

# Quality of Life for DN Patients

**A**s Yogi Berra said, "It is difficult to predict anything, especially the future." This is particularly true if present focuses upon do not bear on the greatest impact. That is to say, our focus on diabetic neuropathy (DN) is on the major presenting symptoms such as pain, foot ulcers or amputations. This is no doubt because of the 85,000 amputations each year in the US and the 87% contribution of neuropathy to limb loss at an annual cost of \$37 billion. What has been neglected in this area has been the impact of neuropathy on QOL and what constitutes the major factors contributing to loss in QOL and what can be done to find the road to a desired destination.



Aaron I. Vinik, MD, PhD  
Associate Medical Editor

## SPECIFIC FOR DN

Etta Vinik and colleagues at the Strelitz Diabetes Institutes reported on the development of a QOL tool specific for DN, sensitive to disordered function of the specific fiber types. They used the tool in two large populations of patients to determine if their a priori division of the domains according to the physiologic function would stand up to the test of factor analysis.<sup>1</sup> One population included about 400 people from a worldwide study of DN in which patients were classified as having stage 1A or 1B neuropathy. The second population of 240 patients included healthy controls, people with diabetes and no neuropathy and people with diabetes and varying severity of neuropathy. Factor analysis revealed five domains similar to that determined a priori. Physical functioning accounted for almost two-thirds of scores contributing to the total QOL score (Figure 1). This factor grossly exceeded the scores for symptoms, cognitive dysfunction, small fiber symptoms and autonomic symptoms.

It became clear that our focus on this condition needs to be redirected and that targeting of weakness or loss of physical functioning could contribute significantly to improving the well being of the person with DN. One needs to ask then what the cause of weakness is in patients with DN. These are the proximal and the distal large fiber neuropathies.

For many years proximal neuropathy and its treatment were neglected with the anticipation that the patient would eventually recover. The condition has a number of synonyms, such as proximal neuropathy and femoral neuropathy. Proximal motor neuropathy can be clinically identified based on recognition of common features: 1) primarily affects the elderly; 2) gradual or abrupt onset; 3) begins with pain in the thighs and hips or buttocks; 4) followed by signif-

icant weakness of the proximal muscles of the lower limbs with inability to rise from the sitting position without using Gower's maneuver; 5) it begins unilaterally and spreads bilaterally; 6) coexists with distal symmetric polyneuropathy; and 7) spontaneous muscle fasciculation, or provoked by percussion. The condition is secondary to a variety of causes that while unrelated to diabetes occur more often in the diabetic population.

## WITHIN DAYS OF THERAPY

It includes patients with chronic inflammatory demyelinating polyneuropathy (CIDP), monoclonal gammopathy, circulating GM1 antibodies and antibodies to neuronal cells and inflammatory vasculitis.<sup>2,3</sup> It was formerly thought to resolve spontaneously in 1.5 to 2 years, but now, if found to be immune-mediated, can resolve within days on immunotherapy. The condition is readily recognizable clinically.<sup>4</sup> In the classic form of diabetic amyotrophy axonal loss is the predominant process, and the condition coexists with distal symmetric polyneuropathy (DSPN).<sup>5</sup> In proximal neuropathies electrophysiologic evaluation reveals lumbosacral plexopathy.<sup>4</sup> In contrast, if demyelination predominates and the motor deficit affects proximal and distal muscle groups, the diagnosis of CIDP, monoclonal gammopathy of unknown significance (MGUS) and vasculitis should be considered.<sup>6,7</sup> It seems probable that these conditions occur more commonly in people with diabetes.<sup>8-10</sup>

## MORE FREQUENT IN DIABETIC PATIENTS

Vinik et al<sup>11</sup> (Figure 2) have pointed out that almost half the patients with proximal neuropathies have a vasculitis and all but 9% have CIDP or MGUS or a ganglioside antibody syndrome.<sup>12</sup> Sharma examined over 1,000 patients with neurologic disorders and found that CIDP was 11 times more frequent among their diabetic than nondiabetic population.<sup>9</sup>

Treatments include IV immunoglobulin for CIDP, plasma exchange for MGUS, steroids and azathioprine for vasculitis

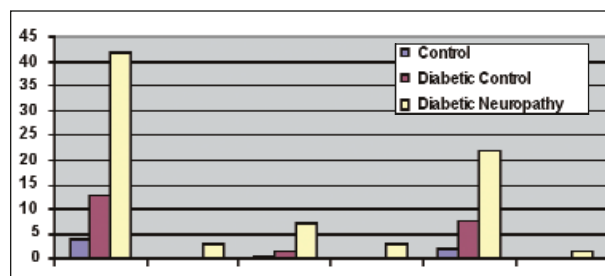


Figure 1. Physical functioning is a major determinant of QOL in diabetes.

and withdrawal from drugs or agents that may cause a vasculitis.<sup>13</sup> IV methylprednisone or dexamethasone may resolve the condition within days. This is indeed a salutary state for a condition that clearly contributes to loss of QOL and for which little was done to abrogate the process until now.

Large fibers subservise motor function, vibration detection, position sense, and cold thermal perception. They are the myelinated, rapidly conducting fibers that begin in the toes and have their first synapse in the medulla oblongata. They tend to be affected first because of their length and the tendency in diabetes for nerves to "die back." Because they are myelinated, they are the fibers represented in the EMG, and subclinical abnormalities in nerve function are readily detected. The symptoms may be minimal: sensation of walking on cotton, floors feeling strange, inability to turn the pages of a book, or inability to discriminate among coins.

Loss of vibration detection predisposes individuals with diabetes to instability, falling and decreased QOL.<sup>14,15</sup> Impairment of vibration detection is associated with "intrinsic minus" feet that predispose the foot to ulceration and amputation.

### LARGE AND SMALL FIBER DAMAGE

Most patients with DSPN have a variety of neuropathy with large and small nerve fiber damages. In the case of DSPN, a glove and stocking distribution of sensory loss is almost universal.<sup>16</sup> Early in the neuropathic process, multifocal sensory loss also might be found. In some patients, severe distal muscle weakness can accompany the sensory loss resulting in an inability to stand on the toes or heels. Some grading systems use this as a definition of severity.<sup>1</sup>

Identification of the impact of large fiber neuropathy on measures of stability, balance and gait have previously been reported.<sup>15</sup> Diabetic neuropaths are 15 times more likely to fall; patients aged 18 years and older have loss of vibration detection and weakness of foot dorsiflexion.<sup>15</sup>

Patients with large fiber neuropathies are uncoordinated and ataxic and as a result, they are more likely to fall.<sup>17</sup> Strength training in these patients resulted in improved coordination and balance quantifiable with backward tandem walking.<sup>18</sup> Thus, it is vital to embark on a program of strength training and improvement of balance. It is clear that the cause of fractures in older subjects is falling and not osteopenia. The potential to mitigate or even abrogate this predisposition adds a whole new dimension to what has become a vexing problem in people with diabetes and the aging population.

DPN is a common diabetic microvascular complication, thus, improvement of sensory symptoms and QOL<sup>19</sup> is recognized as an important clinical endpoint,<sup>20</sup> particularly if there is improved nerve function. The Ad

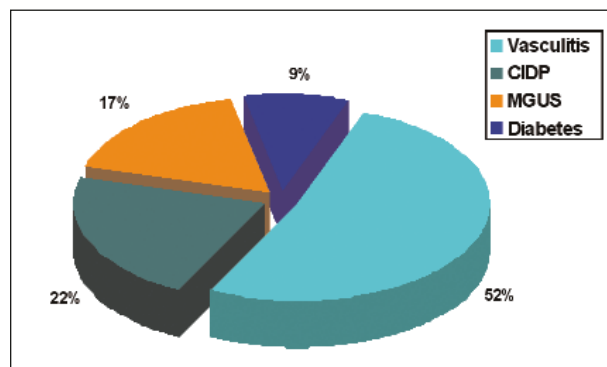


Figure 2. Disabling peripheral neuropathies in older adults.

Hoc Panel on Endpoints for Diabetic Neuropathy Trials has recommended that the effectiveness of potential DPN agents meet three criteria: 1) the agent should significantly reduce positive neuropathic sensory symptoms; 2) improvements should not be related to worsening of neuropathy; and 3) the agent should result in clinically meaningful improvements in positive neuropathic sensory symptoms.<sup>20</sup> Clearly knowing where we are going and the correct path to follow will ensure that we are not lost when we arrive. QOL and ADLs should surely be on the path of nervous system restoration. ■

- Vinik EJ, Hayes C, Oglesby A, et al. Identification of factors in the nerve fiber specific quality of life (QOL-DN) inventory that reflect QOL and health status. *Diabetes*. 2004;53:A295.
- Vinik AI, Pittenger GL, Milicevic Z, et al. Autoimmune mechanisms in the pathogenesis of diabetic neuropathy. *Molecular Mechanisms of Endocrine and Organ Specific Autoimmunity*. 1st ed. Eisenbarth RG, Ed. Georgetown, Landes Company, 1998:217-251.
- Steck AJ, Kappos L. Gangliosides and autoimmune neuropathies: classification and clinical aspects of autoimmune neuropathies. *J Neurol Neurosurg Psychiatry*. 1994;57 (Suppl):26-28.
- Sander HW, Chokroverty S. Diabetic amyotrophy: current concepts. *Semin Neurol*. 1996;16:173-178.
- Said G, Goulon-Goreau C, Lacroix C, et al. Nerve biopsy findings in different patterns of proximal diabetic neuropathy. *Ann Neurol*. 35:559-569.
- Krendel DA, Costigan DA, Hopkins LC. Successful treatment of neuropathies in patients with diabetes mellitus. *Arch Neurol*. 1995;52:1053-1061.
- Britland ST, Young RJ, Sharma AK, et al. Acute and remitting painful diabetic polyneuropathy: a comparison of peripheral nerve fibre pathology. *Pain*. 1992;48:361-370.
- Stewart JD, McKelvey R, Durcan L, et al. Chronic inflammatory demyelinating polyneuropathy (CIDP). *J Neurol Sci*. 1996;142:59-64.
- Sharma K, Cross J, Farronay O, et al. Demyelinating neuropathy in diabetes mellitus. *Arch Neurol*. 2002;59:758-765.
- Vinik AI. Diabetic neuropathy, mobility and balance. *Geriatric Times*. 2003;4(1),13-15.
- Vinik AI. Diagnosis and management of diabetic neuropathy. *Clinics in Geriatric Medicine*. 15:293-319, 1999.
- Milicevic Z, Pittenger GL, Stansberry KB, Vinik AI. Raised anti-GM1 Ab titers in a subset of patients with distal symmetric polyneuropathy (DSPN). (Abstract). *Diabetes*. 1997;46:125A.
- Vinik AI and Mehrabyan A. Diabetic Neuropathies. *Medical Clinics of North America*. 88(4), 947-999. 2004.
- Resnick H, Vinik AI, Schwartz A, et al. Independent effects of peripheral nerve dysfunction on lower-extremity physical function in old age. *Diabetes Care*. 2000;23:1642-1647.
- Resnick HE, Stansberry KB, Harris TB, et al. Diabetes, peripheral neuropathy, and old age disability. *Muscle Nerve*. 2002;25:43-50.
- Vinik AI, Holland MT, LeBeau JM, et al. Diabetic neuropathies. *Diabetes Care*. 1992;15:1926-1975.
- Cavanagh PR, Derr JA, Ulbrecht JS, et al. Problems with gait and posture in neuropathic patients with insulin-dependent diabetes mellitus. *Diabet Med*. 1992;9:469-474.
- Nelson ME, Fiatarone MA, Morganti CM, Trice I, Greenberg RA, Evans WJ. Effects of high-intensity strength training on multiple risk factors for osteoporotic fractures. A randomized controlled trial. *JAMA*. 1994; 272:1909-1914.
- Vinik E, Stansberry K, Doviak M, et al. Norfolk Quality of Life (QOL) Tool: Scoring and reproducibility in healthy people, diabetic controls and patients with neuropathy. *Diabetes*. 2003;52(Suppl 1), A198.
- Apfel SC, Asbury A, Brill V, et al. Positive neuropathic sensory symptoms as endpoints in diabetic neuropathy trials (Abstract). *Journal of the Neurological Sciences*. 2001;189:3-5.