*Review Article*

# Declining Skeletal Muscle Function in Diabetic Peripheral Neuropathy

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## ABSTRACT

**Purpose:** The present review highlights current concepts regarding the effects of diabetic peripheral neuropathy (DPN) in skeletal muscle. It discusses the lack of effective pharmacologic treatments and the role of physical exercise intervention in limb protection and symptom reversal. It also highlights the importance of magnetic resonance imaging (MRI) techniques in providing a mechanistic understanding of the disease and helping develop targeted treatments.

**Methods:** This review provides a comprehensive reporting on the effects of DPN in the skeletal muscle of patients with diabetes. It also provides an update on the most recent trials of exercise intervention targeting DPN pathology. Lastly, we report on emerging MRI techniques that have shown promise in providing a mechanistic understanding of DPN and can help improve the design and implementation of clinical trials in the future.

**Findings:** Impairments in lower limb muscles reduce functional capacity and contribute to altered gait, increased fall risk, and impaired balance in patients with DPN. This finding is an important concern for patients with DPN because their falls are likely to be injurious and lead to bone fractures, poorly healing wounds, and chronic infections that may require amputation. Preliminary studies have shown that moderate-intensity exercise programs are well tolerated by patients with DPN. They can improve their cardiorespiratory function and partially reverse some of the symptoms of DPN. MRI has the potential to bring new mechanistic insights into the effects of DPN as well as to objectively measure small changes in DPN pathology as a result of intervention.

**Implications:** Noninvasive exercise intervention is particularly valuable in DPN because of its safety, low cost, and potential to augment pharmacologic interventions. As we gain a better mechanistic understanding of the disease, more targeted and effective interventions can be designed. (*Clin Ther.* 2017;39:1085–1103) 

**Key words:** diabetic peripheral neuropathy, exercise therapy, MRI, skeletal muscle.

## INTRODUCTION

Diabetes mellitus (DM) affects 26 million people in the United States alone, while approximately another 79 million have prediabetes.[1] Approximately 30% to 50% of patients with DM develop diabetic peripheral neuropathy (DPN).[2–4] DPN, or chronic distal symmetrical polyneuropathy, has been defined by the Toronto

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Diabetic Neuropathy Expert Group as "a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates."[5] DPN develops as a consequence of long-standing hyperglycemia, associated with metabolic derangements such as increased polyol flux, accumulation of advanced glycation end products, oxidative stress, abnormal protein kinase C activity, and other abnormalities that affect mitochondrial bioenergetics.[6,7] Metabolic and microvascular (MV) impairments in DPN damage the endoneurial capillaries that supply the peripheral nerves and lead to sensory loss, pain, and muscle weakness (Figure 1).[8]

Individuals with long-standing DM are at high risk for devastating foot complications such as plantar ulcers, Charcot arthropathy, and amputations. DPN plays a key role in the development of diabetic foot

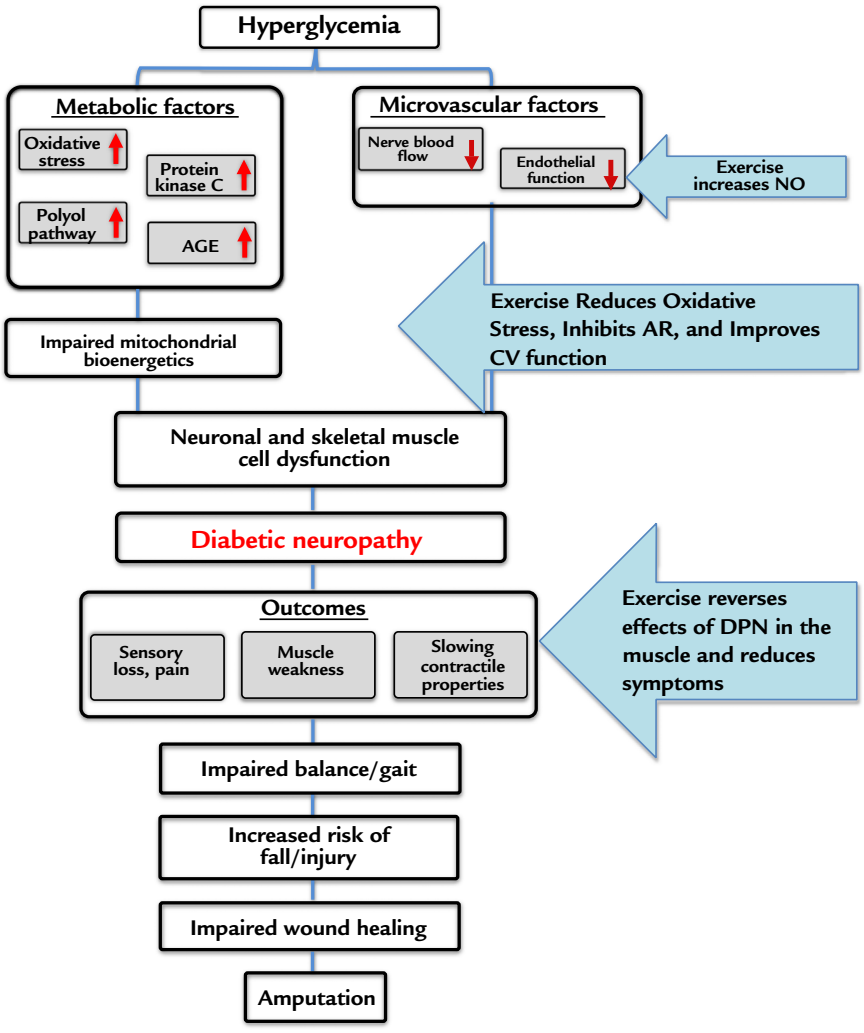


Figure 1. Postulated pathogenesis of diabetic peripheral neuropathy (DPN) and therapeutic effect of exercise. Various metabolic factors have been implicated in the pathogenesis of DPN, as well as vascular factors, such as decreased nerve blood flow and damaged nerve fibers. Prolonged DPN leads to sensory loss, muscle atrophy, and physical disability. Exercise therapy has been shown to improve clinical outcomes by affecting key metabolic and microvascular (MV) pathways, by activating nitric oxide (NO) production, and by reducing oxidative stress and inhibiting aldose reductase (AR), hence relieving the nerves of their hypoxic state. CV = cardiovascular.