

Erin Lawson · Miroslav "Misha" Backonja
Editors

Painful Diabetic Polyneuropathy

A Comprehensive
Guide for Clinicians

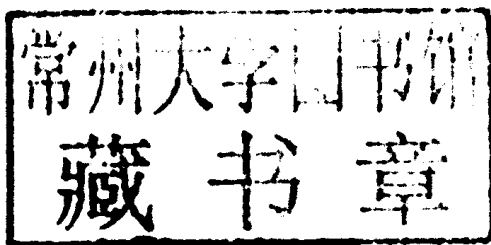


Springer

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Painful Diabetic Polyneuropathy

A Comprehensive Guide for Clinicians



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Painful Diabetic Polyneuropathy

We would like to dedicate this book to our families for their support as well as their generosity for time we needed to work on this textbook. We would also like to dedicate this book to Dr. Mark Wallace for his mentorship, support, and friendship.

Preface

In 2011, the World Health Organization reported that 346 million people worldwide had diabetes [1]. With international rates of diabetes rising (worldwide prevalence of diabetes is estimated to nearly double from 2000 to 4.4 % in 2030), complications including PDN are becoming increasingly prevalent [2]. It is estimated that over 16 % of diabetic patients [3] and approximately 50 % with diabetic neuropathy [4] suffer from painful diabetic neuropathy. Sadly, 40 % of these patients are untreated [3]. Improved appreciation of the scope of the problem based on epidemiology, improved understanding of underlying mechanisms, increased scope of knowledge in diagnosis, and a number of new treatment options should be the basis for improved care for this patient population. The goal of this text is to share with widest readership advances regarding painful diabetic neuropathy from pathogenesis to various therapies with emphasis on the multidisciplinary approach to treatment. It is the intent of this text to also shed the light on and raise the level of appreciation to the ways community is affected by diabetic painful polyneuropathy from patients to healthcare providers and family members.

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Part I

Introduction

Chapter 1

Epidemiology and Scope of Impact of Painful Diabetic Neuropathy

Christopher H. Gibbons and Aristidis Veves

Definition of Painful Diabetic Neuropathy

A recent report on diabetic neuropathy from the NEURODIAB Toronto Symposium on Diabetic Neuropathy classifies the length-dependent sensorimotor polyneuropathy as the most common manifestation of neuropathy in diabetes [1]. The neuropathy is secondary to metabolic and microvascular derangements seen with hyperglycemia and associated with cardiovascular risk factors (hypertension, hyperlipidemia, smoking) [1].

Symptoms of pain in diabetic polyneuropathies are considered manifestations of dysfunction arising from the somatosensory system [2]. The symptoms experienced by patients may vary widely and include spontaneous pains such as burning, shooting “electric shock,” stabbing, tingling (paresthesia), or cold. Symptoms may also present as evoked pain from non-painful stimuli, such as discomfort from contact with the bedsheets or socks (allodynia). Some individuals may also experience increased pain from painful stimuli (hyperalgesia), typically noted on physical exam by a verbal outburst in response to pinprick examination.

Neuropathic pain itself is neither a disease nor a diagnosis, but simply an integrated physiologic manifestation of a dysfunction somewhere within the nervous system and may reflect pain from diabetes, or from some other potential cause [3]. Therefore, epidemiologic data on pain in diabetes will vary widely depending on

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the definition of neuropathic pain, the pain scales that may be used to record the data and the inclusion or exclusion of specific co-morbidities, the duration of pain, and the rigor of diagnosis [3–6].

Epidemiology of Painful Diabetic Neuropathy

A length-dependent polyneuropathy will be seen in approximately 50% of individuals with long-standing diabetes, but this will vary widely on the definition of polyneuropathy used, the population studied, and the examination tools or neurophysiologic testing provided for diagnosis [3, 4, 7]. In a multinational study of primary care physicians in Europe, the diagnosis of diabetic neuropathy was frequently made on the basis of symptoms alone without any physical examination data reported [7]. However, other studies have included rigorous neurophysiologic testing as part of the required diagnosis of diabetic polyneuropathy (DPN) [8].

The prevalence of pain in patients with DPN is typically reported as 10–20% of individuals with diabetes and almost 50% of those with a length-dependent diabetic neuropathy [3, 9–11]. In a cross-sectional study of pain and diabetic neuropathy in the UK, a postal survey was used to determine the frequency of pain in the population of people with diabetes. Of those that responded, 64% reported pain that is typically considered “neuropathic” (i.e., burning, aching, or tenderness in the feet). All survey responders were followed up by a neurologic examination using the Toronto clinical scoring system (83% of survey responders completed the exam) and it was determined that 30% of the patients reporting pain had true neuropathic pain, 58% of those reporting pain had non-neuropathic pain, and 13% reporting pain had mixed pain [4]. Therefore, using the survey criteria 64% of patients with diabetes would have been diagnosed with diabetic neuropathic pain, but using the strict examination criteria only 26% of the original group were diagnosed with painful polyneuropathy [4].

In a study by Gore et al. investigating the comorbid pain conditions in patients diagnosed with painful DPN approximately 2/3 of individuals had at least one or more conditions causing pain (in addition to diabetes) [12]. The most frequently cited causes of non-neuropathy pain were osteoarthritis (34%), nociceptive low back pain (27%), carpal tunnel syndrome (14%), and low back pain with neuropathic involvement (13%). In addition, many patients also had comorbid depression (28%) and/or anxiety (27%).

A number of factors appear to be associated with the development of painful DPN, such as hypertension, smoking, higher glycosylated hemoglobin A1C scores, change in hemoglobin A1C, body mass index, triglycerides, and cholesterol levels [13]. However, these are the same risk factors that are associated with the development of DPN; thus differentiating what may increase the risk for development of pain in the setting of diabetic neuropathy is less clear. Several mechanisms have been postulated to cause pain in DPN including increased blood glucose variability, peripheral nerve epineurial blood flow, altered foot microcirculation, loss of intra-epidermal nerve fibers, increased thalamic vascularity, and autonomic dysfunction [8, 14–16].

One of the challenges facing the medical establishment is the recognition that microvascular complications, such as neuropathy, can develop prior to the onset of diabetes. Several recent studies have reported a high prevalence of impaired fasting glucose or impaired glucose tolerance in the general population [17–19]. A number of studies have also reported an increased incidence of pain in individuals with impaired glucose tolerance or impaired fasting glucose, as well as heightened awareness that patients with small fiber neuropathy frequently have glucose dysmetabolism as the potential causative factor [6, 20, 21]. The rising incidence of prediabetes across the globe will make this an enormous public health problem and will expand the number of individuals with painful DPN in an exponential fashion.

Health Care Burden of Painful Diabetic Neuropathy

What is apparent in patients with DPN that develop pain is the associated increase in health care utilization and health care costs. One of the initial studies to estimate the health care burden of symptoms in patients with DPN determined a cost of \$4.6–\$13.7 billion dollars in the USA on an annual basis in 2001 [11].

A more comprehensive retrospective study of managed care patients estimated the variation in health care utilization and costs associated with pain in patients with DPN from 2003 data [22]. Expenses were compared to a matched group of DPN patients without pain. The study utilized the Kaiser Permanente Colorado group as a closed panel nonprofit source of information on 367,000 members where all data could be captured. Over 1,500 patients with painful DPN and >3,000 matched patients with non-painful DPN were included in the analysis. Patients with painful DPN had greater number of annual physician visits (≥ 9 visits for painful DPN vs. ≤ 5 visits for non-painful DPN) and a 50% increase in emergency room utilization. The associated annual expenses per subject with painful DPN were \$14,062 and for non-painful DPN were \$6,651. The largest difference in cost utilization appeared to be a higher proportion of hospital billing secondary to increased number of limb infections and amputations [22].

Another cost associated with painful diabetic neuropathy is the indirect expense associated with lost work and productivity. A phone survey investigated the work hours among those healthy individuals, individuals with diabetes, and individuals with painful diabetic neuropathy [23]. It was estimated that patients with painful diabetic neuropathy had an 18% loss of productivity compared to controls and a 12% loss of productivity compared to those with diabetes alone. The study estimated a loss of 1.4 h of work per week in the painful diabetic neuropathy group compared to individuals with diabetes alone at an indirect cost of \$3.65 billion dollars in lost productivity per year [23].

A longitudinal study in patients with painful diabetic neuropathy from 2006 to 2008 utilized the US National Health and Wellness Survey data to investigate the effects of pain and neuropathy on health status and health care costs [24]. The patients with painful diabetic neuropathy had a higher body mass index and greater