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Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes

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Abstract

Purpose of Review: Diabetic peripheral neuropathy eventually affects nearly 50% of adults with diabetes during their lifetime, and is associated with substantial morbidity including pain, foot ulcers, and lower limb amputation. This review summarizes the epidemiology, risk factors, and management of diabetic peripheral neuropathy and related lower extremity complications.

Recent Findings: The prevalence of peripheral neuropathy is estimated to be between 6% and 51% among adults with diabetes depending on age, duration of diabetes, glucose control, and type 1 *versus* type 2 diabetes. The clinical manifestations are variable, ranging from asymptomatic to painful neuropathic symptoms. Because of the risk of foot ulcer (25%) and amputation associated with diabetic peripheral neuropathy, aggressive screening and treatment in the form of glycemic control, regular foot exams, and pain management are important. There is an emerging focus on lifestyle interventions including weight loss and physical activity as well.

Summary: The American Diabetes Association has issued multiple recommendation statements pertaining to diabetic neuropathies and the care of the diabetic foot. Given that approximately 50% of adults with diabetes will be affected by peripheral neuropathy in their lifetime, more diligent screening and management are important to reduce the complications and health care burden associated with the disease.

Keywords

peripheral neuropathy; lower extremity disease; type 1 diabetes; type 2 diabetes; microvascular complications

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Conflict of Interest

Caitlin W. Hicks declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Diabetic peripheral neuropathy is defined as, “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes” [1]. The diagnosis relies on both clinical signs as well as quantitative testing, and may be present despite a lack of reported symptoms [1]. The estimated prevalence of peripheral neuropathy among adults with diabetes in the US is 28% [1, 2].

The consequences of diabetic peripheral neuropathy can be devastating. Approximately 50% of people with diabetes will develop a foot ulcer during their lifetime [3–5], and diabetes is a leading cause of lower limb amputation [6]. In addition, neuropathic pain and decreased sensation can contribute to an array of poor outcomes including falls, impaired quality of life, restrictions in activities of daily living, and depressive symptoms [7].

While peripheral neuropathy can occur in adults without diabetes, the prevention and management of peripheral neuropathy in diabetes is largely focused on glycemic control. Pain management also remains an important component in the management of diabetic neuropathy [1], and there is an emerging focus on lifestyle interventions including weight loss and physical activity [1, 8].

Herein, we summarize the epidemiology, risk factors, and management of diabetic peripheral neuropathy and related lower extremity complications.

Types and Presentation of Diabetic Peripheral Neuropathy

There are several forms of diabetic peripheral neuropathy [1]. The most common type is distal symmetric polyneuropathy which can be classified as primarily small-fiber, primarily large-fiber, or mixed small and large fiber [1], and accounts for approximately 75% of all diabetic neuropathies [9, 10]. Distal symmetric polyneuropathy causes neuropathic pain symptoms in approximately 10% to 30% of affected patients depending on the population studied [2, 11–16]. The pain may be described as a burning or stabbing pain, numbness, hyperesthesia, or a deep ache. It is often worse at night and usually affects the lower legs and feet, although in some patients the hands may be affected as well. [17]

Atypical forms of diabetic peripheral neuropathy include mononeuropathies (i.e. mononeuritis multiplex), (poly)radiculopathies, and treatment-induced neuropathies [1]. Mononeuropathies are closely associated with diabetes [9], and tend to affect the median, ulnar, radial, or common peroneal nerves [18]. Cranial nerve involvement is extremely rare, and usually presents as an acute mononeuropathy affecting cranial nerves III, IV, VI, or VII [18]. Diabetic radiculopathies typically involve the lumbosacral plexus, and present primarily as unilateral thigh pain and weight loss with subsequent motor weakness [1, 19, 20]. Treatment-induced neuropathy is a rare iatrogenic event that [17]occurs in patients following periods of extreme metabolic dysregulation (i.e. ketoacidosis), or following a sudden and substation change in glycemic control (i.e. insulin neuritis). Each of the atypical diabetic peripheral neuropathies are largely self-limited, and will resolve over several months with supportive care, medical management, and physical therapy [18–21].

Other diabetic neuropathies include autonomic neuropathies that affect the cardiovascular, gastrointestinal, and urogenital systems. Adults with diabetes may also suffer from sudomotor dysfunction, hypoglycemia unawareness, and abnormal pupillary function [1]. These neuropathies share a similar diffuse pathophysiology with distal symmetric polyneuropathy, but are largely non-sensory.

Epidemiology of Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy is the most common form of neuropathy worldwide [22]. In a landmark historical cohort study of 4,400 adults with diabetes from France who were followed prospectively from 1947 to 1973, 50% of participants developed peripheral neuropathy by the end of the 25 years of follow-up [23]. More recent cross-sectional studies from the US and Europe have reported a prevalence of diabetic peripheral neuropathy ranging from 6% to 51% depending on the population studied [2, 5, 24–26]. In the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DDCT/EDIC) Study, the prevalence of diabetic peripheral neuropathy among adults with type 1 diabetes was 6% at baseline, and increased to 30% after 13–14 years of follow-up [27]. The prevalence of peripheral neuropathy among adults with type 1 diabetes in the Pittsburgh Epidemiology of Diabetes Complications was 34%, and increased significantly with age (18–29 years: 18%; ≥30 years: 58%) [28]. The prevalence of diabetic peripheral neuropathy among youths with type 1 diabetes (mean age 15.7 years) was 8.2% in the SEARCH for Diabetes in Youth Study [29].

The prevalence of diabetes peripheral neuropathy is somewhat higher among persons with type 2 diabetes. In the SEARCH for Diabetes in Youth Study, peripheral neuropathy was present in 26% of youths with type 2 diabetes [29]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, peripheral neuropathy was present in 42% of adults with type 2 diabetes at baseline [30]. This is similar to the 39% prevalence reported in the Veteran Affairs Diabetes Trial [31]. In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial, 51% of adults with type 2 diabetes had a history of peripheral neuropathy at baseline [32].

The burden of diabetic peripheral neuropathy is higher in older age and among adults with long-standing type 1 or type 2 diabetes [26, 33, 34]. There is some evidence to suggest that diabetic peripheral neuropathy may occur less frequently in Asian populations, although this finding has not been consistent [25]. Most estimates suggest that approximately 50% of adults with diabetes will be affected by diabetic peripheral neuropathy over the course of their lifetime [3–5].

Etiology and Risk Factors for Diabetic Peripheral Neuropathy

Diabetic peripheral neuropathy is thought to be caused by nerve dysfunction and cell death that results from oxidative stress and inflammation [35]. Hyperglycemia, dyslipidemia, and insulin resistance all contribute to dysregulation of metabolic pathways that collectively cause an imbalance in the mitochondrial redox state, thereby leading to excess formation of mitochondrial and cytosolic reactive oxygen species [36]. This leads to a loss of axonal energy stores and axonal injury, promoting peripheral neuropathy [35]. The earliest changes

of diabetic peripheral neuropathy occur at the level of unmyelinated C fibers, resulting in pain, allodynia, and hyperesthesias [37]. Mild segmental axonal demyelination then occurs, followed by frank axonal degeneration of myelinated fibers as demyelination surpasses remyelination [38].. These changes lead to a progressive loss of distal sensation in a distal-to-proximal course along the nerve that defines diabetic peripheral neuropathy.

Randomized clinical trials have demonstrated the benefit of glucose control of slowing the progression of microvascular disease in diabetes, including peripheral neuropathy [39]. In the DCCT trial of 1,441 adults with type 1 diabetesy, intensive insulin therapy (versus conventional therapy) reduced the risk of clinical neuropathy by 60% after 6.5 years of follow-up [40]. The benefits of strict glycemic control persisted long-term, as demonstrated in the observational follow-up of the DCCT/EDIC participants, with a reduction in the risk of diabetic peripheral neuropathy in the intensively treated versus conventional group that persisted after the end of the trial (relative risk reduction of 30% during years 6.5 to 14) [27]. Among adults with type 2 diabetes, both the KUMAMOTO Trial [41] and the UK Prospective Diabetes Study (UKPDS) [42, 43] demonstrated fewer microvascular complications, including peripheral neuropathy, among patients treated with intensive *versus* conventional glucose control. In addition, median motor nerve conduction studies [41] and vibration perception threshold [42, 43] were significantly improved in patients treated with intensive therapy in the KUMAMOTO and UKPDS studies, respectively. In a recent Cochrane review and meta-analysis of data from 17 randomized trials (7 in people with type 1 diabetes, 8 in people with type 2 diabetes, and 2 in both types) evaluating the association of glucose control with diabetic peripheral neuropathy, enhanced glucose control significantly reduced the risk of clinical neuropathy as well as nerve conduction and vibration threshold abnormalities in type 1 diabetes. The risk of clinical neuropathy was also reduced in type 2 diabetes, although this was not statistically significant (P=0.06) [44].

In addition to age, duration of diabetes, and glucose control, diabetic peripheral neuropathy is linked to cardiometabolic disease and is associated with modifiable cardiovascular risk factors, including elevated triglyceride levels, body mass index, smoking, and hypertension [45, 46]. Prevalent cardiovascular disease is associated with nearly twice the risk of diabetic peripheral neuropathy, even after accounting for standard cardiovascular risk factors [45]. The temporality of these associations and causal mechanisms linking peripheral neuropathy with cardiovascular disease are less clear, but could be due to the presence of subclinical atherosclerosis and/or microvascular disease that contribute to both progressive cardiovascular and peripheral neuropathy morbidity [47].

Epidemiology of Mononeuropathies

Mononeuropathies, which affect less than 10% of patients, generally present with acute symptoms affecting the medial, ulnar, radial, or common peroneal nerve distributions [17]. The prevalence of mononeuropathy is higher in adults with diabetes compared to those without [9, 48]. In the Early Diabetes Intervention Trial, median nerve mononeuropathy was diagnosed in 23% of adults with diabetes based on electrophysiologic studies [49]. Symptomatic mononeuropathy is less common, occurring in approximately 0.9% of adults with type 1 diabetes and 1.3% of adults with type 2 diabetes, compared to 0–1% of adults

without diabetes [48, 50]. Risk factors mononeuropathy are similar to those for diabetic peripheral neuropathy, and include longer duration of diabetes, female sex, and higher body mass index [49][51][52].

Epidemiology of Lower Extremity Complications in Diabetes

Peripheral neuropathy can cause a range of complications, including chronic pain, foot ulcers, foot infections, and amputations. The estimated global prevalence of diabetic foot ulcers is 6%, with major risk factors including older age, lower body mass index, longer duration of diabetes, hypertension, diabetic retinopathy, and smoking [53]. Approximately 25% of people with diabetes will develop a foot ulcer during their lifetime [54], which can progress to infection and limb amputation in severe cases. Ninety percent of hospital admissions for diabetic foot ulcers are related to peripheral neuropathy and infection, and diabetes accounts for 83% of all major amputations in the United States [55]. Based on data from the Consensus Development Conference on Diabetic Foot Wound Care it is estimated that approximately 14–24% of people with a foot ulcer will ultimately require an amputation [56]. Thus, early diagnosis and treatment are essential. Implementation of regular foot exams among adults with diabetes has been shown to reduce the rate of foot ulcers in a variety of populations [57–59], and is essential to preventing progression of the disease to infection or lower limb amputation.

Patients with diabetic peripheral neuropathy who are at the highest risk for developing foot ulcers that lead to amputation include those with a prior history of foot ulcers, a structural foot deformity, peripheral artery disease, visual impairment, diabetic nephropathy, poor glycemic control, and smoking [60]. While all patients should have annual foot exams and appropriate management of diabetic peripheral neuropathy, patients with major risk factors should be educated on amputation risk and referred for dedicated foot care and surveillance whenever possible. Effective patient education has been shown to reduce the incidence of foot ulcers and amputations by as much as 50% [61].

Treatment Approaches for Diabetic Peripheral Neuropathy

Peripheral neuropathy is usually an irreversible disease, except in rare instances. The treatment is largely supportive and aims to prevent progression of disease and related complications [62]. The three main principles of treatment for peripheral neuropathy are glycemic control, foot care, and pain management. Glycemic control has not been shown to effectively reduce the symptoms among patients with peripheral neuropathy [44], and thus both glycemic control and foot care efforts are largely preventative. There is emerging evidence that lifestyle interventions including weight loss and physical activity may be helpful for managing painful peripheral neuropathy are also emerging, although the data are preliminary [1, 8, 63].

Pharmacologic treatment is indicated for the treatment of painful diabetic peripheral neuropathy, and has been shown to be effective in a number of randomized controlled trials and systematic reviews [1, 64]. The American Diabetes Association recommends medications for the relief of symptoms related to diabetic peripheral neuropathy, which have been shown to improve patients’ quality of life [1, 60]. Currently, only duloxetine and

pregabalin are approved by the US Food and Drug Administration (FDA) for the treatment of diabetic peripheral neuropathic pain [65, 66]. Tricyclic antidepressants have been shown to be reduce neuropathic pain, but are not currently approved by the FDA for this indication largely due to their risk of serious side effects [1, 67, 68]. Pain management with tramadol or oxycodone has also been shown to lower pain scores and improve physical function in some patients [69, 70]. However, opioids have addictive properties and should not be used as first- or second-line therapy for neuropathic pain [1, 71].

Despite a large body of evidence and professional treatment guidelines on the medical management of painful diabetic peripheral neuropathy [1, 60], current medication prescribing patterns are inconsistent. In a study of claims-based data among a cohort of 666 patients with diabetic peripheral neuropathy, 43% received pharmacologic agents within one year of diagnosis [72]. Of these, 53% were prescribed an opioid, including 33% who were prescribed an opioid as a first-line agent. Antidepressants were prescribed in 26% of cases, followed by anticonvulsants (23%), non-steroidal anti-inflammatory drugs (19%), and muscle relaxants (5%). FDA-approved duloxetine and pregabalin were only prescribed in 1% and 6% of cases, respectively [72]. Continuous treatment with duloxetine has been shown to be associated with a reduction in opioid use compared to treatment with other modalities [73, 74], and higher average daily doses of duloxetine are associated with higher treatment compliance and lower healthcare costs [74]. In contrast, inappropriate or excessive medication-taking behaviors occur in 5% to 24% of patients with chronic opioid prescriptions, and the prevalence of opioid addiction ranges from 36% to 50% [71, 75].

Economic Impact of Diabetic Peripheral Neuropathy

The US health care burden of diabetic peripheral neuropathy is substantial, estimated to be $10.9 billion per year overall [76]. As much as 27% of direct medical costs related to diabetes may be related to peripheral neuropathy [76]. The majority of these costs are attributable to the treatment of foot ulcers with superimposed infections and their complications, which is estimated to cost more than $13,000 per admission [77]. The estimated combined direct and indirect costs associated with diabetic peripheral neuropathy were estimated to be between $3000 and $4000 per patient per year in 2009 [74], and have likely increased in the ensuing decade.

Quality of Life and Functional Impact of Diabetic Peripheral Neuropathy

There are also indirect costs associated with diabetic peripheral neuropathy that are more challenging to calculate, including loss of productivity, loss of quality of life, rehabilitation costs, and personal expenditures [17]. The physical and mental components of quality of life are significantly altered among patients with painful diabetic peripheral neuropathy [78], and concomitant anxiety, depression, and sleep disturbance is reported in 43% of affected patients [79]. Employment status is affected in 35% to 43% of patients [79, 80], with employed patients reporting an average of 5.5 missed workdays per month due to pain [80].

In addition to impaired quality of life, patients with diabetic peripheral neuropathy also have an increased risk of falls due to balance challenges [81–83]. The risk of balance impairment is particularly high for patients with severe diabetic peripheral neuropathy, older age, and

concomitant depression [81]. As a result, falls and fractures are frequent among affected patients [84], occurring in an estimated 25% of adults ≥ 65 years with diabetes compared to 18% among similar adults without diabetes [85]. Diabetic peripheral neuropathy is associated with a risk of major fractures due to falls [86, 87], potentially because patients tend to have falls that are sideways, as opposed to forward or backward [82].

Screening and Prevention for Diabetic Peripheral Neuropathy

Due to the substantial impact that diabetic peripheral neuropathy has on patients' health, quality of life, and health care costs, the American Diabetes Association currently recommends that screening for diabetic peripheral neuropathy be performed in all adults at the time of diabetes diagnosis, and annually thereafter [60]. Despite these recommendations, data from the National Health and Nutrition Examination Surveys (2005–2010) demonstrated that 28.6% of adults with diagnosed diabetes reported they had not had a health professional check their feet for sores or irritation in the past year [88]. Similarly, data from the Centers for Disease Control and Prevention showed that the age-adjusted percentage of adults with diagnosed diabetes who received a foot exam in the last year was only 67.5% in 2010 [89]. Although there was an ~20% increase in the percentage of foot exams performed for adults with diabetes between 1994 and 2010 [89], there is still substantial room for improvement. As of 2014, the Centers for Medicaid and Medicare Services included an annual foot exam in primary care as a clinical quality measure [90]. To qualify, the foot exam must include a visual inspection, sensory exam with monofilament testing, and assessment of lower extremity pulses. An adequate foot exam can be performed in 3 minutes [91], and should be implemented as a regular component in the physical exam.

Conclusions

The American Diabetes Associations has issued multiple recommendation statements pertaining to diabetic neuropathies and the care of the diabetic foot [1, 60, 92]. Each of these focus on the importance of glycemic control and foot care for the prevention and treatment of diabetic peripheral neuropathy. Given that approximately 50% of adults with diabetes will be affected by peripheral neuropathy in their lifetime, more diligent screening and management of the diabetic population are important to reduce the complications and health care burden associated with the disease.

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