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

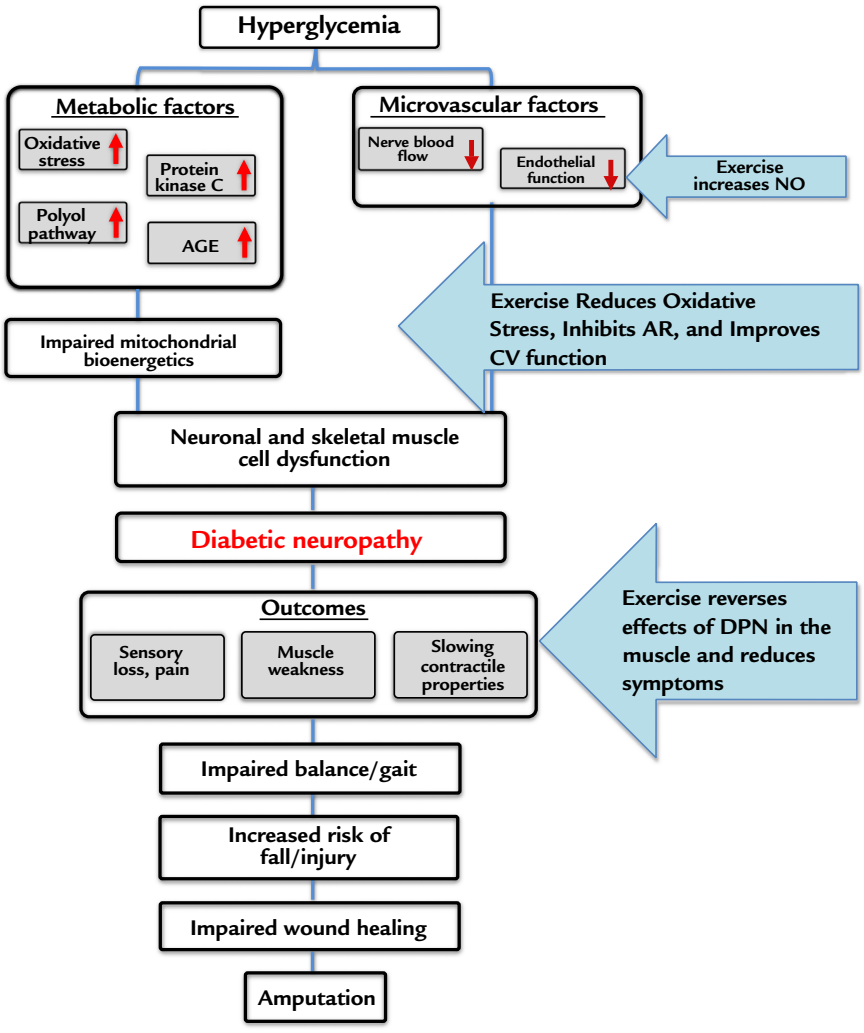

Figure 1. Postulated pathogenesis of diabetic peripheral neuropathy (DPN) and therapeutic effect of exercise. Various metabolic factors have been implicated in the pathogenesis of DPN, as well as vascular factors, such as decreased nerve blood flow and damaged nerve fibers. Prolonged DPN leads to sensory 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.

complications. Nearly 30% of patients with DPN will develop a foot ulcer within 2 years of diagnosis of severe DPN.[9] Despite several therapeutic approaches for wound treatment, ~15% to 20% of all diabetic foot ulcers require amputation.[10,11] Plantar ulcers occur in ~15% of all individuals with DM,[12] with a high financial cost associated with ulcer-related episodes.[13] Ineffective management of diabetic foot complications contributes substantially to the high rate of amputations seen in this population.[14] More than 60% of all nontraumatic lower limb amputations occur in people with DM.[15] Patients with chronic wounds account for 10% of the entire diabetic Medicare population and are responsible for a 4-fold increase in annual per capita health care expenditures, compared with patients with DM without these complications.[16] Besides the enormous financial impact, diabetic foot complications have a profound negative effect on patients' mortality and quality of life.[17–21] Approximately 70% of patients with DPN die at 10 years after the initial diagnosis of DPN, with 50% of these deaths being cardiovascular related.[22,23]

A significant consequence of DPN on the skeletal muscle is the accelerated loss of muscle mass, compared with DM alone.[24] Deficits in lower limb muscles reduce functional capacity and contribute to altered gait, increased fall risk, and impaired balance in patients with DPN. This scenario 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.[25–27] The benefits of combining moderate-intensity aerobic exercise with resistance training to improve glycemic control and insulin sensitivity in individuals with DM are well documented.[28] However, little is known about the benefits of exercise in individuals with DPN. Exercise in DPN has been predominantly discouraged in the past because it was considered as a hazard to further exacerbate DPN and risk of falling or injury. However, recent studies have shown that moderate-intensity exercise programs can improve the cardiorespiratory function of patients with DPN and can partially reverse some of their symptoms.[29,30] It has been hypothesized that exercise can partially reverse DPN progression because it promotes MV dilation, reduces oxidative stress, and increases the abundance of neurotrophic factors, all of which are compromised in DPN.[31] Exercise can also improve lower limb muscle function by inhibiting key metabolic pathways that cause hypoxia. Furthermore, activation of nitric oxide production as a result of exercise is a key mechanism to improve endothelial function in DPN (Figure 1).

The present review describes the current knowledge of the effects of DPN in the skeletal muscle, as well as promising results from exercise interventions targeted at improving DPN muscle function and symptom reversal. We also highlight the mechanistic insights acquired by using noninvasive magnetic resonance imaging (MRI) techniques that can help assess the efficacy of future interventions for DPN.

THE EFFECTS OF DPN ON SKELETAL MUSCLE FUNCTION

Prolonged DPN is known to result in significant skeletal muscle deficits in this patient population, including neurogenic muscle atrophy, loss of muscle strength, power, and endurance.[32–35] These factors synergistically contribute to altered gait and impaired balance, which is particularly important for patients with DPN given that their falls often lead to bone fractures and chronic infections[25–27] that may require an amputation.[36,37] Here we report on the current state of knowledge in terms of the effects of DPN in skeletal muscle impairment.

A significant consequence of DPN on skeletal muscle is the accelerated loss of motor axons.[24,38–40] The loss of motor units has been reported in the intrinsic foot muscles[40] and the dorsiflexors of the leg,[38,39,41] as well as intrinsic hand muscles.[39] The loss can approach 50% compared with age-matched healthy control subjects.[38,39,41] Patients with DPN have been shown to have greater motor unit losses compared with patients with DM with no neuropathy.[40] The size of existing motor units indicated by the motor unit potential is increased[40,41] through the traditional pattern of reinnervation after denervation.

Electromyography studies have shown that DPN results in greater fiber density in the dorsiflexor muscles.[33] This pattern of denervation is accelerated in DPN, compared with nonneuropathic DM. It is clear that complete reinnervation cannot offset the loss of motor neurons, as muscle mass is highly reduced with DPN.[24] Furthermore, accelerated reinnervation is associated with greater loss in dorsiflexor muscle strength.[33] The incomplete

reinnervation in DPN may partially be attributed to declines in neurotrophic factors.[42] The loss of motor units results in muscle weakness, atrophy, and intramuscular fatty infiltration.[39,43] Motor unit loss is directly correlated with loss of muscle mass and increased intermuscular fat.[39]

Motor neuron axon excitability is decreased in DM, although the muscle fiber excitability seems to be preserved in DPN.[44] It has been known for 50 years that DM is associated with slower nerve conduction velocity.[45] Slower conduction velocities have been reported in the tibial nerve,[40,46,47] peroneal nerve,[46–48] and median nerve.[42,46] In some cases, peroneal nerve responses in DPN cannot be detected.[49] Declines in femoral nerve conduction have also been reported in patients with DM with no overt signs of neuropathy.[50] The slower conduction velocities may be linked to enhanced muscle fatigue with DPN. Slower femoral nerve conduction velocities are also associated with higher blood glucose levels.[50] In addition, motor unit discharge frequencies are reduced in DPN. These findings collectively show that the intact motor neurons in DPN have reduced function.

Reduced muscle volume of the intrinsic foot muscles,[51–54] as well as the muscles in the leg,[34,42] occurs with DPN. Over a 12-year period, patients with DPN had a 57% decline in dorsiflexor muscle volume (4.5% per year), a 61% decline in plantar flexion volume (5% per year), and a 29% loss in foot muscle volume (3% per year).[42] These declines were greater for DPN compared with DM without neuropathy. Furthermore, the annual decline of muscle volume was related to neuropathy impairment scores at follow-up.[42] Muscle atrophy is length dependent, with more distal muscle areas showing greater losses.[34] Skeletal muscle atrophy may be related to increased advanced glycation end products and receptors[55] or reduced insulin signaling in skeletal muscle.[56] Adipose tissue in the muscle is increased in DPN, in particular in the posterior leg.[39,43,57] Increases in intermuscular adipose tissue are tied to reduced physical function and ability to complete daily activities.[43]

Declines in muscle strength with DPN have been reported in several muscles, including the ankle extensors (dorsiflexors),[35,38,41,42,49,51,58,59] ankle plantar flexors,[34,35,51,58] knee extensors,[48,58] and knee flexors.[51,58] As expected, the more distal ankle muscles experience greater losses in strength compared with the muscles of the thigh.[42] Ankle dorsiflexors[39,41,51,58] generally exhibit a 15% to 30% reduction compared with healthy control subjects. Declines in strength of the leg muscles are between 3% and 6% per year, depending on the severity of the neuropathy.[35,42] Strength losses across the lower limb are more severe in DPN compared with DM without neuropathy.[35,42,49] Thigh muscle strength has shown reductions in patients with DPN[51,58] but not in those with DM without neuropathy.[58] Importantly, muscle strength losses across the thigh and leg muscles are associated with neuropathy scores.[35,42,51,58]

Muscle performance is generally diminished in DPN. Muscle atrophy directly contributes to the declines in muscle force.[32,38,39,60] Muscle relaxation rates are prolonged,[44] partially attributed to decreased calcium handling as the smooth endoplasmic reticulum ATPase (SERCA) protein content is reduced with DPN.[44] The rate of force development is also reduced with DPN, as indicated by a longer time to reach peak force.[38,44] Specific force relative to muscle area in the dorsiflexors has also been reported in DPN,[39,59] suggesting declines in muscle quality. However, the voluntary activation of skeletal muscle or ability to fully recruit the muscle seems to be preserved in DPN.[39,61] Muscle performance declines in DPN include enhanced muscle fatigue of the dorsiflexors[62] and the knee extensors,[48] indicated by a shorter time to task failure. This reduced muscular endurance is greater in DPN compared with DM without neuropathy.[48]

The diminished endurance time is also related to slower motor nerve conduction velocity.[48] Few data are available on striated muscle fiber type changes in DPN. Surprisingly, muscle fiber size was reportedly not reduced in DPN[63]; however, these patients had a high body mass index, which may have offset changes in fiber diameter. Nonetheless, the results are in agreement with a major role of neurogenic atrophy in decreased muscle strength. Patients with DM type 1 have an increased proportion of type II fibers, which could result in reduced muscular endurance. Other data from electromyography studies suggest that DPN is associated with decreases in fast motor units, as the postactivation potentiation is reduced in DPN and twitch relaxation time is prolonged.[38] However, fiber type proportion is not related to neuropathy scores or any measure of glucose control or duration of DM.[63]

DPN is associated with reduced ankle joint motion for both plantar and dorsiflexion.[34,60] Decreased muscle strength of the ankle plantar and dorsiflexors is associated with shorter stride length and reduced walking speed.[60] Reaction time of the knee and ankle joint muscles is also reduced with DPN.[34] In addition, reduced dorsiflexion range of motion has been tied to declines in mobility[60] and decreased neuropathy scores.[34] Changes in ankle joint range of motions, strength, and reaction time are likely critical factors in balance impairments and fall risk associated with DPN.

Declines in muscle performance in DPN may also be influenced by blood flow and perfusion. Blood flow reductions occur with DPN[64] and may contribute to reduced muscle endurance. Vascular impairments include increased carotid artery intima media thickness and decreased brachial artery flow–mediated dilation with DM.[65] MV density[63] and function[66–68] are compromised in DPN. L-arginine, an important substrate used in nitric oxide–dependent vasodilation, is reduced in DM and importantly related to the development of peripheral neuropathy and microangiopathies.[69] Increased advanced glycation end products occurring in DPN may diminish vascular endothelial function through decreasing nitric oxide bioavailability.[70]

Skeletal muscle metabolism is also decreased in DPN. Resting levels of high-energy phosphates are reduced in the diabetic foot.[71,72] Muscle oxidative capacity is reduced by $>50\%$ in DPN compared with DM without neuropathy.[73] The reduced mitochondrial function in DPN is related to increased inflammatory cytokines. A reduction in oxidative enzymes and mitochondria content has also been reported in striated muscle of DM (see Review).[74] Declines in oxidative capacity are also reflected in slower rates of oxygen consumption during exercise in DM.[75]

Taken together, patients with DPN have shown greater skeletal muscle deficits compared with patients with DM. These deficits reduce functional capacity and result in impaired balance, making these patients susceptible to injuries that can lead to amputation.

THE LACK OF EFFECTIVE TREATMENTS FOR DPN AND THE ROLE OF PHYSICAL EXERCISE

Hyperglycemia is an important factor in the development of DPN. However, the pathophysiologic processes through which hyperglycemia causes DPN are not fully understood. Furthermore, large clinical studies (ACCORD [Action to Control Cardiovascular Risk in Diabetes],[76] ADVANCE [Action in Diabetes and Vascular Disease: PreterAx and Diamicron Controlled Evaluation],[77] and VADT [Veterans Affairs Diabetes Trial][78]) have shown that good glucose control alone is insufficient to reduce the occurrence of foot complications, including DPN. There are no US Food and Drug Administration–approved treatment options that target the underlying pathogenesis of DPN.[79,80]

Several treatments that specifically target pathogenic DPN mechanisms have been tested both on animal models and humans.[7] Most therapies under evaluation attempt to block key metabolic pathways linked to DPN progression[7] and/or improve nerve blood flow by stimulating angiogenesis.[81] These include agents such as α-lipoic acid (an antioxidant targeting hyperglycemia-induced oxidative stress)[82] and actovegin (an agent believed to stimulate oxygen use and cellular energy metabolism).[83] Some revascularization studies suggest that improving tissue blood flow may alleviate DPN.[84] However, despite encouraging early results,[82,83,85–89] there are no therapies to prevent or reverse its progress.[79,90]

A growing body of literature supports the benefits of combining moderate-intensity aerobic exercise with resistance training to improve glycemic control and insulin sensitivity in individuals with DM.[28] Current practice guidelines endorsed by the American Diabetes Association and the American College of Sports Medicine recommend 150 minutes per week of combination (ie, aerobic and resistance) training.[91] Key parameters related to exercise prescription include the following: (1) intensity (50%–80% the maximum rate of oxygen consumption as measured during incremental exercise); (2) frequency (3–4 times per week); and (3) duration (30–60 min per session). The total length of programs ranges from 10 to 26 weeks. Evidence from the DARE (Diabetes Aerobic and Resistance Exercise) and HART-D (Health Benefits of Aerobic and Resistance Training in Individuals With Type 2 Diabetes) clinical trials[92,93] showed that a combination of aerobic and resistance training improved glycosylated hemoglobin levels, which was not achieved by aerobic or resistance training alone. Prescription of resistance training includes a consideration of the following: (1) intensity (usually 2–3 sets

of 12 repetitions each); (2) number of exercises (between 3 and 9 exercises that involve large muscle groups such as bench press, seated row, leg press, back extensions); and (3) frequency (2–3 sessions per week). The total length of programs ranges from 26 to 36 weeks, with weekly increments in 10 or 12 repetition maximum weight. Supervision has been linked to adherence, and adherence, in turn, has been linked to the extent of improvements in postintervention glucose tolerance.[94,95]

Preliminary studies have shown that moderate-intensity supervised exercise programs that include aerobic and resistance training are well tolerated by patients with DPN. The patients can significantly improve their cardiorespiratory function and can also improve DPN symptoms, including nerve function and cutaneous innervation.[29,30,96] In addition, exercise may lead to an improved vascular endothelial function in DPN.[97] It has been hypothesized that exercise can partially reverse DPN progression because it promotes MV dilation, reduces oxidative stress, and increases the abundance of neurotrophic factors, all of which are compromised in DPN.[31] It has been suggested that moderate-intensity aerobic exercise has an anti-inflammatory effect in patients with DM.[98] However, these effects have not been confirmed in patients with DPN. Exercise may be able to improve lower limb muscle function by inhibiting key metabolic pathways that cause hypoxia. Furthermore, activation of nitric oxide production as a result of exercise is a key mechanism to improve endothelial function in DPN.

Resistance training in DPN has the potential to increase muscle mass and muscle strength that are severely reduced with DPN. Recently, functional rates of force development were improved after resistance training in DPN.[99] The effect of resistance exercise and increased muscle mass is essential to improve glycemic control because skeletal muscle is typically responsible for the majority of whole body glucose uptake. Therefore, substantial increases in skeletal muscle mass alone would be expected to lower blood glucose levels. Furthermore, aerobic exercise is associated with improvements in glucose uptake through increases in glucose transporters. Aerobic exercise combined with resistance has been shown to increase metabolic flexibility in type 2 DM, allowing the body to increase glucose metabolism.[100] Aerobic exercise has clearly been shown to improve mitochondrial function across many diseases and conditions. Improving mitochondrial function not only stands to increase glucose uptake and clearance but also induces improvements in oxidative capacity. The improvements in oxidative capacity for DPN would increase muscular endurance and functional performance.

Safety of Physical Exercise in Individuals With DPN

Safety of physical exercise in patients with DPN has been assessed in small clinical studies, during which adverse events (AEs) have been recorded.[29] In a 16-week supervised aerobic exercise, the intensity of the exercise session was individually prescribed on the basis of the heart rate response at the corresponding 50% to 70% oxygen uptake (VO_2R) reserve from a graded exercise test. Sessions were supervised by licensed health care professionals or health care professional students, with no more than 4 participants per supervisor. The number of AEs was reported. The majority of them (56%) occurred in the first 8 weeks of the 16-week exercise program. These included joint or muscle pain that affected exercise duration or attendance, significant hypoglycemia (blood level <70 mg/dL), chest pain, and shortness of breath. There were also AEs reported that were not related to the study procedures but affected participation in exercise. For example, hyperglycemia (blood glucose level >300 mg/dL) was not caused by exercise but resulted in close monitoring during exercise for safety, and cold/flu symptoms occasionally caused cancellation of exercise sessions. Several other issues were noted by the team and resulted in physician referral. These included a significant foot swelling ($n = 1$), hyperglycemia with a positive urine ketone test result ($n = 1$), and significant hypertension at rest ($n = 1$). Of 20 enrolled participants, 18 (90%) completed the study, and no serious AEs occurred as a result of the intervention.

An additional consideration in moderate-intensity exercise prescription in DPN is whether the intervention may contribute to an increased risk of foot ulcers.[101] These concerns stem from data showing that repetitive and elevated plantar stress sustained in DPN contributes to ulcer risk.[102] However, assessment of plantar pressure by itself has modest sensitivity and specificity, underscoring the multifactorial etiology of foot ulcer development.[103,104] The Feet First Trial demonstrated that a community-based

relatively low-intensity weight-bearing intervention was safe in individuals with DPN.[105] A subsequent follow-up study demonstrated that moderate-intensity weight-bearing exercise (1 hour per session, 3 sessions per week) was as safe as nonweight-bearing exercise. Adverse effect monitoring included visual inspection of feet and footwear, as well as skin temperature monitoring. Although the feasibility of skin temperature monitoring is promising,[106] Lemaster et al[105] noted a high rate of false-positive findings (foot temperature differential of $>2.2^{\circ}$ C in response to walking) with skin temperature monitoring.

Taken together, these studies illustrate that moderate-intensity supervised exercise is well tolerated by patients with DPN. However, care providers must carefully prescribe exercise intensity and closely monitor and address anticipated adverse effects, including joint or muscle pain, hypoglycemia, and ulcer risk.

The Effects of Exercise on DPN Symptom Reversal

In a separate study, a 10-week, moderate-intensity supervised exercise program that included aerobic and resistance training was prescribed in 17 patients with DPN.[30] Despite the short duration of the intervention, exercise significantly improved participants' scores on the Michigan Neuropathy Screening Instrument. In addition, skin biopsy specimens revealed increases in intraepidermal nerve fiber density. Consistent with these findings, a recent pilot study showed that participation in a 16-week, moderate-intensity exercise program was accompanied by reduced pain interference in individuals with DPN.[107]

In a follow-up study, preliminary results regarding the effects of physical exercise on vascular endothelial function improvement were reported in patients with DPN.[97] Participation in a 16-week, moderate-intensity resistance training intervention (1 hour per week; exercises included leg press, leg extension, and ankle press) was accompanied by faster torque development during stair negotiation.[99] Taken together, these studies indicate that moderate-intensity aerobic and resistance training have significant potential to improve symptoms and mitigate strength deficits in individuals with DPN.

The Effects of Exercise on Balance in DPN

Interventions focusing on balance training are heterogeneous. Although some include aspects of resistance training,[108] others have focused on activities such as standing on a trampoline for dynamic balance or catching a ball to train anticipatory balance.[109] Overall, these exercise programs have been 8 to 10 weeks in duration, 60 minutes per session, 1 to 3 times per week.[108–110] Significant postintervention effects in reaction time and static and dynamic balance have been reported. Most recently, exercises using real-time feedback have shown promising results in individuals with DPN.[111] Wearable sensors were combined with a virtual environment in a short 4-week intervention, and resulted in a significant improvement in balance in individuals with DM. Longer term follow-up is warranted.

Effects of Targeted Exercise in DPN

Due to the distal to proximal distribution of symptoms and muscle atrophy in diabetic neuropathy,[49] one group has proposed exercise intervention targeted to the distal lower extremity in DPN.[112,113] In their clinical trial, the experimental group received a 12-week intervention (40–60 minutes per session, 2 sessions per week) with exercises to improve range of motion and strength of the foot and ankle, as well as gait training. The control group received standard foot care and medical management but no exercises. Although modest changes in gait-related variables were noted, no changes in neuropathy symptoms or self-reported foot function were found. The modest results accompanying targeted exercise may be explained, at least in part, by recent data showing substantial proximal impairments in DPN and challenging the assumptions related to the distribution of symptoms and impairments.[114,115]

Alternative Exercise Interventions in DPN

Mind/body practices such as tai chi and yoga reportedly have positive effects on glycemic control and balance in individuals with DPN.[116] A 12-week tai chi program (1 hour per session, 2 sessions per week) was accompanied by a reduction in neuropathy symptoms and improved glycemic control and balance.[116] Participation in a 3-month yoga intervention (3 sessions per week) was accompanied by modest decreases in body mass index, improvements in glycemic control, and a more marked reduction in oxidative stress.[117]

CURRENT LIMITATIONS IN ASSESSING INTERVENTION EFFICACY IN DPN

One of the obstacles for the development of effective treatments for DPN is the lack of sensitive and objective tests to detect small changes in symptoms and signs seen in interventions.[79] Typically, a diagnosis of DPN is based on the patient's description of pain. Abnormal findings from clinical examinations are used to determine a neuropathy score.[82] Symptoms can be assessed by using composed scores (ie, Total Symptom Score,[118] Toronto Clinical Neuropathy Score,[119] Neuropathy Symptom Score[120]). Other diagnostic scores focus on neuropathic impairments, such as the appearance of the feet, neuropathic ulceration, loss of Achilles tendon reflexes, and reduced vibration perception when tested using a tuning fork.[121]

These often-used scores, which rely on patients' subjective experience, are extremely variable with poor reproducibility and are considered unsuitable for the successful performance of clinical trials.[122] Motor nerve conduction velocities have been used as surrogate end points in clinical trials. They are highly reproducible and correlate well with underlying structural abnormalities. Although smaller sensory fibers play a large role early in the development of DPN and thus play a greater role in early DPN compared with larger motor nerve fibers, motor nerve conduction velocity is reduced with the further progression of DPN.[40,42,46–49] Minimally invasive skin biopsies can assess intraepidermal fiber density, but the results have shown considerable variability, even among controls, and their invasive nature remains a burden for patients and researchers.[123,124] Corneal confocal microscopy has shown early promising results for noninvasive detection and stratification of the severity of DPN.[125,126] However, the sensitivity and specificity of the technique for feet at risk of ulceration are moderate.[127]

NONINVASIVE MRI TECHNIQUES TO ASSESS DPN FEATURES

Several MRI techniques have been used to assess different aspects of DPN, including skeletal muscle structure, function, and peripheral nerves (Table). These tools have 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.

Magnetic Resonance Neurography

High-resolution magnetic resonance neurography (MRN) has excellent anatomic capability.[128] With improved detection of nerve anatomy and pathology, the value of MRN as a potential biomarker of the nerve effects of DPN has been increasingly recognized.[129,130] MRN is aimed at supressing the vascular and fat signal to create unique tissue selective images. This method is based on T2-weighted sequences with fat suppression, which provides excellent depiction of the peripheral nerves.[131] Intraneural T2-weighted contrast and nerve caliber allows localization and diagnosis of peripheral neuropathy.[132] Nerve T2 signal has been shown to have a high diagnostic accuracy.[133] During the early stages of the disease, sensory signs and symptoms typically occur first at the tip of the toes and in the feet and are later more severe in these distal regions (eg, loss of sensation across modalities, tingling, burning, pain, paresthesia, numbness). Progression of DPN may be associated with the proximal extension of sensory and/or motor signs and symptoms involving the ankle or further proximal levels. Therefore, MRN can play a key role in understanding the spatiotemporal distribution and propagation of microstructural nerve alterations in DPN and for early monitoring of microstructural effects of therapeutic interventions.[134] More recently, several variations of MRN sequences have been proposed, which can achieve both high resolution and good fat suppression on 3T scanners.[135]

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) is a powerful noninvasive MRI technique that allows quantitative assessment of neuronal architecture.[136] As an additional functional technique, DTI is increasingly being investigated with regard to its potential to help detect nerve injury and monitor reinnervation.[137–140] More recent research has shown that DTI can be used for the diagnosis of neuropathy,[141] as well as bring new insights to the involvement of the central nervous system in DPN.[142,143]

The quantitative parameters of DTI include fractional anisotropy and apparent diffusion coefficient values, which reflect the diffusion characteristics of water molecules and are altered with loss of integrity of the nervous tissue. Water molecules diffuse easily along the direction of the nerve fiber bundle, and the diffusion perpendicular to the fiber bundle is limited

Table. Magnetic resonance imaging studies in diabetic peripheral neuropathy (DPN).

Authors (Year)	Population	MR Assessment	Outcome
Allen et al (2014)[39] Allen et al (2016)[61]	12/DPN, 12/controls	TA CSA and % contractile muscle	Significant loss in contractile muscle in DPN in TA
Almurdhi et al (2016)[114]	20/diabetic, 20/controls	Upper/lower leg muscle CSA	Proximal muscle strength impairment relates to severity of DPN
Andersen et al (1997)[34]	8/DPN, 8/diabetic, 16 controls	Lower leg muscle CSA	Significantly lower CSA in dorsal/plantar flexors in DPN at distal and mid-part of lower leg
Andersen et al (2004)[51]	15/DPN, 8/diabetic, 23 controls	Foot muscle CSA	Significant foot muscle atrophy in DPN Foot muscle atrophy relates to DPN severity
Andreassen et al (2009)[42]	8/diabetic (type 1), 4/DPN (type 1)	Leg muscle volume	Significant dorsal flexor and plantar flexor volume loss in DPN compared with diabetes without neuropathy
	7/diabetic (type 1), 7/DPN (type 1)	Foot muscle volume	Significant foot muscle volume loss both in DPN and diabetes without neuropathy
Bittel et al (2015)[57]	54/DPM, 13/diabetic, 24/obese	Leg IMAT/SQAT	DPN relates to shift from SQAT to IMAT
Bus et al (2002)[53]	8/DPN, 8/controls	Foot muscle CSA/ muscle T2	Significant muscle tissue loss distally in DPN
Cheuy et al (2013)[54]	23/DPN, 12/controls	Foot IMAT	Significantly higher in IMAT in foot muscles of patients with DPN
Dinh et al (2009)[71]	18/DPM, 22/diabetic, 24/controls	PCr/Pi in metatarsal head	PCr/Pi were lower in DPN compared with diabetes without neuropathy and healthy control subjects
		Lipid/water in metatarsal head	Lipid/water ratios lower in DPN but similar in patients with diabetes and healthy control subjects
Greenman et al (2005)[72]	5/DPM, 7/diabetic, 8/controls	Pi/PCr in foot muscles	Higher Pi/PCr in DPN and diabetes compared with control subjects
Greenman et al (2005)[52]	12/DPM, 9/diabetic, 12/controls	Foot muscle CSA/^{31}P	Foot muscle area correlates to clinical measures of DPN. ^{31}P levels different in the 3 groups
Moore et al (2016)[59]	9/DPN, 8/diabetic	MTR/T2 in TA	Increased muscle atrophy in DPN compared with healthy control subjects Lower MTR in DPN compared with healthy control subjects
Pham et al (2015)[134]	35/DPN, 15/diabetic, 25/controls	Nerve lesion/proton density	Total burden of nerve lesion increases with DPN severity, particularly at thigh level
		From spinal nerve to ankle level	Increased nerve proton density with DPN severity at thigh level

(continued)

Table. (continued).

Authors (Year)	Population	MR Assessment	Outcome
Tecilazich et al (2013)[73]	10/DPN, 7/DPN + PAD, 11/diabetic 14/controls	Postexercise recovery of Pi/PCr	Significantly increased recovery time of Pi/PCr in DPN and DPN + PAD compared with diabetic and control subjects
Wu et al (2016)[144]	10/DPN, 12/controls	FA and ADC of TN and CPN	FA lower in DPN patients than healthy control subjects and correlates positively with MCV ADC significantly higher in DPN patients and correlates negatively with MCV

^{31}P = phosphorus 31; ADC = apparent diffusion coefficient; CPN = common peroneal nerve; CSA = cross-sectional area; FA = fractional anisotropy; IMAT = intramuscular adipose tissue; MCV = motor nerve conduction velocity; MTR = magnetization transfer ratio; SQAT = subcutaneous adipose tissue; PAD = peripheral arterial disease; PCr = phosphocreatine; Pi = inorganic phosphate; T2 = transverse relaxation time; TA = tibialis anterior; TN = tibial nerve.

as a result of nerve sheath covering. The directional preference of free water proton diffusion leads to high fractional anisotropy values in intact peripheral nerves. The pathologic conditions of the peripheral nerves lead to loss of structural integrity and directional coherence of the nerve fibers, which can be measured as decreased fractional anisotropy values.[144] The apparent diffusion coefficient reflects the degree of diffusion of a molecule and is an index to indirectly assess diffusion barriers such as the cell membrane or myelin sheath. Inflammation, edema, and injury can lead to increased apparent diffusion coefficient in patients with DPN (Figure 2).

Fat Infiltration Assessment

DPN is closely linked to muscle weakness, atrophy, and excess fat infiltration in the extremities.[39,43] Skeletal muscle in DPN has been shown to directly result in greater muscle atrophy compared with DM alone.[145,146] An MRI can be used to depict unique patterns of muscle infiltration in DPN.[57]

Insulin resistance has been associated with the amount of ectopic lipids, including intramyocellular lipids[147] and intrahepatic lipids,[148] as well as the amount and the distribution of fat in different body regions, including visceral adipose tissue[149] and intermuscular adipose tissue (IMAT).[150] IMAT infiltration in large muscle groups of the lower extremity is a particularly important etiologic factor in the onset and progression of type 2 DM and its complications due to its hormonal and structural influences on skeletal muscle, which is responsible for 90% of peripheral glucose uptake.[151] IMAT can be quantified by using MR spectroscopy,[147] high-spatial resolution T1-weighted sequences,[152] and, more recently, chemical shift-based water fat separation MRI techniques.[153] IMAT accumulation has been shown to be higher in patients with DPN compared with those with type 2 DM without DPN and body mass index–matched control subjects.[57] In addition to the IMAT accumulation, the distribution of adipose tissue deposition may also change with the severity and progression of DM complications. The expansion of visceral adipose tissue depots, as opposed to subcutaneous depots, has been associated with peripheral insulin resistance, hyperglycemia, and cardiovascular disease in obese populations.[154] The progression of obesity (control) to type 2 DM with DPN and the accompanying loss of subcutaneous

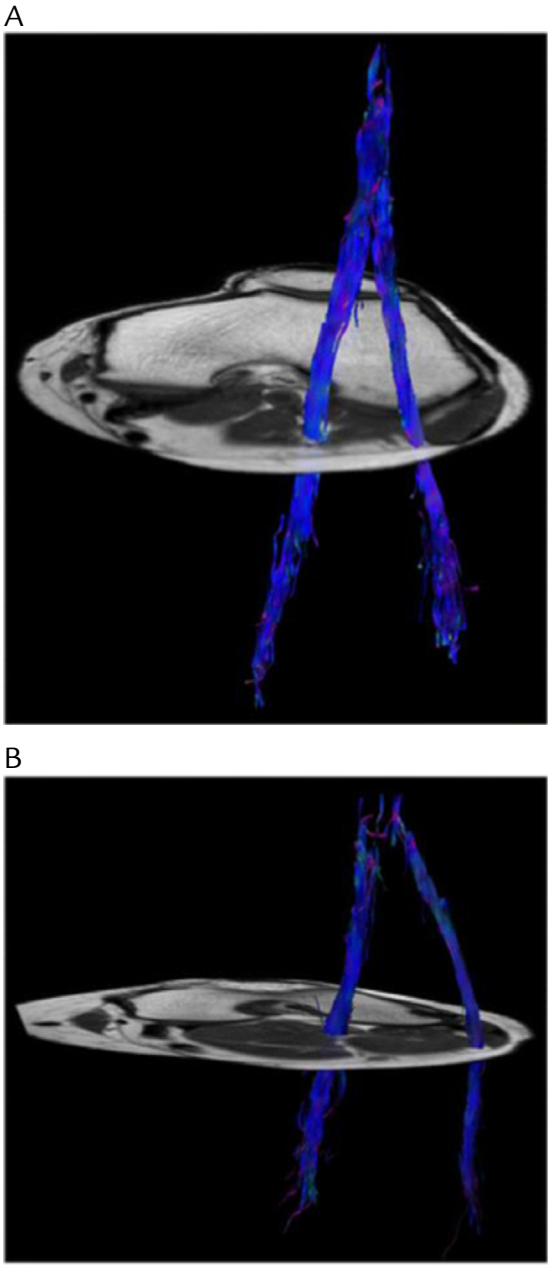

Figure 2. Axial diffusion tensor imaging (DTI). Nerve fiber tracts of the tibial and common peroneal nerves at the level of the right knee of (A) a healthy control subject and (B) a patient with diabetic peripheral neuropathy (DPN). DTI detected decreased fractional anisotropy and increased apparent diffusion coefficient in patients with DPN. Reprinted with permission Wu et al.[144]

depots, accumulation of IMAT, loss of muscle volume (gastroc-soleus % volume), and reduced physical function is shown in Figure 3. IMAT has been a useful index for monitoring intervention related to exercise and nutrition[155,156] and could become a powerful tool in understanding the effects of intervention in DPN.

MRI for Assessment of Perfusion and Microvascular Function in DPN

Blood flow and perfusion reductions may also contribute to the effects of DPN in skeletal muscle.[64] MV density[63] and function[66–68] are compromised in DPN. Blood-oxygenation level-dependent (BOLD) MRI can probe MV function in skeletal muscle[157] by characterizing signals that arise from unresolved veins and venules within skeletal muscle.[158–160] Typically, the experiment involves a brief muscle contraction, which places a small metabolic load on the muscle and results in a postcontraction increase in blood flow. The postcontractile BOLD signal can be a measure of primarily small vessel reactivity and peripheral MV function.[157,159–161] In a preliminary study, it was shown that BOLD MRI is sensitive in identifying MV impairment in patients with type 2 DM and MV disease (ie, DPN, retinopathy). MRI can be useful in assessing reversal of MV function in DPN.

Phosphorus Magnetic Resonance Spectroscopy for Metabolic Assessment of Skeletal Muscle

Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) allows direct measurement of important high-energy phosphates in human tissue,[154] such as adenosine triphosphate (ATP), phosphocreatine (PCr), and inorganic phosphate. Resting levels of high-energy phosphates are reduced in the diabetic foot.[71,72] Foot muscle atrophy has been shown to be accompanied by a reduction in phosphorus 31 metabolites in the foot muscles in patients with DPN compared with patients with DM without neuropathy and healthy control subjects.[52]

^{31}P-MRS has been used extensively to study skeletal muscle metabolism during rest-exercise-recovery protocols.[162–167] During exercise, ATP is consumed and maintained at a constant level through PCr hydrolysis. This action leads to a reduction in PCr and an increase in inorganic phosphate, which can be directly observed in ^{31}P-MRS. During recovery, ATP, and thus PCr, is resynthesized through oxidative phosphorylation, which takes place in the mitochondria.[167–170] The recovery of

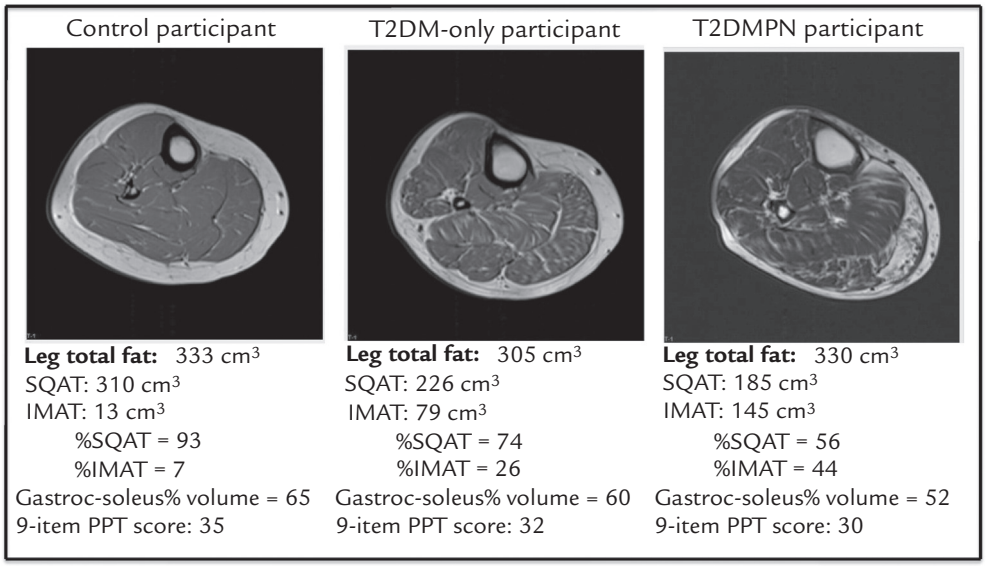

Figure 3. Cross-sectional images of the legs of a control subject, a patient with type 2 diabetes mellitus (T2DM), and a patient with type 2 DM and diabetic peripheral neuropathy (T2DMPN) . These images exemplify the progression of obesity (control) to T2DMPN and the accompanying loss of subcutaneous adipose tissue (SQAT), accumulation of intermuscular adipose tissue (IMAT), loss of muscle volume (gastroc-soleus % volume), and reduced physical function (PPT). Reprinted with permission from Bittel et al.[57]

PCr is considered a valid index of mitochondrial oxidative phosphorylation.[169,171–173] One study showed that the postexercise time of recovery of PCr was prolonged in patients with DPN compared with patients with type 2 DM without neuropathy.[73] This impairment in oxidative capacity was ~50% in DPN compared with DM without neuropathy and was not affected by the presence of peripheral arterial disease.

CONCLUSIONS

DPN is associated with neurogenic muscle atrophy, a reduced rate of muscle contraction, and muscle wasting. In addition, changes in muscle metabolism and blood flow associated with DPN increase fatigability. Impairments in lower limb muscles reduce functional capacity and contribute to altered gait, increased fall risk, and impaired balance in patients with DPN. This is an important concern for patients with DPN because their falls are likely to be injurious. Several treatments that specifically target pathogenic DPN mechanisms have been tested both on animal models and humans. However, despite encouraging early results, there are no therapies to prevent or reverse its progress. A growing body of literature supports the benefits of combining moderate-intensity aerobic exercise with resistance training to improve glycemic control and insulin sensitivity in individuals with DM. Recently, several studies have shown that moderate-intensity supervised exercise is well tolerated by patients with DPN and can help them improve both their cardiovascular function and partially reverse DPN symptoms. Advanced MRI techniques can provide mechanistic insight into the adaptations in peripheral nerve structure and skeletal muscle function after physical exercise interventions.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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