Diabetic Polyneuropathy (DPN) refers generally to peripheral neural dysfunction as a complication of diabetes mellitus (DM). The Centers for Disease Control report that 29.1 million people or 9.3% of the population of the United States has been diagnosed with diabetes (21). Of this group, almost 95% are individuals with type 2 DM (T2DM) (21). Neuropathy is a common and costly complication of both type 1 and type 2 diabetes and DPN is estimated to occur in at least 20% of diagnosed patients (18).

In its broadest context, DPN can refer to any of a group of neuropathic conditions with relatively heterogeneous patterns of neurological involvement. These diverse patterns may include any combination of dysfunction in the sensory, motor, or autonomic nervous systems. More specifically, typical DPN is described as a chronic, symmetrical, length-dependent sensorimotor polyneuropathy, which is the condition referred to throughout this review (25, 26). Typical DPN features sensory (i.e., numbness and paresthesia) and motor (i.e., atrophy and weakness) dysfunction that progresses in a distal to proximal, or length-dependent, manner (25, 26). Academic and clinical discussion of DPN is often centered on its sensory component whereas important DPN-related impacts to the motor and neuromuscular systems, associated with more severe forms of the disease, often are underappreciated and overlooked.

DPN PATHOGENESIS

The precise mechanisms underlying the development of DPN are complex and not entirely clear. DPN is likely caused by DM-related metabolic or vascular disturbances that are not mutually exclusive and may be interrelated or synergistic. These mechanisms lead to axonal loss via retrograde degradation, as well as peripheral nerve segmental demyelination (62). Moreover, the etiologies of DPN caused by type 1 DM (T1DM) vs. type 2 DM (T2DM) may feature subtle distinctions (19). Notwithstanding, the general pathophysiology of
DPN is subsequently outlined in brief and reviewed in detail elsewhere (64, 69).

Microangiopathy has been shown to develop early in DPN, and these abnormalities may relate directly to subsequent nerve dysfunction. Additionally, DM has been associated with increases in blood viscosity, impaired oxygen release from blood to tissue, and dysfunctional structural alterations of red blood cells (50, 53). Thus these combined vascular or hemodynamic changes may contribute to chronic hypoxia and ischemia resulting in nerve damage (56, 69). Metabolic disturbances related to DM also play a causal role in the development of DPN. Neuronal dysfunction or death may be triggered by chronically elevated intraneuronal glucose concentrations, which upregulate several damaging pathways (64, 69). Additionally, neuronal damage may be imparted through the formation of advanced glycated end-products (AGEs) (69); dyslipidemia (65) and impairments in neuronal interaction with various neurotrophic factors (36, 61, 74).

**Key Points**
- DPN is a common complication of diabetes mellitus.
- The precise etiology of DPN has not been completely elucidated; however, it appears a variety of dysfunctional vascular and intraneuronal metabolic processes likely underlie its development.
- Despite greatly improved understanding of mechanisms underlying DPN, no treatments have been found that stop or slow its progression.

**NEUROMUSCULAR PATHOPHYSIOLOGY OF DPN**

Perhaps the most impactful consequence of DPN on the neuromuscular system is the accelerated loss of motor axons or motor units (3, 4, 29, 48), which is associated with neurogenic muscle atrophy (9-13, 32) and likely occurs later in the disease process, following sensory deficits (Fig. 1). DPN-related motor unit loss appears to follow a length-dependent progression (52) and is linked with disease duration and severity (29). Reduced motor unit number estimates (MUNEs), a technique performed using electromyography (EMG), have been documented in the intrinsic muscles of the feet (29), tibialis anterior (3), and first dorsal interosseous muscles (3). The progressive loss of motor units is associated with the development of muscle weakness, muscle atrophy, and intramuscular fatty infiltration (4, 32) (Fig. 2). It is reasonable to conclude from these studies that during the course of DPN, motor axons are progressively lost and collateral reinnervation is outpaced by further denervation, ultimately leading to the death of orphaned muscle fibers. Over years in DPN patients, this process leads to a clinically detectable loss of muscle mass and muscle weakness (4, 13, 32). In addition to neurogenic muscle atrophy, several investigations have demonstrated that patients with DPN have reduced muscle quality, as assessed by strength per unit of muscle area or volume, compared with matched controls (4, 32). This exacerbates the strength loss experienced by DPN patients beyond muscle atrophy alone.

Additionally, there is a concomitant slowing of skeletal muscle contractile properties associated with DPN (4, 32). This has been demonstrated by reduced rates of torque development and prolonged muscle relaxation rates (4, 32). These findings may be related to a preferential loss of type 2 (fast) motor units.
and muscle fibers. This is supported by reduced motor unit firing rates and an impaired ability to elicit postactivation potentiation (4, 28, 67). Muscle slowing could also be caused by impairments in actomyosin cross-bridge kinetics or alterations in whole muscle morphology, including fascicular disruption, which could reduce the number of sarcomeres in series, thereby reducing contractile velocity.

**Key Points**
- In more severe or longer duration cases of DPN, functionally relevant neuromuscular deficits manifest.
- DPN may result in the progressive loss of motor units (more slowly than in other neuromuscular diseases such as amyotrophic lateral sclerosis, but more quickly than in natural adult aging), which likely occurs in an axonal, length-dependent process.
- DPN patients have slowed muscle contractile properties and may experience unstable or intermittently failed neuromuscular signal transmission.

**FUNCTIONAL CONSEQUENCES OF DPN-RELATED NEUROMUSCULAR ALTERATIONS**

**Muscle weakness.** The various insults and alterations occurring within the neuromuscular system associated with DPN have important functional consequences. A well-documented impact of DPN is muscle weakness (9–13, 13, 63) or muscle wasting that is commonly observed in the intrinsic foot muscles (13, 63) and dorsiflexors (i.e., tibialis anterior; 4, 10). However, significant weakness has also been reported in the planar flexors and knee extensors of DPN patients (9, 13). DPN-related weakness is associated with the severity of neuropathy (10, 63), emphasizing the role of neurogenic factors. Also, not surprisingly weakness has been identified as having a close association with reduced mobility and gait speed (66). Importantly, in the early stages of DPN-related muscle weakness, the loss of strength may not be detectable using manual muscle testing alone (10).

**Loss of muscle power.** In addition to weakness, there is a DPN-related loss of muscle power (work per unit time; Refs. 32, 49). Muscle power is defined as the product of muscle strength and muscle contractile velocity. The decrement in muscle power is greater than the loss of strength alone (32); thus the slowing of muscle contractile properties mentioned previously likely plays a role in power-related decrements reported in DPN patients (4, 32). Because most activities of daily living involve dynamic action (i.e., movement), loss of muscle power may have more impactful functional consequences than the loss of muscle strength alone (49, 51). Indeed, loss of muscle power in the lower limbs has been reported as a key factor underlying impairments in both balance and gait in DM patients (47) and in older adults with impaired mobility (23, 43, 51). However, standard measures of strength, including manual muscle testing and isometric dynamometry, do not provide comprehensive information regarding muscle power. Advanced dynamometers, available commercially (e.g., Biodynamic System 4 or CSIMI Humac Norm), with isokinetic- and isotonic-modes are useful in assessing muscle power as well as examining muscle force generating capabilities across the entire range of motion in most major muscles groups (17, 32, 43). Previous studies have demonstrated dorsiflexion power loss is associated with the loss of tibialis anterior motor units in adult aging (43) and deficits in knee extensor power are a stronger predictor of functional ability than knee extensor strength in knee osteoarthritis (17). However, unfortunately these advanced dynamometers are costly, time consuming, and often inaccessible to many clinicians. Performance in clinical tests of functional capacity such as the timed up and go test or the shuttle walk test may be relatively preserved in DPN patients who feature early motor dysfunction only in distal muscles. Thus, at this time, clinically feasible and useful assessments of muscle power, particularly in distal muscle groups such as the dorsiflexors and planter flexors, remain limited.

**Changes in muscle fatigability.** DPN may also cause changes in neuromuscular endurance or fatigability, although those changes may depend on the severity of neuropathy and the specific fatigue task (6, 7, 9). One fatigue study examining muscle endurance in insulin-dependent DM without any clinical signs of DPN found a substantial decrease (approximately 50%) in knee extensor muscle time to fatigue during a sustained isometric task compared with controls (7). Reduced endurance of the DM group in that study was related to lower motor unit firing rates and reduced neuromuscular transmission velocity. Furthermore, a more recent study using a sustained, maximal, isometric contraction to induce fatigue, found DPN patients had significantly reduced neuromuscular endurance despite equally high levels of voluntary activation (6). Interestingly, endurance capacity under sustained high-intensity contractions may be linked to potential neuromuscular transmission failure in patients with relatively severe DPN (5, 39). Additionally, changes in muscle metabolism and blood flow associated with DM may play a role in altered fatigability. For example, DM has been associated with slowed oxygen kinetics and faster: PCr loss, pH decrease, and muscle deoxygenation relative to controls (50). Furthermore, DM is closely linked with dysfunction in microvasculature as well as slowed oxygen kinetics during exercise (16, 40), both of which could reduce skeletal muscle oxidative metabolism and adversely affect endurance.

**Increased fall risk.** Loss of muscle strength, speed, power, and endurance, particularly in lower limb muscles, may synergistically reduce functional capacity and contribute to altered gait, increased fall risk, and impaired balance in patients with DPN (Fig. 3). Additionally, neuromuscular control may be impaired or altered via the loss of motor units and increased average motor unit size, disturbing normal, orderly motor unit recruitment. When motor units are lost, and others enlarged, there may be a reduced ability to finely grade force output compared with healthy controls. This impairment, in conjunction with DPN-related sensory and proprioceptive deficits (62), may further contribute to altered gait, which is associated with an increased fall risk (44). Moreover, an increased fall risk is an especially important concern for DPN patients as their falls are substantially more likely to be injurious, and lead to bone fractures, poorly healing wounds, and chronic infections (33, 54, 55). Therefore, patient education and regular proper foot care is critical to reduce the risk of these debilitating and costly complications.
excitability based on the minimal current needed to depolarize a motor axon (34, 38, 39, 42). These measures have shown subtle differences in early DPN and thus may warrant further investigation as a possible tool in the early detection of progressive motor dysfunction.

Diabetic Neuropathy, the Neuromuscular System, and Exercise

Treatment options directed towards improvement of DPN are limited and have focused on pharmacological and dietary strategies linked to strict glycemic control as mentioned above (8). However, there is evidence of the benefits of exercise training-based interventions in treating and preventing the development or progression of DPN (46, 58). These may be related to exercise-related improvements in glycemic control, as well as other more direct effects on the neuromuscular system. Indeed, several reports suggest aerobic, strength, and balance training regimens all can prove effective in management of DPN (see Ref. 58 for brief review). Integrating these disparate investigations into specific and actionable clinical knowledge remains challenging due to the variety of patient populations, exercise modalities, length of interventions, and outcome measures used. Even so, it does appear that overall, increased physical activity levels and exercise training regimens have positive impacts on DPN.

One longitudinal study conducted over 4 yr found DM patients who engaged in a low-intensity aerobic exercise program (i.e., brisk treadmill walking) were less likely to develop clinical signs of DPN than DM patients who did not partake in the exercise program (15). The exercise group maintained normal motor nerve conduction velocity and vibration sensation, whereas the control group showed relative deterioration in those same measures. Interestingly, there were no differences between the exercise and control group in body mass index, waist circumference, or metabolic profile perhaps due to the low intensity. Thus the authors speculated the effect of exercise on DPN is more complex than simply related to improved glycemic control (15). Another report showed DPN patients in a combined strength and endurance exercise regimen of moderate intensity had increased clinical symptoms of neuropathy and improved cutaneous nerve branching as assessed by biopsy after only 10 wk of moderate-intensity training (37). No changes were detected in the motor nervous system, although the patients included in the study did not feature severe motor involvement at recruitment. Some studies investigating the effect of more intense strength training regimens reported large (30–60%) increases in strength, as well as increases in muscle quality in patients with DPN (2, 35, 41, 57). These studies showed improvements in balance and gait, as well as improved motor, sensory, and metabolic symptoms of DPN (2, 35, 41, 57). It is important to note that overall, increased physical activity levels and exercise training regimens have positive impacts on DPN.

Preventative strategies and early interventions are the mainstay of treatment for both DM and DPN (8, 60). Such strategies include aggressive glycemic control, as well as management of blood pressure and serum lipid levels using standard pharmacological therapy and lifestyle modifications (18, 19). Many patients with DM may have early, undiagnosed, or yet to be diagnosed neuropathy (19). These patients may be at greater risk for skin breakdown, ulceration, and other early complications of diabetic foot dysfunction, due to sensation loss or alteration (1). However, those in the early stages of DPN are unlikely to incur dysfunction related to large fiber sensory afferent or motor fibers such as significant proprioceptive issues including falls, muscle weakness, or gait impairment. Although quantitative EMG and MUNE, in addition to quantitative dynamometry, may not be applicable to early sensory changes in diabetic neuropathy, they may be useful measures of progressive disability in diabetes, particularly those individuals with severe disability (3). Another potentially useful assessment for identifying and following patients with DPN may include electromyographic measures of peripheral nerve excitability (14, 38, 39). These measures provide assessment of the degree of excitability of a nerve and are described in detail elsewhere (14, 38, 39). Excitability studies have shown DPN is associated with shortened nerve refractory periods and decreased excitability based on the minimal current needed to depolarize a motor axon (34, 38, 39, 42). These measures have shown subtle differences in early DPN and thus may warrant further investigation as a possible tool in the early detection of progressive motor dysfunction.
ulcers) or co-morbidities (e.g., cardiac disease). For example, the patient with foot ulceration or major lower limb sensory loss should likely minimize chronic, repetitive, weight-bearing exercise to avoid exacerbating that condition.

Exercise training can indirectly treat or prevent DPN by contributing to the maintenance of healthy glycemic control (see Ref. 22 for review). This is the most discussed and best understood mechanism by which aerobic or strength training can impact DM, and by extension, DPN. Exercise can improve glycemic control primarily via increased insulin sensitivity, increased muscle mass, and increased substrate utilization (8, 20). However, exercise may be beneficial to DPN patients, and those at risk of developing DPN, through more direct mechanisms related to neuromuscular health. This could include upregulation of various neurotrophic factors (e.g., BDNF, IGF; Refs. 24, 27, 31), improved nerve blood flow (45), and improved neuronal resiliency related to intracellular metabolic stressors such as inflammation (30, 68). Although further research is necessary to uncover the precise physiological mechanisms underlying exercise-related benefits to neuromuscular health in DPN, at this time it appears that chronic exercise represents an accessible and inexpensive intervention for individuals with DPN.

**SUMMARY AND CONCLUSIONS**

Severe DPN has debilitating impacts on the neuromuscular system that can be underappreciated clinically. The assessment of DPN would benefit from more precise methods for diagnosis and prognostication. Advances in electrophysiological techniques may have the potential to provide greater information regarding DPN and its motor system impacts as well as the effects of different interventions. Finally, patients with DPN appear to benefit from exercise regimens both via a decreased severity of diabetes but also potentially through direct effects on peripheral nerves and skeletal muscle. Both cardiovascular and strength training regimens are both likely to impart meaningful beneficial effects to DPN patients through improvements in glycemic control and direct effects on the neuromuscular system.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

M.D.A., T.J.D., C.L.R., and K.K. conception and design of research; M.D.A. and K.K. prepared figures; M.D.A., T.J.D., C.L.R., and K.K. drafted manuscript; M.D.A., T.J.D., C.L.R., and K.K. edited and revised manuscript; M.D.A., T.J.D., C.L.R., and K.K. approved final version of manuscript.

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