Reviews in Endocrine & Metabolic Disorders 2005;6:117–127

Diabetic Neuropathy in Older Adults

Kara A. Witzke[1] and Aaron I. Vinik[2]

[1]Department of Health, Physical Education, & Exercise Science, Norfolk State University, 700 Park Ave., Norfolk, VA 23504
[2]Strelitz Diabetes Institutes, Department of Internal Medicine, Eastern Virginia Medical School, 855 West Brambleton Avenue, Norfolk, VA 23510

Key Words. **peripheral neuropathy, large fiber neuropathy, entrapment syndrome, distal polyneuropathy (DPN), painful neuropathy**

Introduction

Diabetic neuropathies (DN) encompass a wide range of nerve abnormalities and are common, with prevalence rates reported between 5–100% depending on the diagnostic criteria [1–3]. Diabetic neuropathies affect both peripheral and autonomic nervous systems and cause considerable morbidity and mortality in both Type 1 and Type 2 diabetic patients. Diabetic neuropathies are the most common forms of neuropathy, they account for more hospitalizations than all other diabetic complications combined, and are responsible for 50–75% of non-traumatic amputations [4,5]. In older adults with diabetes, peripheral neuropathies are especially troublesome due to their detrimental effects on stability, sensorimotor function, gait, and activities of daily living [6–8]. In this review, we present and discuss the most recent approaches to the treatment of the common forms of diabetic neuropathy, including symmetric, focal and diffuse neuropathies (Table 1, Fig. 1). We will also provide the reader with algorithms for recognition and management of common pain and entrapment syndromes, and a global approach to recognition of syndromes requiring specialized treatments based upon our improved understanding of their etiopathogenesis. A comprehensive evaluation of autonomic neuropathy is beyond the scope of this review, but the reader is referred to two excellent reviews on this topic [9,10].

Pathogenic mechanisms

Figure 2 shows our current view on the pathogenesis of diabetes. The figure depicts multiple etiologies, as discussed above, including metabolic, vascular, autoimmune, oxidative and nitrosative stress, and neurohormonal growth-factor deficiency. Impaired blood flow and endoneurial microvasculopathy, mainly thickening of the blood vessel wall or occlusion, play a critical role in the pathogenesis of diabetic neuropathy. Metabolic disturbances in the presence of an underlying genetic predisposition, cause reduced nerve perfusion. Animal and human studies alike have shown major defects arising from chronic hyperglycemia and altered lipid metabolism [11]. Oxidative stress-related mechanisms are also important in vascular dysfunction, and tend to increase vasoconstriction. These alterations in blood flow patterns appear to be important in the understanding of the arterio-venous shunting seen in vasa nervorum, which may occur in part due to autonomic nerve dysfunction.

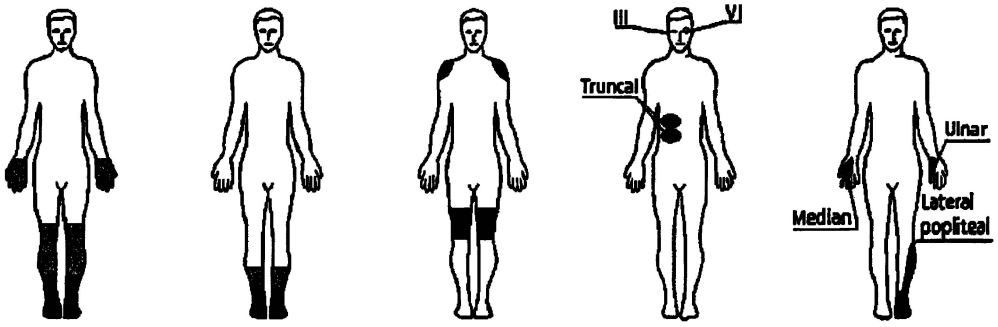
Clinical Presentation and Diagnosis

Focal neuropathies (mononeuropathies and entrapment syndromes)

Mononeuropathies occur primarily in older adults. Their onset is generally acute, associated with pain, and they heal spontaneously, usually within 6–8 weeks. These neuropathies are caused by vascular obstruction, typically in the cranial nerves III, VI, and VII, ulnar, median, and peroneal. Mononeuropathies must be distinguished from entrapment syndromes which start slowly, progress and persist without intervention (Table 2).

Common entrapment sites in diabetic patients involve the median, ulnar, peroneal, lateral cutaneous nerve of the thigh, and the tibial nerve in the tarsal canal. Their onset is gradual and is usually limited to a single nerve [12]. Carpal tunnel syndrome is the most common entrapment syndrome, affecting one in three diabetic patients [13]. It occurs three times more frequently in patients with diabetes compared with the normal healthy population [14] and may be related to diabetic cheiroarthropathy, repeated undetected trauma, metabolic changes, or an accumulation of fluid or edema within the confined space of the carpal

Address correspondence to: Aaron I. Vinik, The Strelitz Diabetes Institutes, 855 West Brambleton Avenue, Norfolk, VA 23510.
E-mail: vinikai@evms.edu



Large fiber Neuropathy	Small fiber Neuropathy	Proximal motor Neuropathy	Acute mono Neuropathies	Pressure Palsies
Sensory loss: 0→ +++ (Touch, vibration) Pain: + → +++ Tendon reflex: N → ↓↓↓ Motor deficit 0 → +++	Sensory loss: 0 → + (thermal , allodynia) Pain: + → +++ . Tendon reflex: N → ↓ Motor deficit: 0	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: ↓↓ Proximal Motor deficit: + → +++.	Sensory loss: 0 → + Pain: + → +++ Tendon reflex: N Motor deficit: + → +++	Sensory loss in Nerve distribution: + → +++ Pain: + → ++ Tendon reflex: N Motor deficit: + → +++

Fig. 1. Schematic representation of different clinical presentations of diabetic neuropathy.

tunnel [15]. Surgical treatment of entrapment syndrome neuropathies are effective, but the decision to proceed with surgery should be based on severity of symptoms, appearance of motor weakness and failure of non-surgical treatment.

Diffuse neuropathies (proximal motor neuropathies)

Proximal motor neuropathy can be clinically identified based on proximal muscle weakness and muscle wasting. It may be symmetric or asymmetric in distribution, and is sometimes associated with pain in the lateral aspect of the thigh. Patients usually present with weakness of the iliopsoas, obturator and adductor muscles, together with relative preservation of the gluteus maximus and minimus, and hamstrings [16,17]. Those affected have great difficulty rising out of chair unaided, although heel or toe standing is surprisingly good. In the classic form of diabetic proximal motor neuropathy, axonal loss is the predominant process and the condition coexists with distal symmetric polyneuropathy (DPN) [18]. Electrophysiologic evaluation reveals lumbosacral plexopathy [19]. Common features include:

1. Primarily affects the elderly
2. Onset may be gradual or acute

Table 1. Classification of diabetic neuropathy

Focal neuropathies
- mononeuritis
- entrapment syndromes

Diffuse neuropathies
- proximal motor (amyotrophy)
  - co-existing chronic inflammatory demyelinating polyneuropathy (CIPD)
  - monoclonal gammopathy of undetermined significance (MGUS)
  - circulating GM1 antibodies and antibodies to neuronal cells
  - inflammatory vasculitis

Generalized symmetric polyneuropathies
- acute sensory
- autonomic
- chronic sensorimotor distal polyneuropathy (DPN)
  - large fiber
  - small fiber

Adapted from Thomas [46] and Vinik [22].
Note: Clinicians should be alert for treatable neuropathies occurring in diabetic patients including CIDP, monoclonal gammopathy, vitamin B_{12} deficiency etc.

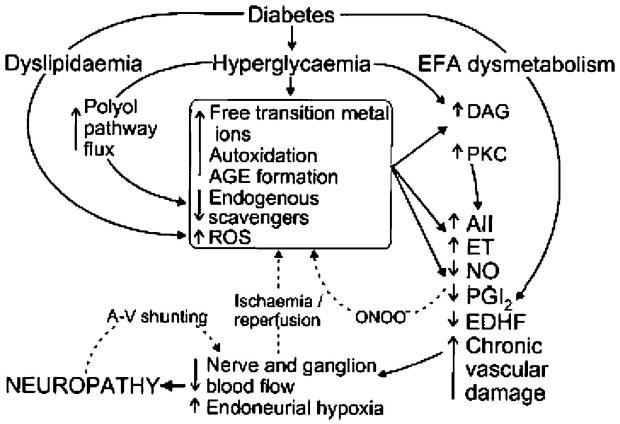


Fig. 2. Pathogenesis of diabetic neuropathy. AII, angiotensin II; AGE, advanced glycation end product; A-V, arteriovenous; DAG, diacylglycerol; EDHF, endothelium-derived hyperpolarizing factor; EFA, essential fatty acid; ET, endothelin-1; NO, nitric oxide; $ONOO^-$, peroxynitrite; PGI_2, prostacyclin; PKC, protein kinase C; ROS, reactive oxygen species [51].

Table 2. *Comparison of features of mononeuropathy and entrapment syndromes*

Mononeuropathies	Entrapment syndrome
Onset sudden	Onset gradual
Usually single nerve	Single nerves exposed to trauma
Common nerves: cranial III, IV, VI, VII, peroneal, sural, sciatic, femoral, ulnar, median	Common nerves: median, ulnar, peroneal, lateral cutaneous of the thigh, tibial
Not progressive, resolve spontaneously	Progressive
Treatment: symptomatic	Treatment: rest, splints, diuretics, steroid injections, surgery for weakness

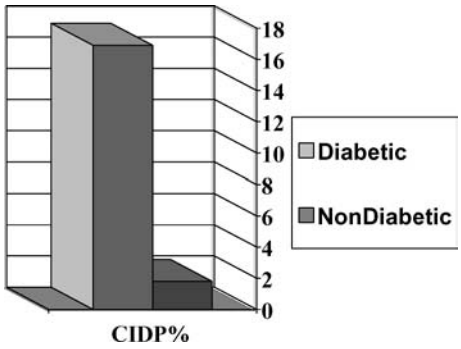


Fig. 4. *Frequency of chronic inflammatory demyelinating polyneuropathy (CIDP) [24]. There is an 11-fold greater frequency of CIDP in patients with diabetes.*

3. Begins with pain in the thighs and hips or buttocks
4. Pain followed by significant weakness of the proximal muscles of the lower limbs with inability to rise from the sitting position (positive Gower's maneuver)
5. Begins unilaterally and spreads bilaterally
6. Coexists with DPN
7. Spontaneous muscle fasciculation, or provoked by percussion

Proximal motor neuropathy is now recognized as being secondary to a variety of causes unrelated to diabetes, but which occur more frequently in patients with diabetes than in the general population. It includes patients with chronic inflammatory demyelinating polyneuropathy (CIDP), monoclonal gammopathy of undetermined significance (MGUS), circulating GM1 antibodies and antibodies to neuronal cells, and inflammatory vasculitis [20,21]. Vinik et al. [22] (Fig. 3) found that almost half of patients with proximal neuropathies have a vasculitis and all but 9% have CIDP, MGUS, or a ganglioside antibody syndrome [22,23]. Sharma examined over 1000 patients with neurologic disorders and found that CIDP was 11× more frequent among diabetic than non-diabetic patients (Fig. 4) [24].

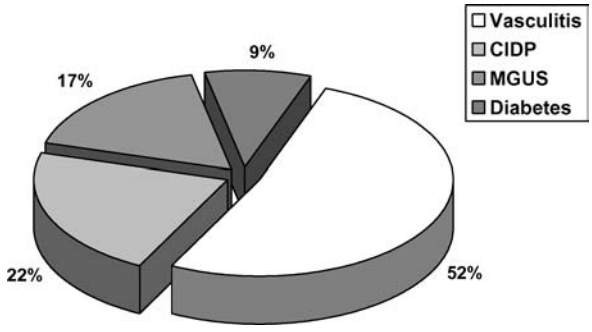


Fig. 3. *Disabling peripheral neuropathies in older adults [24].*

In contrast, if demyelination predominates and the motor deficit affects proximal and distal muscle groups, the diagnosis of CIDP should be considered. It is important to divide proximal syndromes into these two subcategories since the CIDP variant responds dramatically to intervention [22,24,25], with IVIG, plasma phereis, steroids and immunosupperesative agents [22] whereas proximal motor neuropathy runs its own course over months to years (Table 3). Until more evidence is available, we consider them as separate syndromes.

These conditions should be distinguished from spinal stenosis syndromes common in older individuals, which occur due to: (1) encroachment on nerve roots as they emerge from the spinal cord, (2) osteophytes which narrow joint space and cause compression, (3) hypertrophy of the ligamentum flavum due to aging, (4) disk dehydration due to aging, and (5) arachnoiditis. If compression occurs at the level of T12 and L1/2, the vascular system may be involved. This often causes claudication during downhill walking, and is relieved with spinal flexion. Nerve root compression is more typical at L5/S1 and thus in difficult cases it may be necessary to obtain an MRI of the lumbosacral spine. Diagnosis is critical since therapy may range from simple physical therapy to surgical decompression if symptoms are severe or if motor paralysis exists.

Table 3. *Decline in neurologic function between 20–80 years*

Function	Percent dysfunction
Vibratory sensation	97
Stability (Rombergism)	32
Handwriting speed	30
Handgrip strength	22
Ankle jerk	9
Ataxia (finger nose test)	8
Pain perception	0

Data from: [47–49].

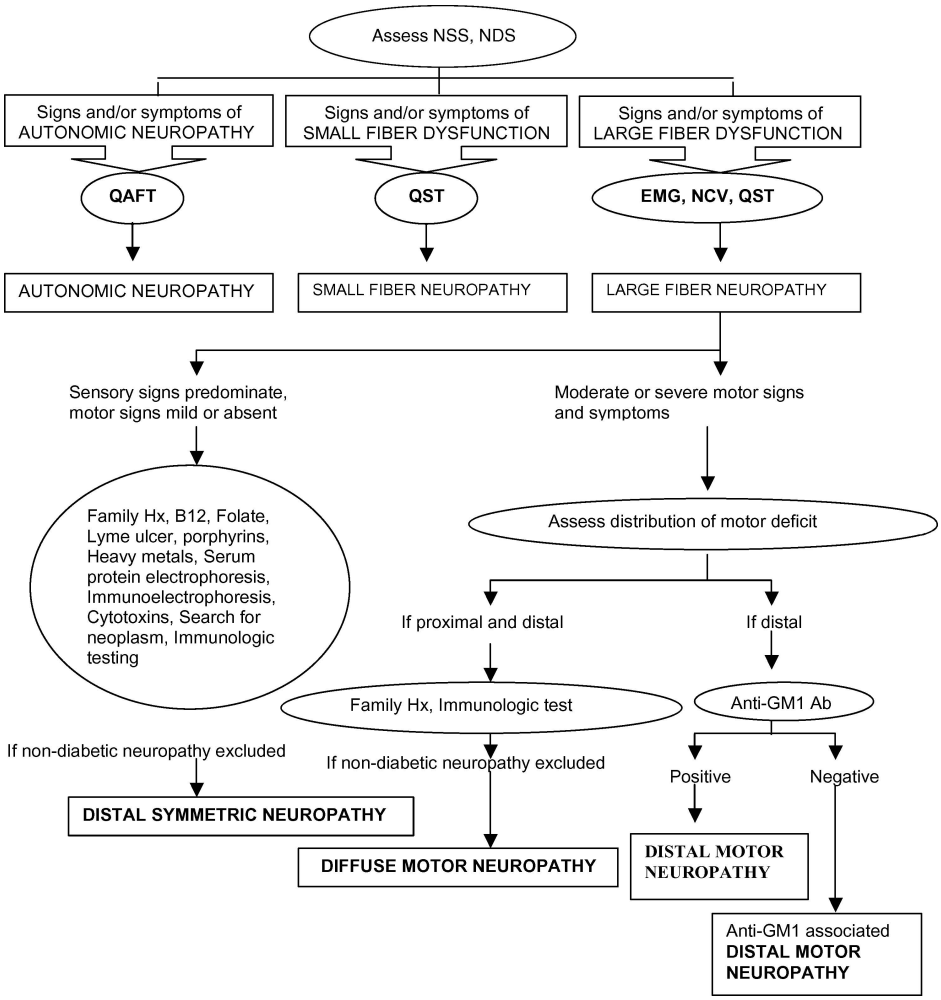


Fig. 5. *A diagnostic algorithm for assessment of neurologic deficit and classification of neuropathic syndrome is given below. NSS; Neurological Symptom Score, NDS; Nerve Disability Score, QST; Quantitative Sensory Test, QAFT; Quantitative Autonomic Function Test, EMG; Electromyography, NCV; Nerve Conduction Velocity [52].*

Chronic sensorimotor distal polyneuropathy (DPN)

Chronic sensorimotor distal polyneuropathy (DPN) is the most common and widely recognized form of diabetic neuropathy. The onset is usually insidious, following stress or initiation of therapy for diabetes. DPN may be either sensory or motor, and involve small fibers, large fibers, or both [26]. Initial neurologic evaluation should focus on detection of the specific part of the nervous system affected by diabetes. Most patients with DPN have a combination of both large and small nerve fiber involvement.

Large fiber neuropathies. A majority of neuropathies in older adults involve large fibers. Large fiber neuropathies may involve sensory and/or motor nerves, and most patients will present with a "glove and stocking" distribution of sensory loss [27]. These tend to be the neuropathies of signs rather than symptoms. They are manifested by reduced vibration (often the first objective evidence of neuropathy) and position sense, weakness, muscle wasting and depressed tendon reflexes. Early in the course of the neuropathic process, multifocal sensory loss might also be found (Table 4). The symptoms may be minimal, such as a sensation of walking on cotton, floors feeling "strange", inability to turn the pages of a book, or inability to discriminate among coins. In some patients, severe distal muscle weakness can accompany the sensory loss resulting in an inability to stand on the toes or heels.

Older adults with large fiber neuropathies have difficulty stabilizing their bodies when walking on irregular surfaces, with concomitant impairment in reaction time and balance [6]. This lack of peripheral sensory input increases the risk of falling and fracture in these patients. In the Women's Health and Aging study, women with diabetes reported difficulty in performing 14 of 15 daily tasks which included walking 2–3 blocks, lifting 10 pounds, using a telephone, and bathing [7]. Failure to perform basic activities of daily living readily compromise an

Table 4. *Differential diagnosis of distal symmetric polyneuropathy*

Type	Syndrome
Congenital/Familial	Charcot Marie Tooth
Traumatic	Entrapment Syndromes
Inflammatory	Sarcoidosis
	Leprosy
	Lyme Disease
	HIV
Neoplastic	Carcinoma—paraneoplastic syndromes
	Myeloma, Amyloid
	Reticuloses, leukemias, lymphomas
Metabolic/Endocrine	Diabetes mellitus
	Uremia
	Pernicious Anemia (B12 deficiency)
	Hypothyroidism
	Porphyria (Acute Intermittent)
Vascular	Diabetes, vasculitis
Toxic	Alcohol
	Heavy metals (lead, mercury, arsenic)
	Hydrocarbons, chemotherapeutic drugs
Autoimmune	Diabetes
	PLA syndrome
	Chronic Inflammatory Demyelinating Neuropathy
	Multifocal Motor Neuropathy
	Guillain Barre Syndrome

individual's independence and quality of life, which increases mortality and morbidity in this susceptible population.

In recent years, several inexpensive devices have been developed for the assessment of somatosensory function, including vibration, thermal energy, and light-touch perception. These instruments allow for the noninvasive assessment of cutaneous sensory functions, which correlate with specific neural fiber function. In addition to the above modalities, quantitative sensory tests (QST) are available for the assessment of pain threshold and cutaneous current perception [26].

Clinical manifestations of large fiber neuropathies

- Impaired vibration perception and position sense
- Depressed tendon reflexes
- Dull (like a toothache), crushing or cramp-like pain in the bones of the feet
- Sensory ataxia (waddling like a duck)
- Wasting of small muscles of feet with hammertoes and weakness of hands and feet
- Shortening of the Achilles tendon with equinus.
- Increased blood flow to the foot (hot foot) with increased risk of Charcot neuroarthropathy.

Small fiber neuropathies. Small nerve fiber dysfunction usually occurs early and is often present without objective signs or electrophysiologic evidence of nerve damage [26]. It manifests first in the lower limbs with symptoms of pain and hyperalgesia, followed by a loss of thermal sensitivity and reduced light-touch and pinprick sensation [28]. Small unmyelinated C-fibers control pain sensation, warm thermal perception and autonomic function. A patient with early damage to these nerves may experience burning, dysesthetic pain, often accompanied by hyperalgesia, and allodynia. This pain is distinct from that of large fiber neuropathy, where the pain is usually described as deep and "gnawing." Because peripheral sympathetic nerve fibers are also comprised of small, unmyelinated C-fibers, it is not surprising that pain is improved with sympathetic blocking agents (e.g. beta-blockers, calcium channel blockers).

It should be noted that dry, cracked skin and impaired skin blood flow in the feet, together with impaired sympathetic regulation of sweat glands and A-V shunt vessels in the feet, create a favorable environment for bacteria. In the absence of pain, which occurs with the depletion of substance P, patients may be led to believe that their neuropathy has subsided, when in fact it is progressing. These patients may also display decreased thermal pain thresholds, which may be due in part to the decrease in nerve growth factor (NGF) which maintains small fiber neurons. The clinical manifestations of small vs. large fiber neuropathies are summarized below:

Clinical manifestations of small fiber neuropathies

- Prominent pain: burning and superficial and associated with allodynia i.e. interpretation of all stimuli as painful (e.g. touch)
- Hypoalgesia late in the condition
- Defective autonomic function with decreased sweating, dry skin, impaired vasomotion and blood flow and cold feet
- Intact reflexes, motor strength
- Silent electrophysiology
- Reduced sensitivity to 1.0 g Semmes Weinstein monofilament and pricking sensation using the Waardenberg wheel or similar instrument
- Abnormal thresholds for warm thermal perception, neurovascular function, pain, quantitative sudorimetry and quantitative autonomic function tests
- Increased risk of foot ulceration and subsequent gangrene

Differential diagnosis

Diabetes as the cause of neuropathy is diagnosed by exclusion of various other causes of neuropathy. In those patients with diabetes and neuropathy who present with symptoms of distal symmetric sensorimotor deficit, differential diagnosis should include: hereditary sensory

Table 5. *Treatment of diabetic neuropathy based on pathogenetic mechanisms*

Abnormality	Compound	Aim of treatment	Status of RCTs
Polyol pathway ↑	Aldose reductase inhibitors	Nerve sorbitol ↓	
	Sorbinil		Withdrawn (AE)
	Tolrestat		Withdrawn (AE)
	Ponalrestat		Ineffective
	Zopolrestat		Withdrawn (marginal effects)
	Zenarestat		Withdrawn (AE)
	Lidorestat		Withdrawn (AE)
	Fidarestat		Effective in RCTs, Trials ongoing
	AS-3201		Effective in RCTs, Trials ongoing
	Epalrestat		Marketed in Japan
myo-Inositol ↓	*Myo*-Inositol	Nerve *myo*-inositol ↑	Equivocal
Oxidative stress ↑	α-Lipoic acid	Oxygen free radicals ↓	Effective in RCTs, trials ongoing
Nerve hypoxia ↑	Vasodilators	NBF ↑	
	ACE inhibitors		Effective in 1 RCT
	Prostaglandin analogs		Effective in 1 RCT
	phVEGF$_{165}$ gene transfer	Angiogenesis ↑	RCTs ongoing
Protein kinase C ↑	PKC ß inhibitor (ruboxistaurin)	NBF ↑	RCTs ongoing
C-peptide ↓	C-peptide	NBF ↑	Studies ongoing
Neurotrophism ↓	Nerve growth factor (NGF)	Nerve regeneration, growth ↑	Ineffective
	BDNF	Nerve regeneration, growth ↑	Ineffective
LCFA metabolism ↓	Acetyl-L-carnitine	LCFA accumulation ↓	Ineffective
GLA synthesis ↓	γ−Linolenic acid (GLA)	EFA metabolism ↑	Withdrawn
NEG ↑	Aminoguanidine	AGE accumulation ↓	Withdrawn

BDNF (brain-derived neurotrophic factor); NEG (non-enzymatic glycation); AGE (advanced glycation end products); EFA (essential fatty acids); LCFA (long-chain fatty acids); AE (adverse events); NBF (nerve blood flow); RCTs (randomized clinical trials). From: [50]

neuropathies, B_{12} and folate deficiency, syphilis, Lyme disease, neuropathy associated with IgM monoclonal gammopathy of undetermined significance (IgM MGUS neuropathy), other paraneoplastic conditions, autoimmune diseases, and toxic neuropathies. In patients with one or more motor neurologic syndromes, chronic motor neuropathies, AIDP, CIDP, and IgG and IgA MGUS neuropathies should actively be sought.

Recent evidence supports an autoimmune etiology for neuropathy in AIDS, Lyme disease, AIDP, CIDP, multifocal motor neuropathy, MGUS neuropathies and even diabetic polyneuropathy [15,27]. Hence, an intensive work up for humoral immune mechanisms should be performed. If any of these conditions are found, the appropriate therapeutic regime for the specific disease must be instituted, before embarking on a regime of diabetic neuropathy management. It is not always possible to determine the exact cause of neuropathy if monoclonal gammopathy and diabetes coexist in the same patient. A course of intravenous immunoglobulin (IVIg) or immunosuppression should be attempted depending on the class of monoclonal antibody. Table 5 summarizes trials based upon pathogenetic mechanisms and the likelihood of drugs entering the clinic.

Nerve tissue biopsy may be helpful for excluding other causes of neuropathy and in the determination of predominant pathologic changes in patients with complex clinical findings as a means of dictating choice of treatment [25,29]. Our laboratory performs nerve biopsies only when noninvasive neurological procedures fail to provide an answer and/or when extensive evaluation is necessary for scientific purposes [29]. We expect a further increase in our dependence on histopathologic and ultrastructural examination of nerve tissue for differentiation of neuropathic syndromes, as our knowledge of pathophysiologic and clinical complexity among diabetic neuropathic variants increases. Figure 6 depicts a diagnostic algorithm for the assessment of neurologic deficit and classification of neuropathic syndromes.

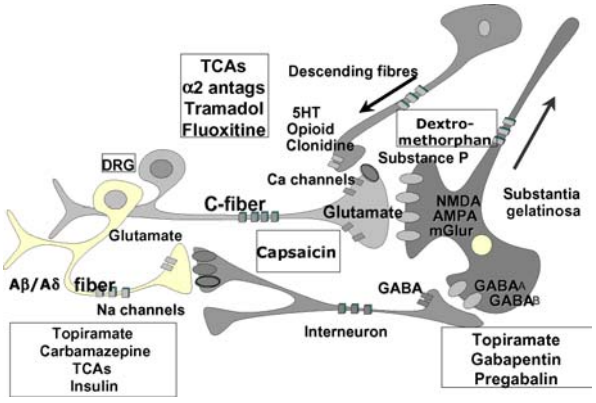


Fig. 6. *Sites of action of drugs used to treat pain in the diabetic patient. Modified from [53].*

Charcot neuroarthropathy

Charcot neuroarthropathy is a progressive condition associated with prolonged neuropathy and characterized by pathological fracture, joint dislocation, and if left untreated, disabling joint deformity. The most common location for Charcot is in the foot. The prevailing theory of Charcot progression suggests that autonomic neuropathy causes increased blood flow to the extremities which increases bone resorption and causes osteopenia. Subsequent motor neuropathies cause muscular imbalance which place abnormal stress on the affected extremity. Sensory neuropathies prevent the patient from sensing abnormal changes in the joints and bones which may occur due to minor trauma, such as during walking [30]. It is further hypothesized that Achilles tendon shortening due to destruction of collagen fibers may be due to accumulation of advanced glycation endproducts (AGEs) [31,32].

Patients with Charcot neuroarthropathy may present acutely with severe pain (or no pain if severe sensory neuropathy), a warm to hot swollen foot with increased skin blood flow (despite decreased warm sensory perception and vibration detection), and possible radiographic evidence of osteopenia. The acute Charcot foot can mimic cellulitis or, less commonly, deep vein thrombosis, so these should be first investigated. It should also be noted that radiographic findings can be normal in the acute phase, with subsequent films showing severe subluxation and/or fracture. Strict immobilization and protection of the foot using a total contact cast is the recommended approach to treating acute Charcot. Pain and inflammation respond to bisphosphonates (e.g. slow IV pamidronate infusion over 12 hours) within 3 to 4 weeks [33]. It is worth noting that oral bisphosphonates may cause esophageal dysfunction and increase the risk of obstruction and perforation. Achilles tendon shortening producing equinus is correctable by surgical lengthening and may prevent further progression. Patient education, protective footwear, and routine foot care are required to prevent further complications such as foot ulceration. In cases of severe joint and bony destruction, reconstructive surgery is effective in salvaging the limb and improving mobility and quality of life.

Management of Neuropathy

Once the diagnosis of neuropathy has been made, therapy to reduce symptoms and prevent further progression should be initiated. Diabetic patients with large fiber neuropathies are incoordinate and ataxic and are 17 times more likely to fall than their non-neuropathic counterparts [34]. Older subjects have a higher incidence of neuropathy than younger subjects, especially involving large fibers. It is vitally important to improve strength and balance in the patient with large fiber neuropathy. Older adults with and without neuropathy can benefit from high intensity strength training by increasing muscle strength, improving coordination and balance, and thus reducing fall and fracture risk [35,36]. Low impact activities which emphasize muscular strength and coordination, and challenge the vestibular system, such as pilates, yoga, and Tai Chi may also be particularly helpful.

Strategies for management of large fiber neuropathies

- Strength, gait, and balance training
- Pain management as detailed below
- Orthotics fitted with proper shoes to treat and/or prevent foot deformities
- Tendon lengthening for equinus caused by achilles tendon shortening
- Bisphophonates to treat osteopenia
- Surgical reconstruction and full contact casting as necessary

Strategies for management of small fiber neuropathies.

There are several simple measures that can protect the foot deficient in functional C-fibers from developing ulceration, and therefore, gangrene and amputation:

- Foot protection is of the utmost importance. Wearing padded socks can promote ulcer healing and/or reduce the likelihood of developing one [37].
- Supportive shoes with orthotics if necessary.
- Regular foot and shoe inspection. Patients should inspect the plantar surface of their feet with a mirror on a daily basis. (Many are too obese to see their feet, let alone the undersurface).
- Extreme caution to prevent heat injury. Patients should test the bathwater with a part of the body that is not insensate before plunging a numb foot into the water. Patients should also be cautioned against falling asleep in front of the fireplace with their insensate feet close to the fire.
- Use emollient creams to moisturize dry skin and prevent cracking and infection.

Therapies aimed at pathogenic mechanisms

Retrospective and prospective studies have suggested a relationship between hyperglycemia and the development and severity of diabetic neuropathy, and significant effects of intensive insulin treatment on prevention of neuropathy [38]. Studies in animal models and cultured cells provide a conceptual framework for the cause and treatment of diabetic neuropathy. However, the limited translational work in diabetic patients continues to generate debate over the cause(s) of human diabetic neuropathy and to date we have

no effective long-term treatment. A summary of the drugs that have been studied in clinical trials aimed at treating the pathogenic mechanisms of DPN are listed in Table 6.

Therapy aimed at treating symptoms in patients with DPN

It is critical to discern the underlying condition in diabetic patients with pain. Physicians, must be able to differentiate painful diabetic neuropathy from other unrelated or coexisting conditions in patients with diabetes. The most common of these are claudication, Morton's neuroma, Charcot neuroarthropathy, fasciitis, osteoarthritis, and radiculopathy (Table 7).

Treatment strategies should aim to decrease the afferent input, reduce local inflammation, suppress sympathetic fortification of the stimulus, reduce the impact of excitatory amino acids, alter the modulation of nociceptors, and suppress Na+ channel activity (Fig. 5).

Amitriptyline is prescribed for diabetic neuropathy [39], but anticholinergic side effects such as orthostatic hypotension and possible cardiac arrhythmias [39,40] warrant caution in its use. Contraindications to amitriptyline and other tricyclic antidepressants include cardiac conduction block, long QT syndrome, myocardial infarction within 6 months, ventricular arrhythmias and/or frequent premature ventricular contractions [40]. Older adults with neuropathy are at risk for adverse events from tricyclic antidepressants especially stability, balance and cognitive problems [41]. For this reason, patients over 40 years old should have a screening electrocardiogram prior to using these medications [41].

Other commonly used drug classes include analgesics (local, simple, and narcotic), antiarrhythmics, and antiepileptic drugs (Table 7) [40]. Based on positive results from randomized, controlled trials and expert clinical opinion of members of the faculty of the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain, recommendations for first-line medications for neuropathic pain include gabapentin, 5% lidocaine patch, opioid analgesics, tramadol hydrochloride, and tricyclic antidepressants [41]. Consideration of the safety and tolerability of different therapies is important in avoiding adverse effects, a common result of treatment of neuropathic pain. Dosages must be titrated based on positive response, treatment adherence, and adverse events [41].

Anti-epileptic drugs (AEDs) have a long history of effectiveness in the treatment of neuropathic pain. Since 1993, nine new AEDs (felbamate, gabapentin, pregabalin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, and zonisamide) have received FDA

Table 6. *Common pain syndromes similar to painful diabetic neuropathy*

Condition	Key characteristics and differentiating features
Claudication	• Doppler ultransonography confirms clinical diagnosis of arterial occlusion • Diabetic patients may present with normal extremities and absent foot pulses • Peripheral arterial occlusion with underlying atherosclerosis • Usually intermittent, worsened by walking; remits with rest; other signs/symptoms suggest arterial insufficiency
Morton's neuroma	• Benign neuroma formation on third plantar interdigital nerve • Generally unilateral • More frequent in women • Pain elicited when pressure is applied with the thumb between the first and fourth metatarsal heads
Osteoarthritis	• Can be secondary to diabetes mellitus, but onset of pain is usually gradual and in 1 or 2 joints • Differential diagnosis based on x-ray • Morning stiffness, diminished joint motion, and flexion contractures • Pain worsens with exercise and improves with rest • Radiculopathy can result
Radiculopathy	• Can be caused by diabetes, but also from arthritis or metastatic disease • Neurologic examinations and imaging can localize lesion site • Pain can occur in thorax, extremities, shoulder, or arm, depending on site of lesion
Charcot neuroarthropathy	• May result from osteopenia due to increased blood flow following repeated minor trauma in individuals with diabetic neuropathy • Warm to hot foot with increased skin blood flow • Decreased warm sensory perception, vibration detection
Plantar fasciitis	• Pain in plantar region of the foot • Tenderness along plantar fascia when ankle is dorsiflexed • Shooting or burning in the heel with each step • Worsening pain with prolonged activity • Often associated with calcaneal spur on radiography
Tarsal tunnel syndrome	• Caused by entrapment of the posterior tibial nerve • Pain and numbness radiate from beneath the medial malleolus to the sole • Clinical examination includes percussion, palpation for possible soft-tissue matter, nerve conduction studies, magnetic resonance imaging

Table 7. *Drugs approved by the FDA for treatment of neuropathic pain syndrome (adapted from [51])*

Medication	Indication	Beginning dosages	Titration	Maximum dosage	Duration of adequate trial
Gabapentin	Postherpetic neuralgia	100–300 mg every night or 100–300 mg 3_/d	Increase by 100–300 mg 3_/d every 1–7 d as tolerated	3600 mg/d (1200 mg 3 _/d); reduce if low creatinine clearance	3–8 wk for titration plus 1–2 wk at maximum tolerated dosage
Pregabalin	Diabetic neuropathic pain	150 mg bid	Increase to 300 bid	600 mg/d	1 wk
Carbamazepine**	Trigeminal neuralgia	200 mg/d (100 mg bid)	Add up to 200 mg/d in increments of 100 mg every 12 h	1200 mg/d	
5% lidocaine patch	Postherpetic neuralgia	Maximum of 3 patches daily for a maximum of 12 hr	None needed	Maximum of 3 patches daily for a maximum of 12 hr	2 wk
Opioid analgesics*	Moderate to severe pain	5–15 mg every 4 hr as needed	After 1–2 wk, convert total daily dosage to long-acting medication as needed	No maximum with careful titration; consider evaluation by pain specialist at dosages exceeding 120–180 mg/d	4–6 wk
Tramadol hydrochloride	Moderate to moderately severe pain	50 mg 1 or 2_/d	Increased by 50–100 mg/d in divided doses every 3–7 d as tolerated	400 mg/d (100 mg 4_/d); in patients older than 75 yr, 300 mg/d in divided doses	4 wk
Tricyclic antidepressants (eg, nortriptyline hydrochloride or desipramine hydrochloride)	Chronic pain	10–25 mg every night	Increase by 10–25 mg/d every 3–7 d as tolerated	75–150 mg/d; if blood level of active drug and its metabolite is <100 ng/mL, continue titration with caution	6–8 wk with at least 1–2 wk at maximum tolerated dosage
Fluoxetine Serotonin/norepinephrine Reuptake inhibitor	Diabetic neuropathic pain	30 mg bid	Increase by 60 to 60 mg bid. No further titration		4 wk

*Dosages given are for morphine sulfate.

**Source: Tegretol [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2003.

approval for the adjunctive treatment of partial seizures [42] (Table 7). Three of these drugs have also been approved for generalized seizures (felbamate, lamotrigine, topiramate) and three (felbamate, lamotrigine, oxcarbazepine) for monotherapy [42]. Principal mechanisms of action include sodium channel blockade (felbamate, lamotrigine, oxcarbazepine, topiramate, zonisamide), potentiation of GABA activity (tiagabine, topiramate), calcium channel blockade (felbamate, lamotrigine, topiramate, zonisamide), antagonism of glutamate at *N*-methyl-D-aspartate (NMDA) receptors (felbamate, memantine, dextromethorphan) or α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) (felbamate, topiramate), and mechanisms of action still undetermined (gabapentin, pregabalin, levetiracetam).

In addition to providing efficacy against epilepsy, these new AEDs may also be effective in treating neuropathic pain. For example, the AED lamotrigine may decrease hyperexcitability in dorsal horn spinal neurons by inhibiting glutamate release-2 mechanisms and decrease spontaneous activity in regenerating primary afferent nerve fibers [43]. In addition, the "wind-up" phenomenon caused by nerve injury and the kindling that occurs in hippocampal neurons in patients with mesial temporal sclerosis both enlist activation of NMDA receptors [44] which can be affected by felbamate [42].

The evidence supporting the use of antiepileptic drugs for the treatment of PN continues to evolve. Patients who have failed one anticonvulsant may respond to another, as drugs in this class often have different mechanisms of action [41]. When these mechanisms are understood, it may prove beneficial to combine drugs for a synergistic effect. For example, a sodium channel blocker such as lamotrigine may be used with a glutamate antagonist such as felbamate. In addition, certain drugs may possess multiple mechanisms of action which increases its likelihood of success (e.g. topiramate). If pain is divided according to its derivation from different nerve fiber types (e.g. Aδ

vs C-fiber), spinal cord or cortical, then different types of pain should respond to different therapies (Fig. 6).

While it would be preferable to rely on FDA-approved medications for the treatment of PN, no drugs have yet received an indication for this purpose. Only a few drugs, including 2 AEDs, have received FDA approval for the treatment of chronic neuropathic pain syndrome [42]. Carbamazepine has FDA approval for the treatment of trigeminal neuralgia, and is effective in controlling the lightning pain of DN and both gabapentin and lidocaine 5% patch [41] are approved for postherpetic neuralgia [41].

Special considerations

The 63rd Annual American Diabetes Association meeting (2003) had an entire symposium devoted to the problem of understanding pain in diabetic neuropathy and to optimize therapeutic approaches in its treatment. The following represents a brief summary of some special considerations when treating painful neuropathy.

Carbamazepine, a Na^+ channel blocker, is effective against trigeminal neuralgia but is being replaced with the safer Oxcarbazine which is useful for "lightning" type pains. Lamotrigine may cause skin rashes if titrated up too rapidly and Gabapentin, whose action still remains obscure and may cause serious CNS side effects, has failed in one of three studies and causes weight gain. Dextromethorphan, an NMDA receptor antagonist was relatively weak and its successor Memantine has not undergone successful trials. Topical capsaicin (3 teaspoons cayenne pepper + 1 jar cold cream) depletes substance P but is difficult to use and can be dangerous if it contacts mucous membranes. Results from topical lidocaine or it oral equivalent mexilitine are equivocal. The anticonvulsant drug, Topiramate, has been used successfully to treat pain in diabetic patients and also promotes weight loss and restful sleep, suggesting that the drug may have other beneficial effects apart from relieving pain [45]. Tramadol and oxycodone are weak opiods which have also shown to be effective but require careful titration and observation.

Another type of pain, Aδ pain, is described as a more deep-seated ache which does not often respond to the medications above. Several different agents have been used with varying success. Continuous intravenous insulin infusion without blood glucose lowering may be useful in these patients. The patient is admitted in the evening and usual diabetes treatment is instituted and a regular meal plan followed. NaCl is administered intravenously. In the morning, insulin is infused in a dose of 0.8-1.0 units hourly. Pain reduction usually occurs within 48 hours at which time the insulin infusion is discontinued. If this measure fails there are several medications available that may abolish the pain.

Conclusions

Diabetic neuropathy is a heterogeneous disease with diverse pathology. Recognition of the clinical homologue of these pathological processes is the first step in achieving the appropriate form of intervention. Treatment should be individualized such that the particular manifestation and underlying pathogenesis of each patient's unique clinical presentation is considered. In older adults, special care should be taken to manage pain while optimizing daily function and mobility, with the fewest adverse side effects from medication. Older adults are at great risk for falling and fractures due to instability, weakness and require strength exercises, coordination training. Ultimately agents that address large fiber dysfunction will be essential if we are to reduce the gross impairment of QOL and ADLs that neuropathy visits upon the older person with diabetes.

References

1. Vinik AI, Mitchell BD, Leichter SB, Wagner AL, O'Brian JT, Georges LP. Epidemiology of the complications of diabetes. In: Leslie RDG, Robbins DC, eds. *Diabetes: Clinical Science in Practice*. Cambridge, United Kingdom: Cambridge University Press, 1995:221–287.
2. Knuiman M, Welborn T, McCann V, Stanton K, Constable I. Prevalence of diabetic complications in relation to risk factors. *Diabetes* 1986;35:1332–1339.
3. Young MJ, Boulton AJM, MacLeod AF, Williams DRR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 1993;36:1–5.
4. Holzer SE, Camerota A, Martens L, Cuerdon T, Crystal-Peters J, Zagari M. Costs and duration of care for lower extremity ulcers in patients with diabetes. *Clin Ther* 1998;20:169–181.
5. Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. *N Engl J Med* 1994;331(13):854–860.
6. Menz HB, Lord SR, St George R, Fitzpatrick RC. Walking stability and sensorimotor function in older people with diabetic peripheral neuropathy. *Arch Phys Med Rehabil* 2004;85(2):245–252.
7. Maty SC, Fried LP, Volpato S, Williamson J, Brancati FL, Blaum CS. Patterns of disability related to diabetes mellitus in older women. *J Gerontol A Biol Sci Med Sci* 2004;59(2):148–153.
8. Richardson JK, Thies SB, DeMott TK, Ashton-Miller JA. A comparison of gait characteristics between older women with and without peripheral neuropathy in standard and challenging environments. *J Am Geriatr Soc* 2004;52(9):1532–1537.
9. Vinik AI, Erbas T. Recognizing and Treating Diabetic Autonomic Neuropathy. *Cleveland Clinic Journal of Medicine* 2001;68(11):928–944.
10. Vinik A, Mehrabyan A. Diagnosis and Management of Diabetic Autonomic Neuropathy. *Comprehensive Therapy* 2003;29(2/3):130–145.
11. Brownlee M. Advanced products of nonenzymatic glycosylation and the pathogenesis of diabetic complications. In: Rifkin H, Porte D, eds. *Diabetes Mellitus: Theory and Practice*. New York, Amsterdam, London: Elsevier, 1990:279.
12. Vinik A, Mehrabyan A, Colen L, Boulton A. Focal entrapment neuropathies in diabetes. *Diabetes Care* 2004;27(7):1783–1788.

13. Wilbourn AJ. Diabetic entrapment and compression neuropathies. In: Dyck PJ, Thomas PK, eds. *Diabetic Neuropathy*. Philadelphia: Saunders, 1999;481–508.
14. Kapritskaya Y, Novak C, Mackinnon S. Prevalence of smoking, obesity, diabetes mellitus and thyroid disease in patients with carpal tunnel syndrome. *Ann Plast Surg* 2002;48(3):269–279.
15. Vinik AI, Holland MT, LeBeau JM, Liuzzi FJ, Stansberry KB, Colen LB. Diabetic neuropathies. *Diabetes Care* 1992;15:1926–1975.
16. Leedman PJ, Davis S, Harrison LS. Diabetic amyotrophy. Reassessment of the clinical spectrum. *Aust. N. Z. J. Med* 1988;18:768–773.
17. Barohn RJ, Sahenk Z, Warmolts JR, Mendell JR. The Bruns-Garland syndrome (Diabetic amyotrophy). *Arch Neurol* 1991;48;1130–1135.
18. Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Ann Neurol* 1995;38(6):869–880.
19. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New Eng J Med* 1993;329:977–986.
20. Vinik AI, Pittenger GL, Milicevic Z, Knezevic-Cuca J. Autoimmune Mechanisms in the Pathogenesis of Diabetic Neuropathy. In: Eisenbarth RG, eds. *Molecular Mechanisms of Endocrine and Organ Specific Autoimmunity*. Georgetown: Landes Company, 1998:217–251.
21. Steck AJ, Kappos L. Gangliosides and autoimmune neuropathies: Classification and clinical aspects of autoimmune neuropathies. *J Neurol Neurosurg Psychiatry* 1994;57(Suppl):26–28.
22. Vinik A. Diagnosis and management of diabetic neuropathy. *Clinics in Geriatric Medicine* 1999;15(2):293–319.
23. Milicevic Z, Pittenger GL, Stansberry KB, Vinik AI. Raised antiganglioside GM1 antibody (GM1 Ab) titers in a subset of patients with distal symmetric polyneuropathy (DSPN). *Diabetes* 1997;46(Suppl. 1):125A.
24. Sharma K, Cross J, Farronay O, Ayyar D, Sheber R, Bradley W. Demyelinating neuropathy in diabetes mellitus. *Arch Neurol* 2002;59:758–765.
25. Krendel DA, Costigan DA, Hopkins LC. Successful treatment of neuropathies in patients with diabetes mellitus. *Arch Neurol* 1995;52:1053–1061.
26. Vinik AI, Suwanwalaikorn S, Stansberry KB, Holland MT, McNitt PM, Colen LE. Quantitative measurement of cutaneous perception in diabetic neuropathy. *Muscle Nerve* 1995;18:574–584.
27. Yu RK, Ariga T, Kohriyama T, Kusonoki S, Maeda Y, Myatani N. Autoimmune mechanisms in peripheral neuropathies. *Ann Neurol* 1990;27(Suppl. 1):S30–S35.
28. Zhuang H-X, Snyder CK, Pu S-F, Ishii DN. Insulin-like growth factors reverse or arrest diabetic neuropathy: effects on hyperalgesia and impaired nerve regeneration in rats. *Exp Neurol* 1996;140(2):198–205.
29. Said G, Goulon-Goreau C, Lacroix C, Moulonguet A. Nerve biopsy findings in different patterns of proximal diabetic neuropathy. *Ann Neurol* 1994;35(5):559–569.
30. Young MJ, Marshall M, Adams JE, Selby P, Boulton AJM. Osteopenia, neurological dysfunction, and the development of Charcot neuroarthropathy. *Diabetes Care* 1995;18:34–38.
31. Haslbeck KM, Bierhaus A, Erwin S, Kirchner A, Nawroth P, Schlotzer U, Neundorfer B, Hess D. Receptor for advanced glycation endproduct (RAGE)-mediated nuclear factor-kappaB activation in vasculitic neuropathy. *Muscle Nerve* 2004;29(6):853–860.
32. Grant WP, Sullivan R, Sonenshine DE, Adam M, Slusser JH, Carson KA, Vinik AI. Electron microscopic investigation of the effects of diabetes mellitus on the Achilles tendon. *J Foot Ankle Surg* 1997;36(4):272–278.
33. Anderson JJ, Woelffer KE, Holtzman JJ, Jacobs AM. Bisphosphonates for the treatment of Charcot neuroarthropathy. *J Foot Ankle Surg* 2004;43(5):285–289.
34. Cavanagh PR, Derr JA, Ulbrecht JS, Maser RE, Orchard TJ. Problems with gait and posture in neuropathic patients with insulin-dependent diabetes mellitus. *Diabet Med* 1992;9(5):469–474.
35. Nelson ME, Fiatarone MA, Morganti CM, Trice I, Greenberg RA, Evans WJ. Effects of high-intensit strength training on multiple risk factors for osteoporotic fractures. A randomized controlled trial. *JAMA* 1994;272:1909–1914.
36. Liu-Ambrose T, Khan KM, Eng JJ, Janssen PA, Lord SR, McKay HA. Resistance and agility training reduce fall risk in women aged 75 to 85 with low bone mass: a 6-month randomized, controlled trial. *J Am Geriatr Soc* 2004;52(5):657–665.
37. Murray H, Veves A, Young M, Richie D, Boulton A. Role of experimental socks in the care of the high risk diabetic foot. A multi-center patient evaluation study. American group for the study of experimental hosiery in the diabetic foot. *Diabetes Care* 1993;16(8):1190–1192.
38. Pirart J. Diabetes mellitus and its degenerative complications: A prospective study of 4,400 patients observed between 1947 and 1973. *Diabetes Care* 1978;1:252–263.
39. Low P, Dotson R. Symptom treatment of painful neuropathy. *JAMA* 280,1863–1864:1998.
40. Morello CM, Leckband SG, Stoner CP, Moorhouse DF, Sahagian GA. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. *Arch Intern Med* 1999;159(16):1931–1937.
41. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DS, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: Diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003;60(11):1524–1534.
42. LaRoche SM, Helmers SL. The new antiepileptic drugs: scientific review. *JAMA* 2004;291(5):605–614.
43. Eisenberg E, Lurie Y, Braker C, Daoud D, Ishay A. Lamotrigine reduces painful diabetic neuropathy: A randomized, controlled study. *Neurology* 2001;57(3):505–509.
44. Backonja MM. Use of anticonvulsants for treatment of neuropathic pain. *Neurology* 2002;59(5 Suppl 2):S14–S17.
45. Raskin P, Donofrio P, Rosenthal N, Hewitt D, Jordan D, Xiang J, Vinik AI. Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects. *Neurology* 2004;63:865–873.
46. Thomas PK. Classification, differential diagnosis and staging of diabetic peripheral neuropathy. *Diabetes* 1997;46(Suppl 2):S54–S57.
47. Barney Y, Bossmeyer R, Kokomen E. Neurological manifestations of aging. *Am Ger Soc* 1990;32:411–419.
48. Maki BE, Holliday PJ, Fernie GR. Aging and postural control. A comparison of spontaneous- and induced-sway balance tests. *J Am Geriatr Soc* 1990;38(1):1–9.
49. Potvin AR, Syndulko K, Tourtellotte WW, Lemmon JA, Potvin JH. Human neurologic function and the aging process. *J Am Geriatr Soc* 1980;1:1–9.
50. Boulton AJ, Vinik A, Arezzo J, Bril V, Feldman E, Freeman R, Malik R, Maser R, Sosenko J, Ziegler D. Position statement: Diabetic neuropathies. *Diabetes Care*. 2004 (Submitted).
51. Cameron NE, Eaton SEM, Cotter MA, Tesfaye S. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia* 2001;44:1973–1988.
52. Vinik AI, Milicevic Z. Recent advances in the diagnosis and treatment of diabetic neuropathy. *The Endocrinologist* 1996;6:443–461.
53. Vinik A, Mehrabyan A. Diabetic Neuropathies. *Medical Clinics of North America* 2004;88(4):947–999.