes than in other individuals, and its hallmark is the involvement of the tibioperoneal vessels with sparing of the pedal vessels.<sup>7</sup> Neuropathy in patients with diabetes is usually distal symmetric sensorimotor polyneuropathy.<sup>6</sup> Emphasis should be placed on use of detection tools, such as the Semmes-Weinstein monofilament examination, which is a significant and independent predictor of future foot ulceration or likely future lower extremity amputations.<sup>8</sup> The diagnosis also comes at a substantial price to society, with a recent estimate of hospital costs for the care of a patient with critical limb ischemia (CLI) of \$47,000.<sup>9</sup> According to the joint statement of the Society for Vascular Surgery and the American Podiatric Medical Association, interdisciplinary team cooperation exercises a pivotal role of reduction of time in management throughout the various diabetic foot conditions with salvage of the lower extremities as the ultimate goal.<sup>10</sup> New therapeutic modalities must be developed, however, when the interdisciplinary team approach is not sufficient to salvage the lower extremities in resistant diabetic ulcers.

Even though management of the ischemic diabetic foot has improved over the past decades with complex multidisciplinary teams, the advancement of modern vascular surgical reconstruction strategies, and improvements in endovascular techniques, the guidelines for management are vague other than the mainstays, such as early revascularization, appropriate prevention, infection control, and wound dressings. In general, the optimal strategy of CIDF management is to perform revascularization, if indicated, as soon as possible.<sup>6</sup>

The simultaneous high occurrence of PAD and foot ulcers in the diabetic population, however, has created a subset of patients with CIDF. This article discusses the efficiency, efficacy, and prognostic outcomes of the emerging new treatment modalities for the CIDF without options for revascularization (**Table 1**).

## CELL THERAPY

### *Autologous Stem Cells Transplantation*

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Stem cell therapy is continuing to raise considerable interest in the field of PAD, specifically for CIDF, mainly due to the mild adverse effects and the lack of transplant

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