Clinical Therapeutics/Volume ∎, Number ∎, 2018

Diabetic Peripheral Neuropathy: Epidemiology, Diagnosis, and Pharmacotherapy

Zohaib Iqbal, MRCP[1]; Shazli Azmi, MRCP, PhD[2]; Rahul Yadav, MRCP, MD[3]; Maryam Ferdousi, PhD[2]; Mohit Kumar, MRCP[4]; Daniel J. Cuthbertson, FRCP, PhD[5]; Jonathan Lim, MRCP[5]; Rayaz A. Malik, FRCP, PhD[2,6]; and Uazman Alam, MRCP, PhD[5,7,8]

[1]Department of Endocrinology, Pennine Acute Hospitals NHS Trust, Greater Manchester, United Kingdom; [2]Institute of Cardiovascular Science, University of Manchester and the Manchester Royal Infirmary, Central Manchester Hospital Foundation Trust, Manchester, United Kingdom; [3]Department of Endocrinology, Warrington and Halton Hospitals NHS Foundation Trust, Warrington, United Kingdom; [4]Department of Endocrinology, Wrightington, Wigan and Leigh NHS Foundation Trust, Wigan, United Kingdom; [5]Diabetes and Endocrinology Research, Department of Eye and Vision Sciences and Pain Research Institute, Institute of Ageing and Chronic Disease, University of Liverpool and Aintree University Hospital NHS Foundation Trust, Liverpool, United Kingdom; [6]Weill Cornell Medicine–Qatar, Doha, Qatar; [7]Department of Diabetes and Endocrinology, Royal Liverpool and Broadgreen University NHS Hospital Trust, Liverpool, United Kingdom; and [8]Division of Endocrinology, Diabetes and Gastroenterology, University of Manchester, Manchester, United Kingdom

ABSTRACT

Purpose: Diabetic peripheral neuropathy (DPN) is the commonest cause of neuropathy worldwide, and its prevalence increases with the duration of diabetes. It affects approximately half of patients with diabetes. DPN is symmetric and predominantly sensory, starting distally and gradually spreading proximally in a glove-and-stocking distribution. It causes substantial morbidity and is associated with increased mortality. The unrelenting nature of pain in this condition can negatively affect a patient's sleep, mood, and functionality and result in a poor quality of life. The purpose of this review was to critically review the current literature on the diagnosis and treatment of DPN, with a focus on the treatment of neuropathic pain in DPN.

Methods: A comprehensive literature review was undertaken, incorporating article searches in electronic databases (EMBASE, PubMed, OVID) and reference lists of relevant articles with the authors' expertise in DPN. This review considers seminal and novel research in epidemiology; diagnosis, especially in relation to novel surrogate end points; and the treatment of neuropathic pain in DPN. We also consider potential new pharmacotherapies for painful DPN.

Findings: DPN is often misdiagnosed and inadequately treated. Other than improving glycemic control, there is no licensed pathogenetic treatment for diabetic neuropathy. Management of painful DPN remains challenging due to difficulties in personalizing therapy and ascertaining the best dosing strategy, choice of initial pharmacotherapy, consideration of combination therapy, and deciding on defining treatment for poor analgesic responders. Duloxetine and pregabalin remain first-line therapy for neuropathic pain in DPN in all 5 of the major published guidelines by the American Association of Clinical Endocrinologists, American Academy of Neurology, European Federation of Neurological Societies, National Institute of Clinical Excellence (United Kingdom), and the American Diabetes Association, and their use has been approved by the US Food and Drug Administration.

Implications: Clinical recognition of DPN is imperative for allowing timely symptom management to reduce the morbidity associated with this condition. (*Clin Ther*. 2018;∎:∎∎–∎∎∎) © 2018 Elsevier HS Journals, Inc. All rights reserved.

Key words: diabetes, diagnosis, epidemiology, neuropathy, pharmacotherapy.

Accepted for publication April 2, 2018.
https://doi.org/10.1016/j.clinthera.2018.04.001
0149-2918/$ - see front matter

INTRODUCTION

Diabetes has reached epidemic proportions worldwide, with International Diabetes Federation estimates suggesting a prevalence of 425 million people worldwide in 2017, rising to 628 million by 2045.[1] This rise will be accompanied by an increase in the prevalence of the complications of diabetes.[2] DPN is the most common cause of neuropathy worldwide, and is estimated to affect around half of people with diabetes.[3,4] It causes considerable morbidity, impairs quality of life, and increases mortality.[5,6] Indeed, approximately one fourth of the US health care expenditure on diabetes is spent on DPN.[7]

Diabetic neuropathy refers to a collection of clinically diverse disorders affecting the nervous system, with differing anatomic features, clinical courses, and phenotypes. The common underlying pathophysiology is a consequence of hyperglycemia and microangiopathy.[8] The commonest form is distal symmetric sensorimotor polyneuropathy[9]; however, most body systems can be affected through involvement of the autonomic nerves. Despite the considerable, health care–related economic burden and effect on quality of life in DPN, treatment options are limited and prevention remains the key goal.[10] The purpose of this review was to critically review the current literature on the diagnosis and treatment of DPN, with a focus on the treatment of neuropathic pain in DPN.

MATERIALS AND METHODS

A comprehensive literature review was undertaken, incorporating article searches in electronic databases (EMBASE, PubMed, OVID) and reference lists of relevant articles with the authors' expertise in DPN. Articles published from inception of databases to December 2017 were identified. Data from articles that were felt not relevant by authors with the guidance of the senior reviewers (R.A.M., U.A.) were excluded from the review.

RESULTS

Databases searches were undertaken and 188 papers were cited in the final manuscript. Authors excluded studies that were not considered relevant to the aims of this article. Further appraisal of selected articles were undertaken and any relevant explanatory data from said articles were included in the present review as descriptive prose.

Epidemiology

Epidemiologic studies of diabetic neuropathy have provided heterogeneous results, owing to different patient populations, definitions of *neuropathy* used, and methods of assessments. Prediabetes is also associated with neuropathy.[11] In the San Luis Valley cohort,[12] the prevalence of peripheral neuropathy in patients with diabetes was 25.8%, as compared to 11.2% in subjects with impaired glucose tolerance (IGT) and 3.9% in control subjects. The MonItoring trends and determinants in CArdiovascular/Cooperative Research in the Region of Augsburg (MONICA/KORA)[13] investigators found the prevalence of neuropathic pain to be 13.3% in patients with diabetes versus 8.7%, 4.2%, and 1.2% in subjects with IGT, impaired fasting glucose, and controls, respectively. PROMISE (Prospective Metabolism and Islet Cell Evaluation)[14] followed up patients longitudinally who were at risk for developing diabetes. At 3 years, the prevalence of neuropathy (as assessed using the Michigan Neuropathy Screening Instrument) was 50% in patients who developed diabetes, 49% in those with prediabetes, and 29% in controls.[15]

In a Spanish study, the reported prevalence of DPN in primary care was 21% compared to 27% in-hospital.[16] The Rochester Neuropathy Study evaluated data from 380 participants[16]; DPN, diagnosed using a multifaceted approach, including the neuropathy symptom score, neuropathy disability score, and nerve conduction studies, was found in 66% and 59% of patients with type 1 and 2 diabetes, respectively. Importantly, approximately 10% of participants had a nondiabetic etiology of the neuropathy.[16]

A large-scale, multicenter study (N = 6500) revealed DPN (based on questionnaire and examination) in 28.5%.[4] A community-based study in ~15,000 patients with diabetes showed that 34% of patients had symptoms of painful neuropathy, with an increased risk in patients with type 2 diabetes, women, and people of South Asian origin.[17]

The prevalence of DPN is considered to be low in patients with early type 1 diabetes; however, among participants in the Diabetes Control and Complications Trial (DCCT), the prevalences of abnormal neurologic exam results were almost 20% in those on conventional treatment and almost 10% in those on intensive treatment, after ~5 years of follow-up.[18] In the EURODIAB IDDM complications study,[19] which evaluated over 3000 patients across 16