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# Molecular Underpinnings of Diabetic Polyneuropathy

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**To the Editor:** Allen and colleagues<sup>2</sup> provided an in-depth review of the pathophysiology and functional outcomes of diabetic polyneuropathy (DPN) among patients with diabetes mellitus (DM). As explained,<sup>2</sup> DPN often manifests in a symmetrical and length-dependent pattern affecting distal portions of long peripheral nerves of patients with DM,<sup>11</sup> Here we highlight the molecular pathogenesis within the soma of the motoneuron, which may also inform clinical treatment. Although DPN manifests in neuronal axons, the deleterious molecular cascade begins within the soma of the peripheral nerve located within the anterior horn of the spinal cord. Glucose is transported into the milieu of nervous tissue independent of insulin,<sup>5</sup>

which results in a hyperglycemic metabolic milieu of nervous system tissue in patients with DM. Excessive glucose is metabolized into sorbitol and fructose, and both activate advanced glycation end products (AGEs), resulting in molecular oxidative stress.<sup>3</sup> Oxidative stress within the soma triggers withdrawal of the longest (typically most distal) nerve axons from their distal terminals *without* cellular death.<sup>12</sup> This observation is clinically relevant, because there is the potential for recovery from structural damage to the axon before death of the nerve soma.<sup>9</sup> The precise mechanism by which oxidative stress triggers distal axonal retraction is unclear but likely involves disruption of sodium-potassium pump activity (Na<sup>+</sup>/K<sup>+</sup>-ATPase)<sup>10</sup> and downregulation of insulin-like growth factor 1 (IGF-1),<sup>8</sup> leading to disruption of the neuromuscular junction. Consequently, denervation of distal muscle fibers occurs and the soma signals lateral sprouting of the retracted distal axon to innervate more proximal muscle fibers.<sup>4</sup> The net result is a loss of motor unit numbers,<sup>12</sup> an increase in the size of surviving motor units,<sup>12</sup> and subsequent reduction of maximal muscle force<sup>1</sup> and control of muscle force.

The distinction between the pathogenesis beginning within the neuronal axon or soma could have important implications for clinical interventions. For example, the nerve soma could be targeted with interventions (e.g., pharmacological) to preserve the function of the neuron. Clinically, the most sensitive tools identified to date for assessing DPN-related impairments of neuromuscular function (compared with DM patients without DPN) are isometric strength of distal muscles (e.g., plantar and dorsiflexors)<sup>1,6</sup> and the timed up and go (TUG) test.<sup>7</sup> Thus the molecular underpinnings of DPN are likely related to the functional outcomes discussed by Allen and colleagues,<sup>2</sup> and further understanding the involved mechanisms may help guide clinical practice.

## **Disclosures**

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

## **Author Contributions**

J.S. drafted manuscript; J.S. and S.K.H. edited and revised manuscript; J.S. and S.K.H. approved final version of manuscript.

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