THE DIABETIC NEUROPATHIES

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Introduction
Diabetes is the most common cause of distal symmetric polyneuropathy in the world. Over half of all neuropathy patients in the United States have diabetes. Distal symmetric diabetic neuropathy is a leading cause for disability due to pain, foot ulcers and amputation, and fall risk. In 2003 the annual health care costs directly attributable to diabetic neuropathy and its consequences were $10.9 billion in the United States alone (1). Patients with severe pain experience 80% greater costs than those with only mild pain (2). Diabetes is associated with a wide range of other peripheral nerve complications including acute neuropathies, polyradiculopathies, mononeuropathies, autonomic neuropathy and cranial neuropathies. There is evolving evidence that patients with prediabetes and its associated metabolic derangements are at high risk for developing neuropathy. Sir William Osler once said that "to know syphilis is to know medicine," and the same can be said of diabetes, to know diabetes is to know peripheral nerve disease. The goal of this syllabus and lecture is to provide an overview of the peripheral nerve complications of diabetes mellitus.

Definition of Diabetes
Diabetes can be classified into four types. Type 1 diabetes is due to autoimmune destruction of pancreatic β cells leading to a deficiency of insulin and resultant hyperglycemia. Type 1 diabetes usually presents at a young age, frequently in childhood. Insulin resistance is the underlying cause for Type 2 diabetes, which is associated with obesity and other aspects of the metabolic syndrome (hypertension and dyslipidemia). In contrast to type 1 diabetes, insulin levels are high. Type 2 diabetes has been called "adult onset" in the past, although the obesity epidemic has led to an expanding number of adolescents and young adults developing the disorder. Type 3 diabetes includes all other types (genetic defects and diseases of the exocrine pancreas such as cystic fibrosis, drug induced). Gestational diabetes is classified as type 4. While neuropathy may occur in any type of diabetes, most patients have type 2 or type 1. The clinical features of neuropathy are similar between type 1 and type 2, although there are likely differential disease mechanism, and some of forms of neuropathy may be more common in one versus the other (e.g. treatment related neuropathy). It is likely that neuropathy risk factors among type 2 patients, such as dyslipidemia, may also contribute to neuropathy risk in type 1 patients as the age and develop coincidental metabolic disease.

A number of studies indicate an elevated risk of prediabetes, defined as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), among patients with otherwise idiopathic peripheral neuropathy. Diagnosis of diabetes and prediabetes may be made using fasting glucose, 2 hour glucose tolerance or recently revised criteria based on hemoglobin A1c measurement (Table 1). The diagnostic sensitivity of A1c for prediabetes is lower than oral glucose tolerance test (OGTT) but it is easier to measure and less prone to test retest variation, thus it is a logical initial diagnostic test. In at risk patients, such as those with neuropathy, OGTT is recommended if A1c is normal.

Table 1: The Diagnostic Criteria for Impaired Fasting Glucose, Impaired Glucose Tolerance, and Diabetes.

Diagnosis	Fasting Plamsa Glucose	2 Hour OGTT	Hemoglobin A1C
Normal	< 100 mg/dl (5.6 mmol/l)	< 140 mg/dl (7.8 mmol/l)	< 5.7%
IFG/IGT	100-125 mg/dl (5.6-6.9 mmol/l)	140-199 mg/dl (7.8-11.0 mmol/l)	5.7-6.4%
Diabetes	≥ 126 mg/dl (7.0 mmole/l)	≥ 200 mg/dl (11.1 mmole/l)	≥ 6.5%

The Spectrum of the Diabetic Neuropathies
The diabetic neuropathies can be classified in several ways. One logical classification system is based on time course. This method divides neuropathies into chronic (DSP and autonomic neuropathy) and acute forms (diabetic amyotrophy, treatment related neuropathy). They can also be classified based on anatomic involvement into distal symmetric, focal (mononeuropathies), and multifocal (diabetic amyotrophy) patterns. By far, the most common diabetic neuropathy is distal symmetric polyneuropathy (DSP). DSP presents with slowly progressive

distal symmetric numbness, mild weakness, and significant neuropathic pain in approximately 20%. Any divergence from this pattern (e.g. acute, asymmetric, proximal or motor involvement) suggests an alternative form (3). The subsequent sections will review the most common forms of diabetic neuropathy, starting with chronic neuropathies (distal symmetric, prediabetic and autonomic) and concluding with acute neuropathies (diabetic amyotrophy and treatment related neuropathies).

Chronic Diabetic Neuropathies

Chronic diabetic neuropathies including distal symmetric polyneuropathy, prediabetes associated neuropathy and diabetic autonomic neuropathy. These disorders are the most common peripheral nerve complications from diabetes, and are what most practitioners envision when they conceive of "diabetic neuropathy." They share a slowly progressive time course. While their etiology remains incompletely defined, metabolic consequences of hyperglycemia, insulin resistance and obesity (including both direct nerve and microvascular injury) are key contributors.

Distal Symmetric Polyneuropathy

Distal Symmetric Polyneuropathy (DSP) is the most common form of diabetic neuropathy, affecting over half of all diabetic patients. DSP may be broadly divided into asymptotic and symptomatic forms, with 20% having significant neuropathic pain. Patients with significant sensory loss, particularly those with longstanding disease, may experience painless injury and ulceration. DSP increases the risk of ulceration 7- fold and contributes to over 60% of lower extremity amputations (4). This increased risk results from a combination of loss of protective sensation, reduced sweating leading to increased friction, abnormal blood flow, and impaired wound healing. While foot ulcers typically occur after many years of DSP, painful neuropathy is more typical early in the disease course. Symptoms include burning, aching or tingling pains that are most severe in the evening, but may also limit activity. The pain is often severe, with a mean intensity of 6/10 in one series (5). The other major cause for disability among DSP patients is fall risk. Among 60 patients over the age of 55 years old, over one-third had fallen in the prior year (6). The risk of falls is greatest when traversing uneven surfaces or while ambulating in the dark (7).

Diagnosis of DSP is based on recognition of symptoms and/or signs and confirmatory testing. Nerve conduction studies are the most frequently employed diagnostic test and confirmed DSP requires their abnormality (3). DSP is characterized by reduced sensory nerve action potential amplitudes, often with mild motor conduction slowing, a finding less common in other axonal neuropathies. Probable clinical DSP requires symptoms and signs of neuropathy with two of the following: symptoms, reduced distal sensation, reduced or absent reflexes. Possible clinical DSP requires symptoms or signs.

Patients with preferential injury to small nerve fibers experience severe symptoms of pain and numbness, but nerve conduction studies may be normal. Diagnosis of small fiber predominant neuropathy depends on confirmatory tests such as sudomotor testing or skin biopsy with measurement of intraepidermal nerve fiber density (IENFD). Skin biopsy is a well tolerated and reliable tool for diagnosis of small fiber neuropathy and is commercially available from a number of academic and industry laboratories (8). Abnormality is based on published age and gender normative data (9).

A key part of the diagnostic evaluation of any patient with DSP is exclusion of an alternative cause for neuropathy. Given the high population prevalence of both neuropathy and diabetes, a sizable percentage of patients have a different or contributing etiology. In a retrospective analysis of 103 sequential DSP patients, over 50% had at least one additional potential cause or contributor for neuropathy (10). Vitamin B12 level, serum protein electrophoresis and immunofixation should be assessed in all neuropathy patients, and an evaluation for connective tissue disease (e.g. Sjogren's syndrome), or infection (e.g. hepatitis C or HIV) should be pursued in appropriately selected at risk patients (11).

DSP is probably due to a combination of direct nerve injury and microvascular injury which in turn leads to nerve ischemia. There are a number of important metabolic pathways including oxidative stress, accumulation of advanced glycation endproducts, and increased flux through the polyol pathway (12). There is growing evidence that metabolic risk factors other than hyperglycemia may play an important role in disease pathogenesis. Obesity and dyslipidemia may be particularly important and both may contribute to oxidative stress. Among 28,700 diabetic patients, serum triglyceride level was an independent stepwise risk factor for lower extremity amputation (13). Among 1172 T1D subjects without baseline neuropathy followed in the Eurodiab study, hypertension, smoking, obesity and serum triglycerides were independent risk factors for neuropathy (14).

Because there have been no medications proven to be effective in altering the natural history of DSP in human patients, the focus has been on aggressive glycemic control. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy reduced the development of clinical neuropathy by 65% over 5 years in over 1400 patients (15). The Epidemiology of Diabetes Interventions and Complications (EDIC) study has continued to follow DCCT subjects. While both treatment groups have had similar glycemic control since the DCCT, those who had were in the intensive treatment group are less likely to have neuropathy 14 years later than those who were in the standard therapy group(25% versus 35%, $p<0.001$) (16). By contrast, there are much less data supporting efficacy of aggressive glycemic control in neuropathy prevention in type 2 diabetes. For example, the ACCORD study randomized 10,251 type 2 diabetes patients who had a HgbA1c of > 7.4% to an intensive glucose control protocol with an A1c goal of 6.5% or a standard protocol whose goal was 7.0-7.9%. The intensive therapy arm was stopped early due to increased mortality. The data from prior to discontinuation of intensive therapy was compared to the standard therapy cohort, and there was only minimally reduced risk of new sensory loss, and no reduction in the risk of new neuropathy symptoms (17). While some other studies suggest there is a reduced neuropathy risk with aggressive glycemic control, the magnitude of benefit is not large.

There are no pharmacologic therapies that have been proven to alter the natural history of DSP in human patients. Multiple trials of aldose reductase inhibitors, (18) and a large trial of recombinant human nerve growth factor have failed to show benefit (19). Alpha lipoic acid has reduced pain in some trials (20) but not others. A number of novel therapeutic approaches are under development including gene therapy approaches. One study of intramuscular injection of a plasmid containing the vascular endothelial growth factor (VEGF) gene suggested a small benefit (21). Another recently described innovative therapeutic approach is injection of a replication deficient herpes virus containing therapeutic genes of interest subcutaneously. The herpes virus vector undergoes retrograde transportation to the sensory neuropathy in the dorsal root ganglion where the therapeutic gene is expressed. A recent phase one study of injection of a herpes simplex virus vector expressing the preproenkephalin gene (an opiate precursor) in patients with cancer related pain showed good tolerance and suggested dose dependent pain reduction (22). The same investigators have used this technique in animal models of diabetic and toxic neuropathies. This approach is appealing because it aims to specifically target the treatment in order to avoid off target side effects.

Identification of patients who are at high risk for foot ulcers and amputation is necessary in order to implement preventative strategies. Indicators of risk include neuropathy severity, association peripheral vascular disease, a prior foot ulcer or amputation, and absent or reduced sensitivity to a 10g monofilament (23). Peripheral neuropathy also causes disability due to falls and pain. Patients at risk for falls should be counseled to take particular care while walking on uneven surfaces or in low lighting. Early referral to physical therapy is appropriate. Treatment of painful neuropathy will be addressed elsewhere in this syllabus.

Prediabetes and Neuropathy

There is a growing literature linking peripheral neuropathy to prediabetic levels of hyperglycemia. It has been recognized for many years that as many as 1 in 5 diabetes patients have neuropathy at the time of diagnosis, suggesting neuropathy may develop early in the disease course (in contrast to retinopathy and nephropathy) (24). A number of studies provide evidence that patients with neuropathy are at higher risk of prediabetes or other metabolic accompaniments of insulin resistance. Several studies have reported a 30-50% prevalence of impaired glucose tolerance among idiopathic neuropathy patients (11). Obesity, dyslipidemia and metabolic syndrome are also more common in neuropathy patients than the general population (25). These same metabolic features predict risk of neuropathy in patients with established diabetes (14, 26). The Steno-2 trial demonstrated that aggressive therapy for hypertension and dyslipidemia in patients with type 2 diabetes reduced risk for complications including autonomic neuropathy. The benefit was independent of glucose control (27). A recent study of sural nerve biopsies from patients participating in a clinical trial used microarrays and a systems biology approach to identify a number of differentially expressed genes among subjects with progressive neuropathy including those involved with lipid metabolism (28). A number of studies in animal models support the hypothesis that intermittent hyperglycemia and obesity increase neuropathy risk (29-31).

The clinical features of the neuropathy associated with IGT and metabolic syndrome mirrors those seen in early diabetes. Most patients have a distal symmetric neuropathy, often with pain (32). Weakness is rare, and protective sensation is generally preserved. Because small diameter axons are preferentially involved, nerve conduction studies are frequently normal, and tests that assess small fibers (e.g. skin biopsy or sudomotor testing) may be required to confirm the suspected diagnosis (33).

The precise nature of the relationship between prediabetes, metabolic syndrome and neuropathy remains to be defined. There is evidence that treatment of prediabetes may impact the disease course. Patients with IGTN enrolled in a diet and exercise counseling program similar to that used in the Diabetes Prevention Program, with goals of losing 7% of body weight (or normalizing BMI) and moderate aerobic exercise for 150 minutes a week showed significant improvement in blood glucose control and lipid metabolism (34). This metabolic improvement was associated with a significant increase in the number of cutaneous nerve fibers by IENFD, and significant improvement in neuropathic pain over a two-year period.

Diabetic Autonomic Neuropathy

Autonomic neuropathy is a common but under-recognized complication of diabetes. Diabetic autonomic neuropathy (DAN) is very important because it is associated with an elevated risk of death. DAN also causes significant disability due to erectile dysfunction, gastroparesis, and failure to recognize hypoglycemia. Estimates of DAN prevalence vary. In one study of 1170 type I and II diabetic subjects 20% had an abnormality of at least three of six cardiovascular autonomic function tests (35). By contrast, the Diabetes Control and Complications Trial, which used similar methods in a pure type I population, found dysautonomia in only 6% (15). Specific forms of DAN are very common. Nearly 1/3rd of diabetic and prediabetic men experience erectile dysfunction.

Sudomotor testing using Quantitative Sudomotor Axon Reflex Testing (QSART) is abnormal in a quarter of newly diagnosed diabetic subjects. Many of the symptomatic forms of DAN are cared for by non-neurologists (e.g. gastroparesis, erectile dysfunction). This review will focus on cardiac autonomic neuropathy, which is associated with an increased risk of mortality, and may manifest as orthostatic hypotension, a symptom neurologists are frequently called upon to manage.

Injury to the autonomic innervation of the heart and central blood vessels disrupts control of heart rate and blood pressure regulation. Orthostatic hypotension is the most easily recognized consequence. Though presyncopal lightheadedness is the classic complaint, patients often have difficulty describing this phenomenon, and may present with fatigue, visual blurring, weakness, dizziness, or neck pain. Cardiac dysautonomia also contributes to exercise intolerance and altered blood pressure regulation (36). Patients complain of rapid fatigue, light headedness or dyspnea with exertion due to a failure to increase heart rate in response to aerobic exercise. Parasympathetic vagal fibers are frequently affected first, resulting in a relative predominance of sympathetic outflow causing hypertension, especially at night. As DAN progresses, blood pressure more labile.

Early recognition of cardiac DAN is important because large epidemiological studies have consistently demonstrate a 2-5 fold increase in mortality risk among those with two or more confirmatory abnormalities of cardiac dysautonomia compared to diabetic patients without these risk factors (37). Sudden death, myocardial infarction, congestive heart failure are more common. Increased prevalence of ventricular and malignant arrhythmias, clinically silent infarction and blunted inotropic response stress all represent primary cardiac contributors to this increased mortality. The EURODIAB study of type I diabetes showed greater QT interval prolongation in those with dysautonomia (38), and found that dysautonomia was the single strongest predictor of mortality during the seven year follow-up period, greater than age, glucose control or common cardiovascular risk factors (39).

There are several simple bedside tests of autonomic dysfunction (40). Paced deep breathing at a rate of six breaths per minute maximizes variability of heart rate. The ratio of the R-R interval during expiration (bradycardia) to inspiration (tachycardia) can be calculated using a basic EKG strip. The E:I ratio is primarily a test of parasympathetic function. Standing from a supine position causes maximum tachycardia at 15 seconds followed by slowest reflex bradycardia at 30 seconds, and is primarily a test of sympathetic function (the 30:15 ratio). Finally, RR interval to Valsalva maneuver tests both sympathetic and parasympathetic outflow. Each test can be performed in routine practice. Valsalva has the highest sensitivity for dysautonomia, but is more technically difficult to perform.

Acute Diabetic Neuropathies

The acute diabetic neuropathies are much less common than chronic forms, but they are frequently very dramatic and disabling. There are probably a variety of underlying mechanisms, which vary between the specific forms. Unlike chronic neuropathies, inflammation and vasculopathy are important mechanisms.

Diabetic Lumbosacral Radiculoplexus Neuropathy (DLRPN or "Diabetic Amyotrophy")
The most common acute neuropathy associated with diabetes is diabetic lumbosacral radiculoplexus neuropathy (DLRPN). DLRPN was first described by Bruns in 1890 and Garland in 1950, and has been called Bruns Garland Syndrome in their honor (41, 42). Many other names have been given this condition, the most lasting of which is "diabetic amyotrophy." DLRPN typically presents with acute unilateral thigh pain that is typically severe, and characterized by a mixture of deep aching, burning and tingling. The pain is soon followed by progressive atrophy and weakness. While proximal muscles are most prominently affected, many patients experience distal weakness as well. Not uncommonly, the opposite side becomes involved. Most patients experience dramatic weight loss and many are rendered wheelchair dependent (43). Symptomatic upper extremity weakness is uncommon, although some patients may have more severe arm weakness (44). The syndrome often progressive over several months followed by a period of gradual improvement, although most do not achieve baseline strength (43).

Typical patient characteristics of DLRPN are different from DSP. DLRPN usually affects older patients with type 2 diabetes who have a shorter diabetes duration and lower hemoglobin A1c than those with DSP. Electrodiagnostic studies demonstrate evidence of a polyradiculoneuropathy, with low amplitude or absent lower extremity sensory and motor action potentials and ongoing denervation in limb and paraspinal muscles, often including thoracic levels. CSF examination is characterized by elevated protein without pleocytosis. Nerve biopsies demonstrate a microvasculitis (45). Given the multiple features suggesting an autoimmune/inflammatory etiology, it has been hypothesized that immunosuppression may be effective (46). A randomized trial of corticosteroids has been published in abstract form, which demonstrated improvement in pain, but not strength. This study was limited because many subjects began therapy many months after disease onset. A well designed randomized trial early in the disease course is needed.

Treatment Related Neuropathy ("Insulin Neuritis")
Patients with poorly controlled diabetes may experience an acute, very painful, sensory neuropathy following rapid glucose control. The pain may be diffuse in 30% of patients, and autonomic neuropathy is common. Most patients have type 1 diabetes, although it has been described in type 2 diabetes patients as well. Symptoms improve over months, although they syndrome may recur if diabetic control lapses and is once again rapidly corrected. Patients who have a history of diabetic anorexia (intentionally withholding insulin for weight loss) may be at particularly high risk. While the condition has been commonly referred to as "insulin neuritis" there is no evidence to support an inflammatory or autoimmune etiology. The neuropathy is associated with progressive retinopathy, suggest a vascular etiology (47).

Diabetic Neuropathic Cachexia
Diabetic Neuropathic Cachexia shares many features with treatment related neuropathy (48). In addition to a severe acute painful neuropathy that may be generalized (e.g. non-length dependent), patients experience dramatic weight loss. Pain is frequently non length dependent and generalized. Cachexia may be provoked by rapid glycemic control, although this is not always present. Unlike treatment related neuropathy, it is more frequent in type 2 diabetes. Like treatment related neuropathy, it improves spontaneously and therapy is focused on pain control (49).

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Diabetes.
It is a commonly held belief that CIDP is more common in diabetes patients, and more severe. In one study of 1127 patients seen in an academic EMG laboratory, there was an 11 times higher risk of CIDP in subjects with diabetes compared to those without (50). However, several more recent epidemiological studies have not corroborated this finding (51, 52). Patients with severe diabetic neuropathy frequently have motor conduction slowing, and in those with associated renal failure, this slowing can be in the range typical of CIDP. However, patients with diabetic/uremic neuropathy have length dependent weakness as opposed to the proximal weakness typical for CIDP (53).

Conclusions
The varied peripheral nerve complications of diabetes serve as a model for the broader spectrum of neuropathy. They encompass metabolic/degenerative distal symmetric and autonomic neuropathies, inflammatory polyradiculopathy, and acute vasculopathy. Diabetes patients are at higher risk for compressive mononeuropathies and cranial neuropathies. While definitive treatment is not yet available for most diabetic neuropathies, there have been major advances in our understanding of disease pathogenesis, which promise to lead to novel therapeutic opportunities.

References

1. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the US. Diabetes Care 2003;26:1790-1795.
2. Dibonaventura MD, Cappelleri JC, Joshi AV. Association between Pain Severity and Health Care Resource Use, Health Status, Productivity and Related Costs in Painful Diabetic Peripheral Neuropathy Patients. Pain Med 2011.
3. Tesfaye S, Boulton AJ, Dyck PJ, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010;33:2285-2293.
4. Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care 1999;22:382-387.
5. Galer BS, Gianas A, Jensen MP. Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. Diabetes Res Clin Pract 2000;47:123-128.
6. Macgilchrist C, Paul L, Ellis BM, Howe TE, Kennon B, Godwin J. Lower-limb risk factors for falls in people with diabetes mellitus. Diabet Med 2010;27:162-168.
7. DeMott TK, Richardson JK, Thies SB, Ashton-Miller JA. Falls and gait characteristics among older persons with peripheral neuropathy. Am J Phys Med Rehabil 2007;86:125-132.
8. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on the use of skin biopsy in the diagnosis of small fiber neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. J Peripher Nerv Syst 2010;15:79-92.
9. Lauria G, Bakkers M, Schmitz C, et al. Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study. J Peripher Nerv Syst 2010;15:202-207.
10. Gorson KC, Ropper AH. Additional causes for distal sensory polyneuropathy in diabetic patients. J Neurol Neurosurg Psychiatry 2006;77:354-358.
11. Smith AG, Singleton JR. The diagnostic yield of a standardized approach to idiopathic sensory-predominant neuropathy. Arch Intern Med 2004;164:1021-1025.
12. Fernyhough P, Roy Chowdhury SK, Schmidt RE. Mitochondrial stress and the pathogenesis of diabetic neuropathy. Expert Rev Endocrinol Metab 2010;5:39-49.
13. Callaghan BC, Feldman E, Liu J, et al. Triglycerides and amputation risk in patients with diabetes: ten-year follow-up in the DISTANCE study. Diabetes Care 2011;34:635-640.
14. Tesfaye S, Chaturvedi N, Eaton SE, et al. Vascular risk factors and diabetic neuropathy. N Engl J Med 2005;352:341-350.
15. Group DR. The effect of intensive diabetes therapy on the development and progression of neuropathy. Annals of Internal Medicine 1995;122:561-568.
16. Albers JW, Herman WH, Pop-Busui R, et al. Effect Of Prior Intensive Insulin Treatment During The Diabetes Control And Complications Trial (DCCT) On Peripheral Neuropathy In Type 1 Diabetes During The Epidemiology Of Diabetes Interventions, And Complications (EDIC) Study. Diabetes Care 2010.
17. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419-430.
18. Chalk C, Benstead TJ, Moore F. Aldose reductase inhibitors for the treatment of diabetic polyneuropathy. Cochrane Database Syst Rev 2007:CD004572.
19. Apfel SC, Schwartz S, Adornato BT, et al. Efficacy and safety of recombinant human nerve growth factor in patients with diabetic polyneuropathy: A randomized controlled trial. rhNGF Clinical Investigator Group. JAMA 2000;284:2215-2221.
20. Ziegler D, Ametov A, Barinov A, et al. Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. Diabetes Care 2006;29:2365-2370.
21. Ropper AH, Gorson KC, Gooch CL, et al. Vascular endothelial growth factor gene transfer for diabetic polyneuropathy: a randomized, double-blinded trial. Ann Neurol 2009;65:386-393.
22. Fink DJ, Wechuck J, Mata M, et al. Gene therapy for pain: results of a phase I clinical trial. Annals of Neurology 2011:In Press.
23. Abbott CA, Carrington AL, Ashe H, et al. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med 2002;19:377-384.
24. Cohen JA, Jeffers BW, Faldut D, Marcoux M, Schrier RW. Risks for sensorimotor peripheral neuropathy and autonomic neuropathy in non-insulin dependent diabetes mellitus (NIDDM). Muscle Nerve 1998;21:72-80.
25. Smith AG, Rose K, Singleton JR. Idiopathic neuropathy patients are at high risk for metabolic syndrome. J Neurol Sci 2008.

26. Costa LA, Canani LH, Lisboa HR, Tres GS, Gross JL. Aggregation of features of the metabolic syndrome is associated with increased prevalence of chronic complications in Type 2 diabetes. Diabet Med 2004;21:252-255.
27. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-393.
28. Hur J, Sullivan KA, Pande M, et al. The identification of gene expression profiles associated with progression of human diabetic neuropathy. Brain 2011.
29. Russell JW, Sullivan KA, Windebank AJ, Herrmann DN, Feldman EL. Neurons undergo apoptosis in animal and cell culture models of diabetes. Neurobiol Dis 1999;6:347-363.
30. Vincent AM, McLean LL, Backus C, Feldman EL. Short-term hyperglycemia produces oxidative damage and apoptosis in neurons. FASEB J 2005;19:638-640.
31. Vincent AM, Hinder LM, Pop-Busui R, Feldman EL. Hyperlipidemia: a new therapeutic target for diabetic neuropathy. J Peripher Nerv Syst 2009;14:257-267.
32. Singleton JR, Smith AG, Bromberg MB. Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. Diabetes Care 2001;24:1448-1453.
33. Singleton JR, Bixby B, Russell JW, et al. The Utah Early Neuropathy Scale: a sensitive clinical scale for early sensory predominant neuropathy. J Peripher Nerv Syst 2008;13:218-227.
34. Smith AG, Russell J, Feldman EL, et al. Lifestyle intervention for pre-diabetic neuropathy. Diabetes Care 2006;29:1294-1299.
35. Ziegler D, Dannehl K, Muhlen H, al e. Prevalence of cardiovascular autonomic dysfunction assessed by spectral analysis, vector analysis and standard tests of HR variation and blood pressure responses at various stages of diabetic neuropathy. Diabet Med 1992;2:806-814.
36. Pop-Busui R. Cardiac autonomic neuropathy in diabetes: a clinical perspective. Diabetes Care 2010;33:434-441.
37. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care 2003;26:1895-1901.
38. Veglio M, Borra M, Stevens LK, Fuller JH, Perin PC. The relation between QTc interval prolongation and diabetic complications. The EURODIAB IDDM Complication Study Group. Diabetologia 1999;42:68-75.
39. Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M, Fuller JH. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). Diabetes Care 2008;31:1360-1366.
40. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553-1579.
41. Garland H. Diabetic myelopathy. BMJ 1955;2:1405-1408.
42. Bruns L. Ueber neuritsche Lahmungen beim diabetes mellitus. Berlin Klin Wochenschr 1890;27:509.
43. Barohn RJ, Sahenk Z, Warmolts J, Mendell J. The Bruns-Garland syndrome (diabetic amyotrophy) revisited 100 years later. Arch Neurol 1991;48:1130-1135.
44. Dyck PJ, Windebank AJ. Diabetic and nondiabetic lumbosacral radiculoplexus neuropathies: new insights into pathophysiology and treatment. Muscle Nerve 2002;25:477-491.
45. Dyck PJ, Norell JE. Microvasculitis and ischemia in diabetic lumbosacral radiculoplexus neuropathy. Neurology 1999;53:2113-2121.
46. Chan YC, Lo YL, Chan ES. Immunotherapy for diabetic amyotrophy. Cochrane Database Syst Rev 2009:CD006521.
47. Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. Ann Neurol 2010;67:534-541.
48. Ellenberg M. Diabetic neuropathic cachexia. Diabetes 1974;23:418-423.
49. Neal JM. Diabetic neuropathic cachexia: a rare manifestation of diabetic neuropathy. South Med J 2009;102:327-329.
50. Sharma KR, Cross J, Farronay O, Ayyar DR, Shebert RT, Bradley WG. Demyelinating neuropathy in diabetes mellitus. Arch Neurol 2002;59:758-765.
51. De Sousa EA, Chin RL, Sander HW, Latov N, Brannagan TH, 3rd. Demyelinating findings in typical and atypical chronic inflammatory demyelinating polyneuropathy: sensitivity and specificity. J Clin Neuromuscul Dis 2009;10:163-169.
52. Laughlin RS, Dyck PJ, Melton LJ, 3rd, Leibson C, Ransom J. Incidence and prevalence of CIDP and the association of diabetes mellitus. Neurology 2009;73:39-45.
53. Koski CL, Baumgarten M, Magder LS, et al. Derivation and validation of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy. J Neurol Sci 2009;277:1-8.