Reply to Senefeld and Hunter: Physiology in Medicine: Neuromuscular consequences of diabetic neuropathy. The authors’ reply

TO THE EDITOR: We thank Senefeld and Hunter (1) for their interest and for providing a thoughtful discussion of the distinction between neuron cell body and axonal cellular processes implicated in diabetic polyneuropathy (DPN). They succinctly highlight several of the key underlying pathophysiological mechanisms leading to the development of DPN. We agree neuronal stress, dysfunction, and death are primarily related to harmful consequences of hyperglycemia and subsequent high intraneuronal concentrations of glucose. Thus controlling blood glucose remains the primary goal in managing diabetes mellitus and DPN. However, it is important to recognize that there is a complex array of pathological mechanisms at the cellular level leading to the development of DPN. One mechanism is the potential role played by dyslipidemia in nerve cell damage.

The notion that dyslipidemia contributes to the development of DPN has garnered more attention relatively recently (see Ref. 2, 3 for detailed reviews). Evidence is derived from cultured neuronal cell lines, experimental rodent models of diabetes, and large-scale studies investigating both patients with type 1 and type 2 diabetes mellitus. Vincent and colleagues proposed three main mechanisms by which dyslipidemia causes nerve cell damage: 1) free fatty acids; 2) oxidized and glycated low-density lipoproteins (LDLs); and 3) oxysterols. Detailed description of these pathways is provided elsewhere (2, 3), but we will summarize them briefly here.

Much like glucose, high levels of serum free fatty acids (FFA) may also accumulate intraneuronally. This accumulation of FFAs can lead to inappropriate lysosomal-mitochondrial activated cellular injury and oxidative stress. Additionally, given the oxidizing milieu present in diabetes mellitus, LDLs are more likely to become glycated or oxidized, forming ox-LDLs. These damaging molecules can be internalized by the neuronal soma and initiate pathways related to NADPH oxidase that induce substantial oxidative stress. Similar to LDLs, serum cholesterol is subjected to an oxidative environment leading to increased formation of oxysterols, which have been shown to initiate mitochondrial-mediated cell death in studies using cultured neurons. Finally, dyslipidemia may indirectly impact neuronal health by promoting insulin resistance in skeletal muscle and thereby promoting hyperglycemia.

Thus, although glycemic control remains the primary goal in managing DPN and preventing its progression, there is evidence that dyslipidemia is another key factor. This raises the importance of maintaining optimal blood lipid profiles in patients with diabetes (and DPN) through diet, exercise, and pharmacological intervention, including, but not limited to, statin therapy. Furthermore, it highlights additional cellular pathways as possible targets for future therapeutic interventions in DPN (2).

It is likely that in DPN multiple targets are important not only in initial prevention but also in reducing the disease burden when more significant impairment of the neuromuscular system is present. It could be argued that a multifactorial approach will likely have a greater chance of maintaining any preserved neuromuscular function available in these more severely affected DPN patients. This is significant given the increased risks of harm due to impaired mobility, decreased functional capacity, altered gait, and fall risk.

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. approved final version of 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. provided laboratory space.

REFERENCES