Physical Training and Activity in People With Diabetic Peripheral Neuropathy: Paradigm Shift

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Diabetic peripheral neuropathy (DPN) occurs in more than 50% of people with diabetes and is an important risk factor for skin breakdown, amputation, and reduced physical mobility (ie, walking and stair climbing). Although many beneficial effects of exercise for people with diabetes have been well established, few studies have examined whether exercise provides comparable benefits to people with DPN. Until recently, DPN was considered to be a contraindication for walking or any weight-bearing exercise because of concerns about injuring a person's insensitive feet. These guidelines were recently adjusted, however, after research demonstrated that weight-bearing activities do not increase the risk of foot ulcers in people who have DPN but do not have severe foot deformity. Emerging research has revealed positive adaptations in response to overload stress in these people, including evidence for peripheral neuroplasticity in animal models and early clinical trials. This perspective article reviews the evidence for peripheral neuroplasticity in animal models and early clinical trials, as well as adaptations of the integumentary system and the musculoskeletal system in response to overload stress. These positive adaptations are proposed to promote improved function in people with DPN and to foster the paradigm shift to including weight-bearing exercise for people with DPN. This perspective article also provides specific assessment and treatment recommendations for this important, high-risk group.

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Peripheral neuropathy, one of the most common complications of diabetes mellitus,[1] typically is characterized as a symmetrical distal degeneration of peripheral nerves and impaired nerve regeneration. Diabetic peripheral neuropathy (DPN) can cause impairments in tactile sensitivity, vibration sense, lower limb proprioception, and kinesthesia. The loss of sensation associated with the neuropathy is thought to contribute to impaired balance, altered gait patterns, and increased risk of falling.[2,3] The presence of DPN in older adults has been found to be strongly associated with decreased activity levels, as measured by steps per day.[4,5] Moreover, the associated sensory impairments, along with accelerated arterial disease, result in an increased susceptibility of lower extremities to injury and infection, which can result in diabetic amputations.[6]

The fact that diabetes and associated complications can be prevented by tightly regulating blood glucose through diet, exercise, or medication has been well established.[7–9] More recently, several large randomized controlled trials established that aerobic exercise improves physical fitness, glycemic control, and insulin sensitivity in people with diabetes.[10] Therefore, exercise is recommended as a way for people with diabetes to improve glycemic control and minimize diabetic complications. However, people with DPN have historically been advised to be cautious about increasing their activity level.

Before 2009, the Standards of Medical Care in Diabetes position statement published by the American Diabetes Association (ADA) included the recommendation that "in the presence of severe peripheral neuropathy, it may be best to encourage non–weight-bearing activities such as swimming, bicycling, or arm exercises" because of the increased risk of skin breakdown, infection, and Charcot joint destruction.[11,12(p S23)] However, a randomized controlled trial published in *Physical Therapy*[13] was instrumental in leading to a substantial change in these guidelines. LeMaster et al[13] compared the incidence of foot ulcers in people who had DPN and were assigned to a walking exercise group with that in a control group. They concluded that assignment to the weight-bearing activity group did not increase the rate of foot ulcers.[13]

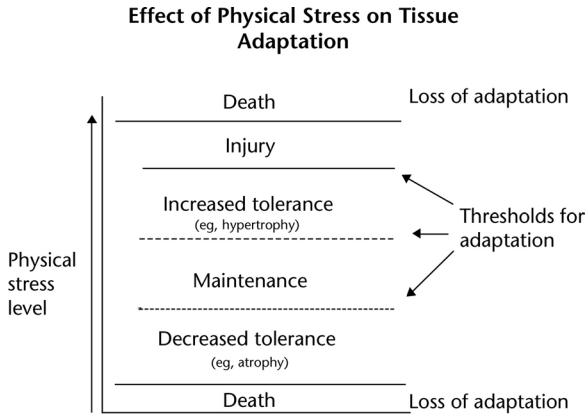

Figure 1.
Tissue adaptation to physical stress. Reprinted with permission from Mueller MJ, Maluf KS. Tissue adaptation to physical stress: a proposed "physical stress theory" to guide physical therapist practice, education, and research. *Phys Ther.* 2002;82:383–403.

The study by LeMaster et al[13] has been cited as evidence to support the latest ADA guideline statement, which does not preclude weight-bearing activity in people with DPN.[14] The guidelines do include a cautionary statement: "All individuals with peripheral neuropathy should wear proper footwear and examine their feet daily to detect lesions early. Anyone with a foot injury or open sore should be restricted to non–weight-bearing activities."[14(p S29)] Physical therapists need to be aware of these guidelines and understand how to implement them in clinical practice and health promotion or wellness settings.

In addition to these recent changes in exercise guidelines for people with DPN, an emerging body of research has found positive adaptations to exercise and physical activity (referred to here as "overload stress") in people with DPN. In this perspective article, we review the evidence for peripheral neuroplasticity in animal models and early clinical trials, as well as adaptations of the integumentary system and the musculoskeletal system in response to overload stress. We propose that these positive adaptations promote improved function in people with DPN and foster the paradigm shift of including weight-bearing exercise for people with DPN. We also provide specific assessment and treatment recommendations for this important, high-risk group.

Physical Stress Theory (PST) as a Framework to Support a Paradigm Shift

Prescribing physical activity for people with DPN can be challenging because they often have multiple comorbidities in addition to their peripheral insensitivity and they may be easily injured by high levels of physical stress. The PST can provide a conceptual framework to help guide and interpret research and intervention in this area.[15] The basic premise of the PST is that changes in the relative level of physical stress cause a predictable response in all biological tissues (Fig. 1), even those affected by diabetes and peripheral neuropathy. For the purposes of this perspective article, we focus on the following characteristic responses to physical stress: injury, resulting from excessively high levels of physical stress; decreased stress tolerance, resulting from low physical stress levels; and increased stress tolerance, resulting from physical stress at a level between the maintenance and injury thresholds.

Somewhat justifiably, the concern for avoiding the "injury" threshold has been the main focus of care for people with

DPN. Excessive physical stress on the insensitive feet of people with DPN clearly has been associated with neuropathic ulcers and subsequent skin breakdown.[16,17] A large body of evidence has indicated that high levels of localized stress, often encountered during walking, can result in skin breakdown, usually under the metatarsal heads, where plantar pressure (stress) is highest.[6] Along with the understanding that high levels of stress can cause skin breakdown came the understanding that protection from such stress can allow the skin to heal. Some randomized controlled trials[18,19] have demonstrated that unloading plantar ulcers through total contact casting or protective walking boots allows most neuropathic ulcers (without vascular compromise) to heal in 6 to 8 weeks.

Previous guidelines primarily focused on protecting the insensitive foot from physical stress. Unloading was recommended to heal wounds, protective footwear was prescribed to help prevent skin breakdown of insensitive feet, and people with neuropathy were advised to avoid weight-bearing exercise.[11] Although unloading injured tissues clearly can help them heal, according to the PST, prolonged levels of low stress will lead to subsequent decreased tolerance of the tissues for stress and an even lower threshold for injury. The theory predicts that although unloading in the short term will help tissues to heal, long-term stress protection will lead to an ever-decreasing tolerance for stress and for activity in general.

Contrary to traditional clinical approaches and even to most current clinical approaches, the PST hypothesizes that people with DPN may benefit from overload stress to become more tolerant of subsequent stress. Despite the very real concerns for safety and the potential for adaptation, the PST offers hypotheses and expectations for improvements in each of the major physiological systems comprising the movement system, namely, the peripheral nervous system, the integumentary system, and the musculoskeletal system. Although no one would argue against a clear "injury" window that occurs because of excessive stress, the PST postulates that there is a window of "increased tolerance" that is just below the injury threshold but above a "maintenance" level of stress (Fig. 1). The level of overload stress would need to be high enough to allow stress above the typical stress experienced by the tissues but not high enough to cause damage or injury.[15]

Various diabetic complications and pathologies likely make this window of adaptation to stress narrower and more difficult to identify in a person with DPN than in a person without DPN. Peripheral neuropathy often robs a person of the ability to detect potentially harmful high pressure and pain. Diabetes results in the accumulation of advanced glycation end products that make tissues thicker, stiffer, and more susceptible to injury[20]; peripheral vascular disease, which may delay healing; and foot deformity, which places excess stress on the foot.[6] These considerations and risk factors are specifically addressed in subsequent sections.

DPN Pathology, Progression, and Plasticity: Evidence From Animal Models

Diabetic peripheral neuropathy is a neurodegenerative disease that targets the peripheral nervous system. It is now recognized that hyperglycemia or insulin resistance associated with prediabetes is sufficient to cause damage to distal nerves, suggestive of early nerve targeting in DPN.[21] Knowledge of the molecular pathways implicated in the pathogenesis of DPN has grown considerably and is briefly summarized in Figure 2.[22] The initiating events of hyperglycemia, obesity, and dyslipidemia trigger increases in advanced glycation end products, chronic inflammation, oxidative stress, and mitochondrial dysfunction, which contribute to metabolic dysregulation.[22–25] Changes in any of these contributors to metabolic dysregulation are believed to alter neurotrophin expression and cause growth factor deficiency (including that of insulin) to influence nerve growth or regeneration, protection, and survival.[24] The cascade of events and associated microvascular complications result in the structural and physiological features of DPN: distal degeneration of peripheral axons, which leads to cutaneous denervation of the skin; diminished axonal regeneration; axonal atrophy; and myelin thinning, with slowed conduction velocity.[24]

The predominant early clinical manifestations of DPN are sensory in nature,[21] suggesting that primary afferent neurons are uniquely sensitive to damage. The anatomical structure of the sensory axons and the location of cell bodies outside the protection of the blood-brain barrier put them at risk for the negative effects of altered glucose metabolism.[26] Moreover, the high metabolic demands of long sensory afferent neurons coupled with exposure to a hyperglycemic environment result in direct axonal damage in parallel with the microvascular complications.[24]

Insights into potential mechanisms of recovery from DPN have been obtained with diabetic animal models. In a type 1 diabetic model, mice that showed spontaneous recovery of beta-cell function and restoration of glucose levels showed improvements in all aspects of neuropathy (electrophysiological improvements, myelin thickness) and marked reinnervation of the epidermis but did not show recovery from the loss of sensory neurons reported in this model.[27] These findings indicate that plasticity or growth of preserved sensory fibers is an important feature of recovery from neuropathy and that therapies targeting neuron growth may lead to successful clinical strategies.

Beneficial effects of exercise on nerve function have been reported in both prediabetic and diabetic animal models; these effects include decreased pain,[28,29] normalized epidermal innervation,[29] enhanced nerve regeneration,[30] and restored electrophysiological function.[31] Notably, human studies and animal models have shown that marked improvements in metabolic syndrome features do not necessarily include rescue of nerve regeneration and prevention of early painful symptoms.[29,32,33] These findings support the notion that exercise mediates peripheral nerve plasticity in part through mechanisms independent of metabolic status.

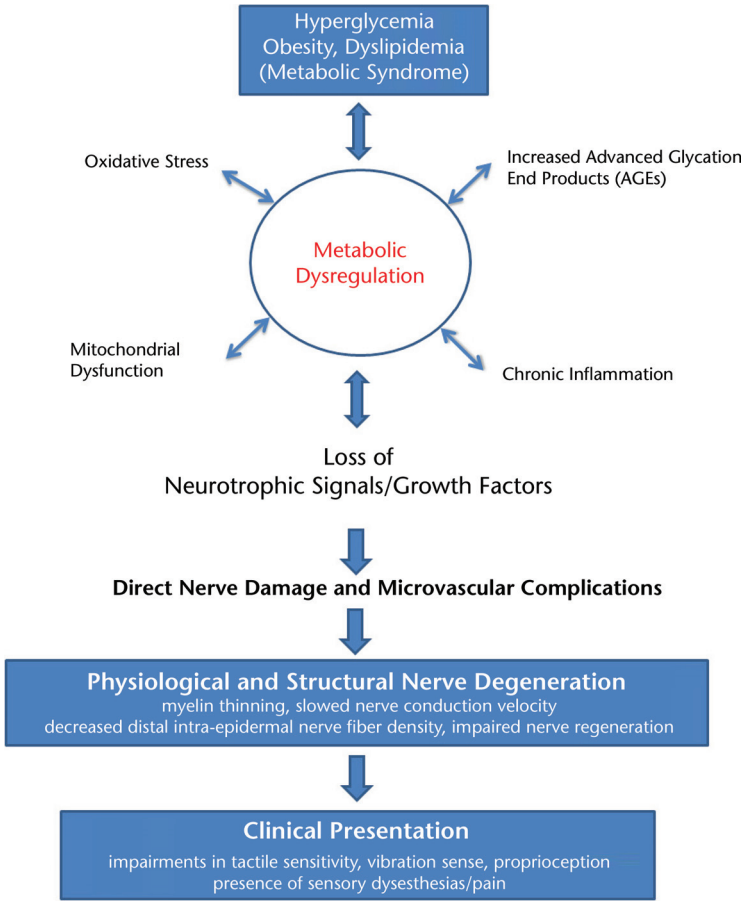

Figure 2.
Signaling events involved in diabetic peripheral neuropathy pathogenesis. Initiating events (insulin resistance, hyperglycemia, and dyslipidemia) contribute to metabolic pathway dysregulation events that are interactive and collectively result in cellular damage and nerve dysfunction.

The precise mechanisms of exercise-induced nerve protection or recovery are unknown, but evidence from animal models has shown that exercise is effective at restoring neurotrophin levels, reducing oxidative stress, and reducing inflammation.[29,34,35] Exercise also can prevent myelin damage[36] and reduce Ca2+ channel dysfunction to improve electrophysiological function.[37] A growing body of evidence has suggested that restoring neurotrophic growth factor support serves as a key mediator of these effects.[38] Collectively, there is compelling evidence from animal studies that exercise has a distinct advantage over a single-factor approach by influencing multiple pathways to restore peripheral nerve milieus and enhance nerve regeneration.

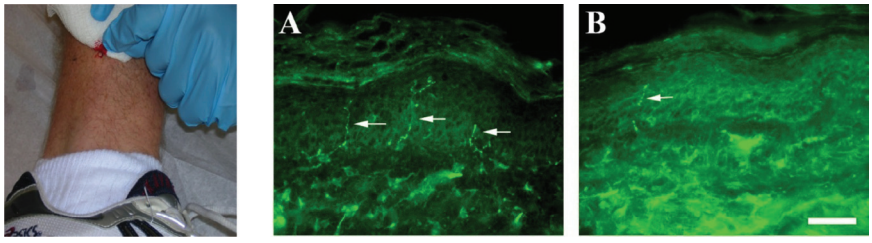

Figure 3.
Determination of intraepidermal nerve fiber density from punch skin biopsy. (Left) A 3-mm skin biopsy was removed and processed for protein gene product 9.5 (PGP 9.5) immunocytochemistry. (A and B) Arrows indicate PGP 9.5–positive fibers in the epidermis of a person without diabetes (A) and in that of a person with diabetes (B). Scale bar=50 μm. Photographs courtesy of Douglas E. Wright, PhD.

Exercise and Peripheral Nerve Plasticity in DPN: Emerging Clinical Trials

Despite the identification of numerous molecular pathways involved in DPN pathogenesis, clinical trials targeting specific molecules have demonstrated only modest benefits in slowing disease progression and have been largely ineffective at reducing pain[22,39]; these results suggest that pharmacological therapies may not be sufficient to reverse or slow DPN. Exercise is known to improve multiple metabolic factors that may affect nerve health[40,41] and microvascular function, which may indirectly protect against peripheral nerve damage.[42] However, the effect of exercise on the prevention of neuropathy is not well understood. In a longitudinal study,[43] nearly 80 people with diabetes (no signs or symptoms of DPN) were monitored for 4 years. Compared with a control group, people who participated in supervised brisk walking for 4 h/wk had a lower frequency of motor or sensory neuropathy at the end of the study. Further support for a potentially protective effect of exercise came from a study of lifestyle intervention in 29 people who had prediabetes, impaired glucose tolerance, and clinical signs of neuropathy; diet modification and exercise in this cohort resulted in partial cutaneous reinnervation that was associated with decreased neuropathic pain severity.[33]

As reported by Smith et al,[33] changes in cutaneous innervation can be measured with epidermal (skin) biopsies, which serve as a reliable and sensitive index of small-fiber degeneration in people with DPN.[44] A skin biopsy and immunohistochemical staining of nerve fibers are shown in Figure 3. This standardized technique for assessing intraepidermal nerve fiber density has been used to

show that prediabetic neuropathy and DPN are associated with the loss of small epidermal axons and impaired regeneration capacity.[44,45] As a validated technique for assessing structural nerve plasticity, intraepidermal nerve fiber density is an objective end point measure for assessing the efficacy of neuropathy therapies, including exercise,[32,46,47] and may be more sensitive than nerve conduction studies for detecting early damage in nerve fibers.[48]

Exercise training is a unique therapeutic strategy for improving metabolic dysregulation[11,49] (diabetic risk factors) and, in parallel, may directly promote nerve regeneration and function.[50] Emerging evidence from human[40,41] and animal[28–31] research is expanding knowledge about the molecular transducers that promote positive nerve adaptations (morphological and physiological) in response to exercise.

Providing Positive Overload for the Integumentary System Without Causing Injury

Intuitively, people understand and appreciate that skin can adapt to changes in physical stress. The glabrous skin on the palms of people's hands and the bottoms of their feet—skin that includes a weight-bearing or stress transfer function—is thicker than other skin and appears to be adaptable to increasing physical stress.[51] A gradual increase in new physical stress to the skin is important in several areas of physical therapist practice; for example, a wearing schedule is used to gradually increase the wearing time for a new orthotic or prosthetic device. This slow progression is necessary for the skin to adapt to the change in weight-bearing stress and to avoid the negative consequences of pain or skin breakdown.

Very little quantitative or basic research on the adaptive changes that occur within skin to make it more tolerant of physical stress has been completed. In an early study, Brand[16] described the results of applying various levels of repetitive stress to the anesthetized footpads of rats over 6 weeks. Brand[16] noticed hyperplasia of the epithelium in the rat footpad that was overstressed, resulting in "strong, well-conditioned feet." Other authors demonstrated that collagen fibrils have increased diameter after exposure to compressive and shear stresses[52] and are organized and packed into structures that appear to adapt to their mechanical environment.[53] Research has suggested that control of this epigenetic adaptation of connective tissue extracellular matrix is provided primarily by fibroblasts that sense and communicate mechanical loads to effect an optimized remodeling response.

The above-described observations about and experiments with nonpathologic skin suggest the ability of skin to adapt positively to overload stress. Less is known about the adaptive capabilities of neuropathic skin. However, the paradigm shift described in this perspective article proposes that, consistent with the PST, neuropathic skin—like all skin—can adapt to increasing levels of stress but that the window of adaptation bordered by stress that is too high (that causes injury) and stress that is too low (that causes atrophy or reduced stress tolerance) is fairly narrow and needs to be monitored carefully, especially in the presence of comorbidities (eg, peripheral artery disease and foot deformity). This paradigm shift represents a true change from traditional thinking, with the new perspective that people with DPN should be encouraged to maintain and even increase weight-bearing activities, rather than avoid them.

A growing body of evidence supports this theoretical perspective. For example, evidence has indicated that people who have DPN and are less active are more at risk for skin breakdown than those who are more active.[4,15,54,55] We also have documented that a subset of people who had DPN (5/22; mean age=65 years, SD=13; mean body mass index=33 kg/m^2, SD=6), were living in the community, and were screened to participate in an exercise program (ie, excluded if they had any comorbidity or medications that would interfere with exercise) were walking 10,000 to 20,000 steps per day without a history of skin breakdown.[56] Finally, preliminary randomized controlled trials have shown that people with DPN can increase their weight-bearing activities without an increased incidence of injury.[13,57,58] Although these improvements may be modest, they are in contrast to the expected and observed declines in this population with chronic disease.

Musculoskeletal Impairments in DPN

Although impairments in the peripheral nerves and the integumentary system may be more widely recognized, several musculoskeletal impairments accompany or result from chronic diabetes. The fact that these impairments may be appropriately treated with exercise provides additional support for the paradigm shift toward exercise as a primary treatment approach for people with DPN. Although some musculoskeletal impairments can be attributed in part to the primary disturbances of carbohydrate, fat, and protein metabolism associated with insulin resistance,[59] other musculoskeletal impairments can arise from accompanying complications, such as DPN, diabetic nephropathy, systemic inflammation, and cardiovascular and peripheral vascular diseases. Musculoskeletal impairments may also include sarcopenia with excessive intermuscular adipose tissue (IMAT), decreased muscle performance (strength, power, and fatigue), and limited joint mobility.[56,60,61]

People with diabetes may experience premature and progressive sarcopenia with low muscle quality because of excessive IMAT accumulation in ectopic sites, including key skeletal muscles.[56,60] Several studies[61–64] have shown that lower extremity skeletal muscles of people with DPN accumulate excessive volumes of IMAT, with concomitant decreases in muscle volume in the intrinsic and extrinsic muscles of the foot. The observation that intrinsic muscle volume loss and replacement of intrinsic muscle volume with IMAT in the foot[61] may exceed the percentage of IMAT volume observed in the leg[60,64] and thigh[65] muscles supports the belief that DPN is the contributing cause because a distal-to-proximal, symmetrical progression is characteristic of DPN. Two studies[60,64] have shown that people who have DPN have excessive IMAT volumes in the leg

muscles compared with people who have diabetes but do not have DPN. Interestingly, the larger percentage of IMAT volume in people with DPN was inversely correlated with gastrocnemius-soleus lean muscle volume, plantarflexor muscle power, vertical stair power, 6-minute walk distance, and Physical Performance Test scores.[64] Bittel et al[64] demonstrated, using dual-energy x-ray absorptiometry, that people who have DPN are more likely to be classified as having sarcopenia than people who have diabetes but do not have DPN. Of importance to physical therapists is the fact that sarcopenia in people with DPN typically occurs at a much younger age, 50 to 60 years old,[64] than age-related sarcopenia in people who do not have diabetes; the latter typically occurs in people 65 years old or older.[66]

It has been well documented that people who have DPN have reduced foot and leg muscle strength and power compared with those in people who do not have DPN.[60,64] Decreased ankle strength and power accounted for lower 6-minute walk distances, Physical Performance Test scores, and power generated while ascending stairs.[60] Recently, it was recognized that DPN is a major determinant for premature declines in functional activities leading to the early onset of physical frailty in people with diabetes.[64]

Limited joint mobility, another prevalent musculoskeletal impairment in people with diabetes, affects both large and small joints of the spine and the upper and lower extremities. Because limited joint mobility is a systemic impairment that progresses with the severity and duration of diabetes, it is largely attributed to persistent hyperglycemia.[67] Persistent hyperglycemia increases the levels of advanced glycation end products and receptors for advanced glycation end products on most body organs and connective tissues (bone, tendon, ligament, and cartilage).[20,67] Advanced glycation end products and receptors for advanced glycation end products have been shown to be directly related to shoulder impairments in people with diabetes, contributing to pain and disability.[20] Limited joint mobility is readily observable in the wrists and hands of people with DPN, and limited joint mobility combined with DPN in the leg may contribute to acquired deformities of the forefoot[61,62] and the midfoot and hindfoot,[63,68] abnormally high vertical and shear pressures, and plantar ulceration.[69,70]

Musculoskeletal impairments may be overlooked in people with DPN because of the complex interactions of underlying metabolic and neurological dysfunctions. These effects may be even more pronounced in older adults, as poor peripheral nerve function appears to be associated with a more rapid decline in muscle strength.[71] The effect of aging on the paradigm shift toward the use of exercise to address DPN-induced musculoskeletal impairments and related movement dysfunctions opens up a new perspective for physical therapist practice.

Effect of Exercise on Function in DPN

Evidence of the effect of exercise training on impairments and patient-centered functional outcomes in people with DPN can be found in recently published trials on this topic. A systematic review suggested a lack of high-quality evidence for evaluating the effect of exercise on functional ability in people with peripheral neuropathy.[72] According to that review, the inclusion of participants with different types and severity of neuropathy; the types, intensity, and duration of exercise interventions; and a lack of consensus in reporting outcome measures strongly suggested the need to develop high-quality, sufficiently powered trials. More recently, however, Streckmann et al[73] identified 10 exercise intervention studies, 9 of which have been published since 2009, that included adults with DPN. As shown in Table 1, the interventions provided varied widely. In general, balance, gait, and mobility outcomes were all shown to improve with individual[74–78] or multimodal[58,79] exercise interventions. Additionally, recent single-group trials with an aerobic exercise intervention demonstrated decreased pain interference as well as decreased general and physical fatigue.[80–82] In a randomized controlled trial, Dixit et al[83] also found that aerobic exercise had a positive effect on nerve conduction velocity. Whole-body vibration (WBV) training used to supplement balance exercise was also recently shown to benefit people with DPN,[74] and 12 weeks of tai chi has resulted in improved median and tibial nerve conduction velocities[84] and improved quality of life, balance, and neuropathic symptoms.[85] Although the intensity of exercise is a key variable for the interpretation of positive tissue adaptations, we did not include intensity in Table 1 because many of the studies used exercises (eg, tai chi) that are difficult to quantify and compare.

In summary, on the basis of the increasing amount of literature on the impact of exercise training on physical activity and physical function in people with diabetes and DPN, it appears that with appropriate monitoring, weight-bearing exercise is safe and feasible for this population and leads to positive outcomes. Modest improvements in gait speed and habitual physical activity can be expected. Exercise for this population should be multicomponent, including aerobic, resistance, and balance interventions. Exercise programs that meet or exceed the US Department of Health and Human Services physical activity guidelines for Americans,[86] with sufficient intensity, frequency, and duration to result in positive tissue adaptations and gains in physical function, are recommended. Because exercise training in people with DPN may also result in higher risk and occurrence of adverse events, there is also a need to closely monitor people who have DPN and are initiating exercise programs, as described in the next section.

New Directions for Clinical Practice

There is no question that exercise has numerous potential advantages for people with DPN and that physical therapists have an important role in implementing ADA guidelines for activity.[14] The PST[15] and individual factors that moderate the risks and benefits of exercise participation can be used to form a framework for physical therapist practice and the development of an exercise program. The goal of the exercise prescription is to increase the tissue level stress to allow positive adaptations with-

Table 1.
Recent Evidence of Impact of Exercise in People With Diabetic Peripheral Neuropathy[a]

Type of Trial	Study	Group (No. of Participants)	Intervention	Duration and Frequency (Follow-up)	Key Outcomes
Single group	Yoo et al[80]	Diabetes (14)	Supervised aerobic exercise	16 wk, 3×/wk	↓ pain interference, → pain intensity
	Kluding et al[81]	Diabetes (18)	Supervised aerobic exercise	16 wk, 3×/wk	↓ general fatigue, ↓ physical fatigue, ↑ peak $\dot{V}o_2$
	Fisher et al[82]	Diabetes (5)	Supervised aerobic exercise and HEP	24 wk total, 8 wk supervised, 16 wk HEP	↑ motor and sensory conduction velocities, ↑ motor conduction amplitudes, ↑ F-wave latencies
Nonrandomized controlled	Akbari et al[75]	Intervention for diabetes (10); control (healthy) (10)	Balance, Biodex (Biodex Medical Systems, Shirley, NY) stability	20 wk, 10 sessions	↑ stability indexes
	Ahn and Song[85]	Intervention (20); control (19)	Tai chi	12 wk, 2×/wk	↑ balance, ↑ quality of life, ↑ total neuropathic symptom score
	Hung et al[84]	Intervention for diabetes (28); control (healthy) (32)	Tai chi chuan	12 wk, 3×/wk	↑ median and tibial nerve conduction velocities, → amplitudes
	Richardson et al[78]	Intervention (10); control (10)	Balance	3 wk, daily	↑ balance, → ABC, → motor response amplitudes
Randomized controlled	Dixit et al[83]	Intervention (40); control (47)	Aerobic exercise	8 wk, 3–6×/wk	↑ distal peroneal nerve conduction velocity; ↑ sural sensory nerve conduction velocity; ↑ MDNS; → latency, duration, and amplitude
	Lee et al[74]	WBV+balance (19); balance (18); control (18)	WBV and balance exercise; balance exercise only	WBV+balance: 6 wk, 3×/wk (WBV) and 2×/wk (balance); balance only: 6 wk, 2×/wk	WBV+balance group compared with balance and control groups: ↑ postural sway, ↑ HbA_{1C}; WBV+balance and balance groups compared with control group: ↑ OLS; WBV+balance group compared with balance group: ↑ OLS; WBV+balance group and balance group: ↑ postural sway, ↑ BBS, ↑ TUG, ↑ 5 times sit-to-stand test, ↑ OLS, ↑ FRT
	Mueller et al[58]	WB (15); NWB (14)	WB: balance, flexibility, strength, aerobic walking exercise; NWB: balance, flexibility, strength, aerobic stationary cycling exercise	12 wk, 3×/wk	WB group: ↑ 6MWD, ↑ average daily step count; NWB group: ↑ HbA_{1c}
	Song et al[76]	Intervention (19); control (19)	Balance exercise; both groups received education	8 wk, 2×/wk	↑ balance and trunk proprioception: decreased sway paths; ↑ OLS, BBS, FRT, TUG; ↑ 10-m walk; ↓ trunk repositioning errors
	Allet et al[77]	Intervention (35); control (36)	Balance, gait, function-oriented strength	12 wk, 2×/wk (6-mo follow-up)	↑ gait speed, ↑ dynamic balance (time to walk over beam, balance index), ↑ POMA, ↑ FES, ↑ hip flexion mobility, ↑ hip strength
	Kruse et al[79]	Intervention (41); control (38)	Intervention: leg strength, balance, self-monitored walking with pedometer, motivational telephone calls; control: self-care instruction, telephone calls for activity reporting	Part I: 12 wk, 8 individual sessions, HEP; part II: 13–52 wk, HEP, bimonthly telephone calls (12-mo follow-up)	→ ankle dorsiflexion strength; → OLS with eyes open, BBS, TUG; → FFIDS, FES; ↑ OLS with eyes closed; → falls reported by participants

[a] ↓=decrease, →=no change, ↑=increase (improvement), $\dot{V}o_2$=oxygen consumption, HEP=home exercise program, ABC=Activities-specific Balance Confidence Scale score, MDNS=Michigan Diabetic Neuropathy Score, WBV=whole-body vibration, HbA_{1c}=hemoglobin A_{1c}, BBS=Berg Balance Scale score, TUG=Timed Up "&" Go Test score, FRT=Functional Reach Test score, OLS=one-leg stance test score, WB=weight bearing, 6MWD=6-minute walk distance, NWB=non–weight bearing, POMA=Performance-Oriented Mobility Assessment score, FES=Falls Efficacy Scale score, FFIDS=Foot Function Index Disability Scale score.

Table 2.
Risk Factors for Foot Skin Breakdown[6]

Variable	Risk Factor
Skin	History of ulcer[87] Presence of callus, blister, or reddened areas Dry or cracked skin Distal hair loss Overgrown and thickened toenails
Nervous system[89]	Loss of protective sensation (inability to feel 5.07 monofilament, absent Achilles tendon reflex, inability to perceive vibration)
Musculoskeletal system	Foot deformity[90,91] Muscle weakness[92] Limited ankle mobility (<10°) and toe joint mobility (<50°)[70] Inappropriate footwear (incorrect size, insufficient protection of the foot)
Vascular system	Impaired distal blood flow (absent distal pulses)

out exceeding the window of adaptability and causing tissue injury. This goal can be particularly challenging in people with DPN because they have loss of protective sensation in the involved tissues, typically the skin, joints, and muscles of the foot and leg.

Recommendations for Assessment

The stress threshold for exercise prescription in people with DPN is moderated by several individual factors that may increase or decrease the risks associated with exercise. A preexercise screening examination should include an assessment of all of the risk factors shown in Table 2.[6,13,14,58]

Integumentary System Assessment

Foot skin health is a particularly important moderator of risk for skin breakdown. A thorough visual inspection will help assess the adaptability of the skin to increased stress through a weight-bearing exercise program. Screening of the integumentary system involves the following components[6]:

1. Skin breakdown or amputations (current or past) are strong predictors of future skin breakdown.[87]

2. The presence of callus, blisters, or redness is an indicator of friction, high pressure, or both and is a common precursor to skin breakdown.

3. Dry skin and distal hair loss on the feet and legs may indicate autonomic neuropathy. Dry skin is less resilient, tolerating less stress before breakdown. Cool, pale skin can indicate vascular compromise, whereas red, warm skin can indicate a potential infection or skin irritation.

4. Overgrown and thickened nails can cause injury during exercise but can also result in self-inflicted injuries during routine nail care. In the presence of sensory neuropathy, callus, nail, and wound care should be provided by a professional to prevent inadvertent injury from self-care.

Nervous System Assessment

Loss of protective sensation limits feedback (pain or discomfort) from the lower extremity to ensure that skin, muscles, tendons, and bones of the leg and foot remain healthy and intact during the increase in activity. If there is loss of protective sensation, then participants in exercise must be taught to use other senses (touch and vision) to regularly inspect their feet before, during, and after an exercise bout for signs of high stress (redness, warmth, bruising, swelling, and callus formation). The peripheral sensory system is easily assessed with the following tools and methods:

1. Light touch sensation is assessed with the 5.07 (10-g) Semmes-Weinstein monofilament. It is applied to the skin with brief, even pressure until the filament bends. Locations at high risk for skin breakdown (metatarsal heads, heel, and pad of the great toe and any plantar bony prominence) are assessed.[88] Additional sites can be tested if the examiner has any concerns. A person is determined to have loss of protective sensation if he or she is unable to consistently (>80%) sense the 5.07 monofilament on even one weight-bearing site.[89]

2. Large afferent nerve fiber function is assessed with the Achilles tendon reflex[6] and the ability to detect onset and damping of vibration with a 128-Hz tuning fork.[88]

Musculoskeletal System Assessment

Assessment of the alignment and function of the foot and ankle is important in relation to the risk of skin breakdown. Metatarsophalangeal hyperextension and midfoot deformities result in bony prominences that are potential sites for high pressure and friction[90,91] and that are associated with an increase in the risk of ulcers. The presence of midfoot deformity is also often accompanied by joint instability and the potential for extensive multijoint deterioration. In all types of deformity, bony prominences can become sites of high stress and skin breakdown but can also be sites for bony fractures and additional joint subluxation and dislocation.[6] Weakness of the lower extremity muscles can contribute to poor movement patterns that increase foot joint stress and risk of injury at the ankle and foot during weight-bearing activities.[92] Limited mobility of the ankle and metatarsal joints has been associated with forefoot deformity, an increase in plantar pressure, and forefoot ulcers in people with DPN.[62,70] Footwear should maximize force distribution and minimize rubbing[6] and should fit the length of foot, and the toe box must be the width and depth necessary to accommodate any forefoot deformities. Shoes with laces can prevent slipping without being overly tight, and enclosed footwear offers greater protection from foreign objects entering the shoe. All types of activities that a person performs should be considered, and suggestions for

appropriate footwear (eg, beach, pool, and shower shoes) should be provided. The insoles should be examined for wear and appropriateness. A total-contact insert is often indicated for people with DPN, particularly when there is a history of an ulcer or when there are prominent deformities that need to be unloaded. A well-made insole is one with materials that will not be easily compressed, that helps to disperse forces, and that reduces areas of high stress.[6]

Vascular System Assessment

Peripheral artery disease, another important risk factor for skin breakdown, is a component cause in approximately one-third of foot ulcers.[6] A vascular examination should include palpation of the dorsalis pedis and tibialis posterior arteries[93]; capillary refill of 4.5 seconds or longer at the nail bed can indicate compromised circulation and tissue perfusion.[94] Peripheral artery disease is common in people with diabetes and can limit the ability of foot tissues to adapt to stress and heal when wounds occur. If a physical therapist suspects insufficient vascular perfusion, then referral to a vascular specialist is recommended.

Endocrine System Assessment

Participants in exercise should be able to verbalize their blood glucose management plan. They should know their hemoglobin A_{1c} value (the ADA recommends $<7.0\%$),[14] what their blood glucose level was when they last checked it, and what they should do in response to a hypoglycemic or a hyperglycemic measurement.

Cardiovascular System Assessment

Prescribing exercise for people with DPN is further complicated by the frequent occurrence of cardiovascular comorbidities (hypertension and cardiovascular disease). It is important to gather information about a history of hypertension and a person's knowledge about his or her blood pressure treatment plan. American Heart Association and ADA recommendations state that a systolic blood pressure of greater than 140 mm Hg, a diastolic blood pressure of greater than 90 mm Hg, or both, require medical attention.[14,95]

A medical history, blood pressure measurement, and physical therapist screening as described above will assist in determining a person's risk factors for injury and whether additional medical screening is necessary before participation in an exercise program (preexercise considerations are shown in the Appendix). In a joint position statement from the American College of Sports Medicine and the ADA,[49] exercise stress tests and physician clearance are not considered necessary before exercise that is no more strenuous than a brisk walking program in people who have diabetes and are sedentary. If there is significant concern regarding cardiovascular disease and risk associated with starting an exercise program or a more intense program is being considered, then evaluation by a physician should be done before exercise participation. The physician should determine the risk of cardiovascular disease and whether additional testing (exercise stress test or electrocardiogram) is of benefit.[49]

Recommendations for Treatment

The safety and feasibility of exercise in people with DPN were addressed in recent studies in which participants were given the option of selecting weight-bearing or non–weight-bearing exercises.[81] Lower extremity strengthening, balance, and walking exercises did not increase the incidence of falls in people with DPN,[79] and aerobic and resistance exercises did not increase pain or neuropathic symptoms.[81] Monitoring of neuropathic symptoms and physiological parameters, including glucose, heart rate, and blood pressure, is critically important in people who have diabetes and are participating in exercise training. Although major adverse responses are rare, the occurrence of minor adverse events, including joint and muscle pain, hypoglycemia, angina, or skin irritation, is to be expected.[81] Importantly and consistent with other recent studies,[13,46,58,96] participants who did not have severe foot deformity or open foot ulcers had only minimal intervention-related adverse events.

Once a full assessment is completed and the risk of skin breakdown is understood, an informed decision can be made regarding the exercise mode, intensity, duration, and frequency (exercise goals are shown in the Appendix). The aim is to complete 150 minutes of aerobic exercise per week, spread over 3 days, with no more than 2 consecutive days between exercise bouts. To achieve this aim, the physical therapist should assess the baseline activity level with a quantitative device such as a step monitor. Mueller et al[58] showed that increasing the step count by 10% every 2 weeks was a safe and gradual method for increasing the activity level without increasing skin breakdown. Additional research is needed to determine the value and safety of various exercises for people with a history of ulcers and people with severe foot deformity. The current ADA guidelines recommend a non–weight-bearing exercise program (eg, upper body ergometer or stationary bicycle, depending on the location of the wound) for a person who has DPN and a current ulcer, a severe plantar deformity that cannot be unloaded by footwear, or an unstable lower extremity joint.[14] A history of ulcers or the presence of mild foot deformities does not automatically preclude participation in weight-bearing activities but should prompt consideration of compensations that may be required to maintain the physical stress level below the injury threshold.

In addition to aerobic conditioning, the joint statement of the American College of Sports Medicine and the ADA recommends 2 or 3 days of large-muscle-group resistance training per week. This training should include a minimum of 1 set of 5 or more resistance exercises.[49] Flexibility exercises should also be included because they address joint range-of-motion limitations, particularly in the ankle, hip, and shoulder. Finally, a thorough musculoskeletal examination by a physical therapist can identify individual needs that should be addressed to maximize joint alignment and minimize movement-related injuries.

Changes in footwear may be needed to optimize fit and force distribution; alternatively, people may just need to be reminded to wear appropriate footwear. In addition, regular and frequent moni-

toring of the skin and footwear will assist in the early detection of problems so that they can be corrected quickly, thereby avoiding serious complications from the exercise program. Regardless of the type of exercise chosen, a slow, progressive weight-bearing program will allow the time required to assess the tissue response after exercise and to modify the prescription to ensure that the exercise program is safe and beneficial.[58]

In general, these recommendations should be applied to older adults with DPN, with special consideration of coexisting medical conditions, including not only cardiovascular and microvascular diseases but also functional impairments. Aging and diabetes are both risk factors for functional impairments,[97,98] in part because of the interactions of coexisting medical conditions, DPN, and hearing, vision, gait, and balance problems.[99] Diabetic peripheral neuropathy, in particular, increases the risks of postural instability, impaired balance, muscle loss, and falls in older adults.[100–103] However, physical activity should be encouraged in older adults with DPN, with necessary modifications for optimal frequency, duration, and volume and with careful consideration of safety.

Conclusion

Historically, many patients and health care providers have viewed DPN-associated nerve, skin, and musculoskeletal impairments as nonadaptable and even refractory to exercise or other interventions. In this perspective article, we summarized available evidence to the contrary and proposed that many DPN-induced impairments and related movement dysfunctions are amenable to exercise or movement-based interventions. We agree with traditional thinking that people with DPN should be monitored closely for comorbidities (eg, peripheral artery disease and foot deformity) that may contribute to injury or skin breakdown but also advocate a paradigm shift to maintain and even increase weight-bearing activities rather than avoid them.

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References

1 Pasnoor M, Dimachkie MM, Kluding P, Barohn RJ. Diabetic neuropathy, part 1: overview and symmetric phenotypes. *Neurol Clin.* 2013;31:425–445.

2 Mueller MJ, Minor SD, Sahrmann SA, et al. Differences in the gait characteristics of patients with diabetes and peripheral neuropathy compared with age-matched controls. *Phys Ther.* 1994;74:299–308.

3 Simoneau GG, Ulbrecht JS, Derr JA, et al. Postural instability in patients with diabetic sensory neuropathy. *Diabetes Care.* 1994;17:1411–1421.

4 Maluf KS, Mueller MJ. Comparison of physical activity and cumulative plantar tissue stress among subjects with and without diabetes mellitus and a history of recurrent plantar ulcers. *Clin Biomech.* 2003;18:567–575.

5 van Sloten TT, Savelberg HH, Duimel-Peeters IG, et al. Peripheral neuropathy, decreased muscle strength and obesity are strongly associated with walking in persons with type 2 diabetes without manifest mobility limitations. *Diabetes Res Clin Pract.* 2011;91:32–39.

6 Boulton AJ, Armstrong DG, Albert SF, et al. Comprehensive foot examination and risk assessment: a report of the Task Force of the Foot Care Interest Group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. *Phys Ther.* 2008;88:1436–1443.

7 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346:393–403.

8 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977–986.

9 Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol.* 2015;3:866–875.

10 Sigal RJ, Kenny GP, Boule NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. *Ann Intern Med.* 2007;147:357–369.

11 Sigal RJ, Kenny GP, Wasserman DH, et al. Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care.* 2006;29:1433–1438.

12 American Diabetes Association. Standards of medical care in diabetes: 2008. *Diabetes Care.* 2008;31:S12–S54.

13 LeMaster JW, Mueller MJ, Reiber GE, et al. Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: Feet First randomized controlled trial. *Phys Ther.* 2008;88:1385–1398.

14 American Diabetes Assocation. Standards of medical care in diabetes: 2016. *Diabetes Care.* 2016;39(suppl 1):S1–S112.

15 Mueller MJ, Maluf KS. Tissue adaptation to physical stress: a proposed "physical stress theory" to guide physical therapist practice, education, and research. *Phys Ther.* 2002;82:383–403.

16 Brand PW. The diabetic foot. In: Ellenberg M, Rifkin H, eds. *Diabetes Mellitus: Theory and Practice*. 3rd ed. New Hyde Park, NY: Medical Examination Publishing Co Inc; 1984:829–849.

17 Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care.* 1990;13:513–521.

18 Mueller MJ, Diamond JE, Sinacore DR, et al. Total contact casting in treatment of diabetic plantar ulcers: controlled clinical trial. *Diabetes Care.* 1989;12:384–388.

19 Armstrong DG, Nguyen HC, Lavery LA, et al. Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care.* 2001;24:1019–1022.

20 Shah KM, Clark BR, McGill JB, et al. Relationship between skin intrinsic fluorescence—an indicator of advanced glycation end products—and upper extremity impairments in individuals with diabetes mellitus. *Phys Ther.* 2015;95:1111–1119.

21 Brown MJ, Asbury AK. Diabetic neuropathy. *Ann Neurol.* 1984;15:2–12.

22 Vinik A, Ullal J, Parson HK, Casellini CM. Diabetic neuropathies: clinical manifestations and current treatment options. *Nat Clin Pract Endocrinol Metab*. 2006;2:269–281.

23 Edwards JL, Vincent AM, Cheng HT, Feldman EL. Diabetic neuropathy: mechanisms to management. *Pharmacol Ther.* 2008;120:1–34.

24 Zochodne DW. Diabetes mellitus and the peripheral nervous system: manifestations and mechanisms. *Muscle Nerve.* 2007;36:144–166.

25 Farmer KL, Li C, Dobrowsky RT. Diabetic peripheral neuropathy: should a chaperone accompany our therapeutic approach? *Pharmacol Rev.* 2012;64:880–900.

26 Devor M. Unexplained peculiarities of the dorsal root ganglion. *Pain.* 1999;August(suppl 6):S27–S35.

27 Kennedy JM, Zochodne DW. Experimental diabetic neuropathy with spontaneous recovery: is there irreparable damage? *Diabetes.* 2005;54:830–837.

28 Chen YW, Hsieh PL, Chen YC, et al. Physical exercise induces excess Hsp72 expression and delays the development of hyperalgesia and allodynia in painful diabetic neuropathy rats. *Anesth Analg.* 2013;116:482–490.

29 Groover AL, Ryals JM, Guilford BL, et al. Exercise-mediated improvements in painful neuropathy associated with prediabetes in mice. *Pain.* 2013;154:2658–2667.

30 Malysz T, Ilha J, Nascimento PS, et al. Beneficial effects of treadmill training in experimental diabetic nerve regeneration. *Clinics (Sao Paulo).* 2010;65:1329–1337.

31 Li H, Shen Z, Lu Y, et al. Muscle NT-3 levels increased by exercise training contribute to the improvement in caudal nerve conduction velocity in diabetic rats. *Mol Med Rep.* 2012;6:69–74.

32 Singleton JR, Marcus RL, Lessard MK, et al. Supervised exercise improves cutaneous reinnervation capacity in metabolic syndrome patients. *Ann Neurol.* 2015;77:146–153.

33 Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. *Diabetes Care.* 2006;29:1294–1299.

34 Ozay R, Uzar E, Aktas A, et al. The role of oxidative stress and inflammatory response in high-fat diet induced peripheral neuropathy. *J Chem Neuroanat.* 2014;55:51–57.

35 Yoon H, Thakur V, Isham D, et al. Moderate exercise training attenuates inflammatory mediators in DRG of type 1 diabetic rats. *Exp Neurol.* 2015;267:107–114.

36 Selagzi H, Buyukakilli B, Cimen B, et al. Protective and therapeutic effects of swimming exercise training on diabetic peripheral neuropathy of streptozotocin-induced diabetic rats. *J Endocrinol Invest.* 2008;31:971–978.

37 Shankarappa SA, Piedras-Renteria ES, Stubbs EB, Jr. Forced-exercise delays neuropathic pain in experimental diabetes: effects on voltage-activated calcium channels. *J Neurochem.* 2011;118:224–236.

38 Verge VM, Andreassen CS, Arnason TG, Andersen H. Mechanisms of disease: role of neurotrophins in diabetes and diabetic neuropathy. *Handb Clin Neurol.* 2014;126:443–460.

39 Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. *Pain.* 2010;150:573–581.

40 Tucker PS, Fisher-Wellman K, Bloomer RJ. Can exercise minimize postprandial oxidative stress in patients with type 2 diabetes? *Curr Diabetes Rev.* 2008;4:309–319.

41 Nimmo MA, Leggate M, Viana JL, King JA. The effect of physical activity on mediators of inflammation. *Diabetes Obes Metab.* 2013;15(suppl 3):51–60.

42 Roque FR, Hernanz R, Salaices M, Briones AM. Exercise training and cardiometabolic diseases: focus on the vascular system. *Curr Hypertens Rep.* 2013;15:204–214.

43 Balducci S, Iacobellis G, Parisi L, et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. *J Diabetes Complications.* 2006;20:216–223.

44 Polydefkis M, Hauer P, Sheth S, et al. The time course of epidermal nerve fibre regeneration: studies in normal controls and in people with diabetes, with and without neuropathy. *Brain.* 2004;127:1606–1615.

45 Kennedy WR, Wendelschafer-Crabb G, Johnson T. Quantitation of epidermal nerves in diabetic neuropathy. *Neurology.* 1996;47:1042–1048.

46 Kluding PM, Pasnoor M, Singh R, et al. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. *J Diabetes Complications.* 2012;26:424–429.

47 Singleton JR, Marcus RL, Jackson JE, et al. Exercise increases cutaneous nerve density in diabetic patients without neuropathy. *Ann Clin Transl Neurol.* 2014;1:844–849.

48 Dyck PJ, Norell JE, Tritschler H, et al. Challenges in design of multicenter trials: end points assessed longitudinally for change and monotonicity. *Diabetes Care.* 2007;30:2619–2625.

49 Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association—joint position statement. *Diabetes Care.* 2010;33:e147–e167.

50 Singleton JR, Smith AG, Marcus RL. Exercise as therapy for diabetic and prediabetic neuropathy. *Curr Diab Rep.* 2015;15:120.

51 Swensson O, Langbein L, McMillan JR, et al. Specialized keratin expression pattern in human ridged skin as an adaptation to high physical stress. *Br J Dermatol.* 1998;139:767–775.

52 Sanders JE, Goldstein BS. Collagen fibril diameters increase and fibril densities decrease in skin subjected to repetitive compressive and shear stresses. *J Biomech.* 2001;34:1581–1587.

53 Flynn BP, Bhole AP, Saeidi N, et al. Mechanical strain stabilizes reconstituted collagen fibrils against enzymatic degradation by mammalian collagenase matrix metalloproteinase 8 (MMP-8). *PLoS One.* 2010;5:e12337.

54 LeMaster JW, Reiber GE, Smith DG, et al. Daily weight-bearing activity does not increase the risk of diabetic foot ulcers. *Med Sci Sports Exerc.* 2003;35:1093–1099.

55 Armstrong DG, Lavery LA, Holtz-Neiderer K, et al. Variability in activity may precede diabetic foot ulceration. *Diabetes Care.* 2004;27:1980–1984.

56 Tuttle LJ, Sinacore DR, Cade WT, Mueller MJ. Lower physical activity is associated with higher intermuscular adipose tissue in people with type 2 diabetes and peripheral neuropathy. *Phys Ther.* 2011;91:923–930.

57 Taveggia G, Villafane JH, Vavassori F, et al. Multimodal treatment of distal sensorimotor polyneuropathy in diabetic patients: a randomized clinical trial. *J Manipulative Physiol Ther.* 2014;37:242–252.

58 Mueller MJ, Tuttle LJ, LeMaster JW, et al. Weight-bearing versus nonweight-bearing exercise for persons with diabetes and peripheral neuropathy: a randomized controlled trial. *Arch Phys Med Rehabil.* 2013;94:829–838.

59 Sinacore DR, Gulve EA. The role of skeletal muscle in glucose transport, glucose homeostasis, and insulin resistance: implications for physical therapy. *Phys Ther.* 1993;73:878–891.

60 Tuttle LJ, Sinacore DR, Mueller MJ. Intermuscular adipose tissue is muscle specific and associated with poor functional performance. *J Aging Res.* 2012;2012:172957.

61 Cheuy VA, Hastings MK, Commean PK, et al. Intrinsic foot muscle deterioration is associated with metatarsophalangeal joint angle in people with diabetes and neuropathy. *Clin Biomech (Bristol, Avon).* 2013;28:1055–1060.

62 Cheuy VA, Hastings MK, Commean PK, Mueller MJ. Muscle and joint factors associated with forefoot deformity in the diabetic neuropathic foot. *Foot Ankle Int.* 2016;37:514–521.

63 Hastings MK, Mueller MJ, Woodburn J, et al. Acquired midfoot deformity and function in individuals with diabetes and peripheral neuropathy. *Clin Biomech (Bristol, Avon).* 2016;32:261–267.

64 Bittel DC, Bittel AJ, Tuttle LJ, et al. Adipose tissue content, muscle performance and physical function in obese adults with type 2 diabetes mellitus and peripheral neuropathy. *J Diabetes Complications.* 2015;29:250–257.

65 Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. *Am J Clin Nutr.* 2000;71:885–892.

66 Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology—update 2014. *J Cachexia Sarcopenia Muscle.* 2014;5:253–259.

67 Yamagishi S, Nakamura N, Suematsu M, et al. Advanced glycation end products: a molecular target for vascular complications in diabetes. *Mol Med.* 2015;21(suppl 1):S32–S40.

68 Sinacore DR, Gutekunst DJ, Hastings MK, et al. Neuropathic midfoot deformity: associations with ankle and subtalar joint motion. *J Foot Ankle Res.* 2013;6:11.

69 Mueller MJ, Diamond JE, Delitto A, Sinacore DR. Insensitivity, limited joint mobility, and plantar ulcers in patients with diabetes mellitus. *Phys Ther.* 1989; 69:453–459.

70 Fernando DJ, Masson EA, Veves A, Boulton AJ. Relationship of limited joint mobility to abnormal foot pressures and diabetic foot ulceration. *Diabetes Care.* 1991;14:8–11.

71 Ward RE, Boudreau RM, Caserotti P, et al. Sensory and motor peripheral nerve function and longitudinal changes in quadriceps strength. *J Gerontol A Biol Sci Med Sci.* 2015;70:464–470.

72 White CM, Pritchard J, Turner-Stokes L. Exercise for people with peripheral neuropathy. *Cochrane Database Syst Rev.* 2004;4:CD003904.

73 Streckmann F, Zopf EM, Lehmann HC, et al. Exercise intervention studies in patients with peripheral neuropathy: a systematic review. *Sports Med.* 2014;44: 1289–1304.

74 Lee K, Lee S, Song C. Whole-body vibration training improves balance, muscle strength and glycosylated hemoglobin in elderly patients with diabetic neuropathy. *Tohoku J Exp Med.* 2013;231:305–314.

75 Akbari M, Jafari H, Moshashaee A, Forugh B. Do diabetic neuropathy patients benefit from balance training? *J Rehabil Res Dev.* 2012;49:333–338.

76 Song CH, Petrofsky JS, Lee SW, et al. Effects of an exercise program on balance and trunk proprioception in older adults with diabetic neuropathies. *Diabetes Technol Ther.* 2011;13:803–811.

77 Allet L, Armand S, de Bie RA, et al. The gait and balance of patients with diabetes can be improved: a randomised controlled trial. *Diabetologia.* 2010;53:458–466.

78 Richardson JK, Sandman D, Vela S. A focused exercise regimen improves clinical measures of balance in patients with peripheral neuropathy. *Arch Phys Med Rehabil.* 2001;82:205–209.

79 Kruse RL, LeMaster JW, Madsen RW. Fall and balance outcomes after an intervention to promote leg strength, balance, and walking in people with diabetic peripheral neuropathy: "Feet First" randomized controlled trial. *Phys Ther.* 2010;90:1568–1579.

80 Yoo M, D'Silva LJ, Martin K, et al. Pilot study of exercise therapy on painful diabetic peripheral neuropathy. *Pain Med.* 2015;16:1482–1489.

81 Kluding PM, Pasnoor M, Singh R, et al. Safety of aerobic exercise in people with diabetic peripheral neuropathy: single-group clinical trial. *Phys Ther.* 2015;95: 223–234.

82 Fisher MA, Langbein WE, Collins EG, et al. Physiological improvement with moderate exercise in type II diabetic neuropathy. *Electromyogr Clin Neurophysiol.* 2007;47:23–28.

83 Dixit S, Maiya AG, Shastry BA. Effect of aerobic exercise on peripheral nerve functions of population with diabetic peripheral neuropathy in type 2 diabetes: a single blind, parallel group randomized controlled trial. *J Diabetes Complications.* 2014;28:332–339.

84 Hung JW, Liou CW, Wang PW, et al. Effect of 12-week tai chi chuan exercise on peripheral nerve modulation in patients with type 2 diabetes mellitus. *J Rehabil Med.* 2009;41:924–929.

85 Ahn S, Song R. Effects of tai chi exercise on glucose control, neuropathy scores, balance, and quality of life in patients with type 2 diabetes and neuropathy. *J Altern Complement Med*. 2012;18:1172–1178.

86 Office of Disease Prevention and Health Promotion. Physical activity guidelines. health.gov website. Available at: https://health.gov/paguidelines/. Updated August 12, 2016. Accessed August 12, 2016.

87 Waaijman R, de Haart M, Arts ML, et al. Risk factors for plantar foot ulcer recurrence in neuropathic diabetic patients. *Diabetes Care.* 2014;37:1697–1705.

88 Perkins BA, Olaleye D, Zinman B, Bril V. Simple screening tests for peripheral neuropathy in the diabetes clinic. *Diabetes Care.* 2001;24:250–256.

89 Mueller MJ. Identifying patients with diabetes mellitus who are at risk for lower-extremity complications: use of Semmes-Weinstein monofilaments. *Phys Ther.* 1996;76:68–71.

90 Sinacore DR, Bohnert KL, Hastings MK, Johnson JE. Mid foot kinetics characterize structural polymorphism in diabetic foot disease. *Clin Biomech (Bristol, Avon).* 2008;23:653–661.

91 Mueller MJ, Hastings M, Commean PK, et al. Forefoot structural predictors of plantar pressures during walking in people with diabetes and peripheral neuropathy. *J Biomech.* 2003;36:1009–1017.

92 Hastings MK, Woodburn J, Mueller MJ, et al. Kinematics and kinetics of single-limb heel rise in diabetes related medial column foot deformity. *Clin Biomech (Bristol, Avon).* 2014;29:1016–1022.

93 Khan NA, Rahim SA, Anand SS, et al. Does the clinical examination predict lower extremity peripheral arterial disease? *JAMA.* 2006;295:536–546.

94 Schriger DL, Baraff L. Defining normal capillary refill: variation with age, sex, and temperature. *Ann Emerg Med.* 1988; 17:932–935.

95 American Heart Association. Understanding blood pressure readings. Available at: http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/Understanding-Blood-Pressure-Readings_UCM_301764_Article.jsp. Updated March 23, 2016. Accessed August 12, 2016.

96 Otterman NM, van Schie CH, van der Schaaf M, et al. An exercise programme for patients with diabetic complications: a study on feasibility and preliminary effectiveness. *Diabet Med.* 2011;28:212–217.

97 Gregg EW, Mangione CM, Cauley JA, et al. Diabetes and incidence of functional disability in older women. *Diabetes Care.* 2002;25:61–67.

98 Gregg EW, Sorlie P, Paulose-Ram R, et al. Prevalence of lower-extremity disease in the US adult population ≥40 years of age with and without diabetes: 1999–2000 National Health and Nutrition Examination Survey. *Diabetes Care.* 2004;27: 1591–1597.

99 Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care.* 2012;35:2650–2664.

100 Richardson JK, Thies SB, DeMott TK, Ashton-Miller JA. Gait analysis in a challenging environment differentiates between fallers and nonfallers among older patients with peripheral neuropathy. *Arch Phys Med Rehabil.* 2005;86: 1539–1544.

101 Richardson JK, Thies S, Ashton-Miller JA. An exploration of step time variability on smooth and irregular surfaces in older persons with neuropathy. *Clin Biomech.* 2008;23:349–356.

102 Menz HB, Lord SR, St George R, Fitzpatrick RC. Walking stability and sensorimotor function in older people with diabetic peripheral neuropathy. *Arch Phys Med Rehabil.* 2004;85:245–252.

103 Schwartz AV, Hillier TA, Sellmeyer DE, et al. Older women with diabetes have a higher risk of falls: a prospective study. *Diabetes Care.* 2002;25:1749–1754.

Appendix.
Preexercise Considerations and Exercise Goals[14,49]

Preexercise Considerations

Blood glucose

Low blood glucose (<100 mg/dL): ingest glucose before exercise

High blood glucose (≥250 mg/dL): exercise is allowed unless ketones are in the blood or urine

Blood pressure

Seek medical consultation if blood pressure is >140/>90 mm Hg

Physician clearance

Physician clearance is recommended when exercise intensity is greater than a brisk walking program in sedentary people

Exercise Goals

Aerobic

150 min/wk at 50%–70% of maximum heart rate initially, spread over 3 days, with no more than 2 consecutive days between bouts. Increase intensity as tolerated.[a]

Weight-bearing or non–weight-bearing activities are safe for people with diabetes and peripheral neuropathy. However, if there is a history of or current foot ulcer or significant foot deformity, then non–weight-bearing activity (eg, stationary bike, rowing ergometer, or swimming) is recommended.

Resistance training

Moderate to vigorous resistance training at least 2 or 3 d/wk

Should include a minimum of one set of 5 resistance exercises involving large muscle groups (quadriceps, back, chest, hamstring)

Flexibility

Design flexibility program to address joint range-of-motion limitations, with a special focus on ankle, hip, and shoulder joints

Individual needs

A physical therapist examination may reveal additional exercises needed to address specific concerns or to prevent movement-related injury

[a] The initial exercise prescription should be determined by taking into account the current exercise level and an assessment of risk of injury with exercise participation. The speed at which the intensity and duration of the exercise program are increased and the monitoring required during these changes should reflect the level of concern about exercise-related injury. People with significant risk factors (eg, peripheral neuropathy and cardiovascular disease) should start with short bouts of low-intensity exercise and gradually increase duration and intensity.