Social Impact and Public Health Burden of Illness in Diabetic Peripheral Neuropathy: An Evidence-Informed Update

Kumar Senthil P.*, Adhikari Prabha, Jeganathan P.S.***, D'Souza Mariella****, D'Souza Sydney C.****, Misri Z.K.******

Abstract

Background and Purpose: Painful neuropathy is a common complication of diabetes mellitus and the clinical presentation of bilateral tingling and numbness, with sensory and/or motor deficits and autonomic dysfunction in both lower limbs is termed as diabetic peripheral neuropathy (DPN) of distal symmetric polyneuropathy type. The objective of this paper was to perform a systematic review of articles on impact and burden of DPN in order to provide an evidence-informed reappraisal of existing findings. **Materials and Methods:** Systematic review using independent blinded search by search terms 'diabetic neuropathy' and 'impact or burden' was done to identify studies under four themes: impact of DPN on other factors; impact of other factors on DPN; impact of other factors on comorbidities in DPN; and, impact of comorbidities on other factors in DPN. **Results- main findings:** 29 studies were included for review and the multidimensional impact of DPN on individual in terms of physical and psychosocial influences; on the society in terms of work-related disability and healthcare utilization costs; and to the nation in terms of public health burden was consistently reflected across identified studies. **Conclusion:** DPN has a multidimensional impact on the person, society and nation, and is a physical, physiological, psychological and psychosocial burden for patients and their caregivers. A strong interdisciplinary collaborative working relationship is essential to combat the consequences of this disorder so that interventions might be aimed along a symptom control to quality of life continuum.

Keywords: Diabetic peripheral neuropathy; Public health burden; Health impact; Evidence-based practice.

Introduction

Painful neuropathy is a common complication of diabetes mellitus and the clinical presentation of bilateral tingling and numbness, with sensory and/or motor deficits and autonomic dysfunction in both lower limbs is termed as diabetic peripheral neuropathy (DPN) of distal symmetric polyneuropathy type.[1]

Chronic neuropathic pain may be secondary to many other etiologies including post-herpetic neuralgia and fibromyalgia, which is a debilitating condition that imposes a significant burden on individuals and society alike.[2]

Health care professionals need to assess the full impact of painful neuropathy since the chronic painful form of DPN may fail to respond to drugs or may have unacceptable adverse side effects thus severely affecting the patients' quality of life.[3] The objective of this paper was to perform a systematic review of articles on impact and burden of DPN in order to provide an evidence-informed reappraisal

Author's Affilation: *Professor, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation (Maharishi Markandeshwar University), Mullana-Amabla, Haryana, **Professor, Dept. of Medicine, ***Professor, Dept. of Physiology, ****Selection Grade Lecturer, Dept. of Psychiatry, *****Professor, Dept. of Neurology, ******Associate professor, Dept. of Medicine, Kasturba Medical College (Manipal University), Mangalore, Karnataka, India.

Reprint's request: Senthil P. Kumar, Professor, Maharishi Markandeshwar Institute of Physiotherapy and Rehabilitation (Maharishi Markandeshwar University), Mullana- Ambala, Haryana, India.

E-mail: senthilparamasivamkumar@gmail.com

of existing findings.

Methodology

Study Design

Systematic review.

Search Methods

A parallel independent blinded search was performed by two testers using a pre-determined search strategy using search terms, "(impact [Title] OR burden [Title]) AND (diabetes [Title] OR diabetic [Title]) AND (neuropathy [Title] OR neuropathic [Title]) NOT autonomic [Title]" in PubMed with search filters for 'abstract available' articles published in English language. Disagreements between testers were resolved through mutual consensus with the third tester.

Data Extraction and Synthesis

Both testers independently extracted data using a checklist into four distinct themes: impact of DPN on other factors; impact of other factors on DPN; impact of other factors on comorbidities in DPN; and, impact of comorbidities on other factors in DPN.

Results - Main Findings

Total number of 30 studies were found, and after excluding one study (experimental model of DPN), we had 29 studies which were grouped and descriptively summarized under the four themes.

Impact/ Burden of DPN on Other Factors

Physical Factors

Rix *et al*[4] investigated whether peripheral neuropathy (PN), as part of the microangiopathic complex, affects bone mineral density (BMD) of the peripheral or the axial skeleton in patients with type 1 diabetes by comparing BMD between three groups (21 male patients with DM+PN, 21 DM patients without PN and 21 healthy controls). Group-1 had reduced BMD at all sites, followed by group-2, while the group-3 had normal values. The authors concluded that in patients with type 1 diabetes, PN may be an independent risk factor for reduced BMD in the affected limbs as well as in the skeleton in general.

Roman de Mettelinge *et al*[5] investigated the impact of peripheral neuropathy and cognition on gait performance in 101 older adults with type 2 diabetes mellitus (56 patients with diabetes, 28 with peripheral neuropathy and 28 without peripheral neuropathy; and 45 matched controls). The authors found that all older adults with diabetes walked slower, took shorter strides during all walking conditions, and showed more gait variability especially during dual-task conditions, compared to controls. Gait patterns did not differ between participants suffering from diabetes mellitus with and without neuropathy. Gait was affected by reduced cognitive function, irrespective of the presence/ absence of neuropathy.

Gore *et al*[6] assessed the patient-level burden among subjects with painful diabetic peripheral neuropathy (DPN) using measures of pain experience (Brief Pain Inventory-DPN [BPI-DPN]), health status (EuroQoL [EQ-5D]), healthcare utilization (consults, prescription [Rx], and over-the-counter [OTC] medications), and work productivity/ functioning. During the preceding 3 months, 59.6% had >or=2 health professional consults; 59% reported decreased home productivity; 85.5% reported activity limitations; and 64.4% of patients who worked (N = 73) reported missing work/decreased work productivity due to painful DPN.

Sadosky *et al*[7] assessed pain, functioning, sleep, anxiety and depression, health status, and productivity in DPN patients and found that subjects with pDPN exhibited high pain levels, which were associated with poor sleep, function, and productivity. Health care resource utilization in pDPN was prevalent

and costs increased with greater pain severity. The burden of pDPN was greater among subjects with greater pain severity.

Wienemann *et al*[8] assessed cutaneous pressure pain perception threshold (CPPPT) and deep pressure pain perception threshold (DPPPT) in 18 diabetic patients with PDN and plantar injury, partly involving the skeleton (Wagner grade I-II ulcer), 10 non-neuropathic subjects with acute painful skeletal injury (sprain, fracture) and 20 healthy control subjects without foot injury. Compared to control subjects, non-neuropathic acutely injured (and contralateral) feet displayed lowered CPPPT and DPPPT. Conversely, ulcerated and contralateral feet with PDN displayed unmeasurably elevated thresholds in 100% (CPPPT), 72% (DPPPT over joint), and 28% (DPPPT over muscle) of patients, respectively.

Psychological Factors - Quality of Life

Barrett et al[9] in their systematic review found the psychological impact on QoL and social impact through estimates of cost for pain medications to be $1,004 per DPNP patient thus impacting both patients and the health care system.

Davies *et al*[10] found that patients with neuropathic pain had poorer quality of life than those with no pain and those with non-neuropathic pain suggesting that both pain and neuropathy score were independently associated with quality of life.

Treatment-related Impact

Ziegler *et al*[11] evaluated the impact of baseline disease variables related to diabetes and diabetic neuropathy severity on efficacy and safety of duloxetine in the management of diabetic peripheral neuropathic pain, and found that duloxetine was more effective in the subgroup with more severe neuropathic pain.

Healthcare Utilization and Treatment-related Costs

Candrilli *et al*[12] estimated the burden of illness of symptoms of diabetic peripheral neuropathy (SDPN), diabetic retinopathy (DR), and comorbid SDPN and DR on 850 respondents and found that those with SDPN, DR, or comorbid SDPN and DR were more likely than those without the corresponding condition to have had four or more health care visits in the past year. Those of working age with SDPN, DR, or comorbid SDPN and DR were more likely unable to work due to physical limitations.

Dworkin *et al*[13] determined health care costs associated with postherpetic neuralgia (PHN) and painful diabetic peripheral neuropathy (DPN), and the results indicated that the annual excess health care costs associated with peripheral neuropathic pain in patients of all ages range from approximately $1600 to $7000, depending on the specific pain condition. Total excess health care costs associated with painful DPN were substantially greater than those associated with PHN, which might reflect the great medical comorbidity associated with DPN.

Happich *et al*[14] evaluated the health-related quality of life (HRQOL), the resource utilization and annual costs associated with diabetic neuropathy (DN) on 185 adult type 1 and type 2 diabetic patients with DN. The majority of DN patients were severely impaired with regard to general physical HRQOL. Disease specific HRQOL decreased continuously with increasing DN severity. In accordance, costs associated with DN increased as DN progressed, with costs from the societal perspective increasing about 50-fold from the lowest severity stage (patients with sensory-motor neuropathy without symptoms) (euro431) to patients with lower extremity amputation in the year 2002 (euro21,476).

Hoffman *et al*[15] evaluated functional and health status impairments among 401 patients (163 in Asia, 110 in Latin America and 128 in the Middle East), and found that patients in all 3 regions reported difficulties with functioning, sleep, and overall health status, which increased with higher pain severity levels. Patients in Asia had substantial impairments; however, they reported less serious problems than the other regions.

Impact/ Burden of Other Factors on DPN

Duration of Diabetes

Sangiorgio *et al*[16] studied the impact of risk factors on DPN in 374 diabetic patients (66 with type 1 and 308 with type 2 diabetes mellitus) through electrophysiological and clinical examination, and found that longer duration of diabetes > 20 years was an important risk factor for DPN.

Duration of diabetes and poor glycemic control were risk factors for DPN which may also interfere with general activity, mood, mobility, work, social relations, sleep, leisure activities, and enjoyment of life.[17]

Impact of Treatment

Pharmacological Management: Boyle *et al*[18] evaluated the impact of pharmacological management on polysomnographic sleep, daytime functioning, and quality of life in patients with DPNP in their double-blind, randomized, parallel group investigation of type 1 and 2 diabetic subjects with DPNP. Each treatment group had a single-blind, 8-day, placebo run-in followed by 14 days of lower-dose and 14 days of higher-dose medication. The study found that all medications reduced pain when compared with placebo, but no one treatment was superior to any other. For sleep, pregabalin improved sleep continuity, whereas duloxetine increased wake and reduced total sleep time.

Tesfaye *et al*[19] evaluated the change in neuropathy symptoms and disease progression in 262 placebo-administered patients from two 1-year studies in which the impact of ruboxistaurin (RBX) in mild diabetic peripheral neuropathy (DPN) was tested. In placebo-administered patients with mild symptomatic DPN, there was a progressive improvement in symptoms over 12 months, whereas nerve conduction studies and heart rate deep breathing (HRDB) declined, and clinically significant worsening of DPN would require > 1 year of observation.

Dziemidok *et al*[20] evaluated the association between glycemic control and indices of diabetic neuropathy in 204 patients with diabetes (type 1 - 29; type 2 - 175) and found that persons with sensation deficits and neuropathy symptoms had not significantly higher (Neuropathy Syndrome Total Score, temperature sensation disturbances) and not significantly lower (vibration and touch) glycatedhaemoglobin level compared to patients without neuropathy.

Non-pharmacological Management: Forst *et al*[21] evaluated the impact of treatment comparing transcutaneous electrical nerve stimulation (TENS) device "Salutaris" (verum group) or a placebo treatment with an identical but electrically inactive device (placebo group) in 19 DPN patients and found that active TENS-treatment resulted in a significant improvement in NTSS-6 score after 6 wk (-42%) and after 12 wk (-32%) of treatment. Subanalysis of the different qualities of the NTSS-score revealed an improvement in numbness; lancinating pain and allodynia. Also, a significant improvement in the VAS rating was found after 6 wk of TENS therapy, while no change was observed in the placebo arm.

Diet and Nutrition

McCarty[22] reported that a low-fat, whole-food vegan diet, coupled with daily walking exercise, leads to rapid remission of neuropathic pain in the majority of type 2 diabetics expressing this complication, probably due to improved blood rheology - decreased blood viscosity and increased blood filterability, that lead to impaired endoneurial microcirculatory perfusion in diabetic

neuropathy. The author suggested that a vegan diet could also reduce risk for other major complications of diabetes - retinopathy, nephropathy, and macrovascular disease - independent of its tendency to improve glycemic control in type 2 patients.

Impact/ Burden of Other Factors on Comorbidities in DPN

Chin *et al*[23] evaluated the effects of health belief model factors (action cues, self-efficacy and perceived barriers) on daily foot-exam practice among 277 DPN patients and found that select action cues (recommendations from family, friends, or health professionals), perceived self-efficacy and perceived barriers interactively influenced the participants' daily foot-exam practice.

Impact of Treatment

Charles *et al*[24] examined the effects of early detection and intensive treatment (IT)of type 2 diabetes in primary care on the prevalence of diabetic peripheral neuropathy (DPN) and peripheral arterial disease (PAD) 6 years later in a pragmatic, cluster-randomized parallel group trial of 1,533 people with type 2 diabetes who were randomized to deliver either IT or routine care (RC) as recommended through national guidelines. The authors found no statistically significant effect of IT on the prevalence of DPN and PAD compared with RC.

El-Nahas *et al*[25] studied the impact of topical phenytoin on the healing of recalcitrant neuropathic diabetic foot ulcers in patients with no clinical evidence of ischaemia or infection, and evaluated its antibacterial effect in 32 patients and found that Topical phenytoin significantly improved healing of recalcitrant neuropathic diabetic foot ulcers, with little antibiotic effect.

Impact/Burden of Comorbidities on Other Factors in DPN

Physical

Van Acker *et al*[26] conducted a cross-sectional study that included 1111 patients (767 type 2 and 344 type 1 diabetic patients) and measured the association of DPN and DPN-P with other diabetic complications, the impact on quality of life (QoL) and pain management were also investigated. Nephropathy, obesity, low HDL cholesterol and high triglyceride levels were independently associated with DPN and/or DPN-P. Physical and mental components of QoL were significantly altered by DPN-P, but not DPN. Only half of the DPN-P patients were using analgesic treatment, while 28% were using anticonvulsants or antidepressants.

Psychosocial

Boulanger *et al*[27] evaluated the burden of comorbid anxiety and depression on healthcare costs and economic burden in DPN patients into 2 subgroups- 1,699 patients with depression/anxiety and 16,831 patients without depression/anxiety. The former group had higher prevalence of diabetes-related comorbidities for cardiovascular disease, cerebrovascular/peripheral vascular disease, nephropathy, obesity, and hypoglycemic events than DN-only patients. They also had higher total healthcare costs than patients with DN-only.

Boulanger *et al*[28] evaluated the burden of comorbid anxiety and depression by measuring their relationship with patterns of treatment, healthcare utilization, and associated costs in DPN patients (11,854 DPNP-only and 1512 DPNP-DA). Patients with depression/anxiety reported a significantly higher pain and DPNP-related medication. All components of healthcare utilization, except home healthcare visits and physician office visits, were more likely to be provided to DPNP-DA patients versus the DPNP-only cohort. Controlling for differences in demographic and clinical characteristics, DPNP-DA patients had significantly higher total costs than those of DPNP-only patients.

Zhao *et al*[29] evaluated the impact of diabetes-related complications or comorbidities

on health-related charges and found that the presence of any other diabetes-related complication or comorbidity was associated with higher outpatient pharmacy and total charges for both DN patients and controls. Total and outpatient pharmacy charges were also significantly higher for DN patients than for controls, among those with or without any other diabetes-related complications or comorbidities.

Zhao *et al*[30] examined the impact of Type 1 diabetes and having any other diabetes-related complication or comorbidity on healthcare charges and utilization in patients with diabetic neuropathy (DN). Type 1 and Type 2 patients with DN but no other diabetes-related complication or comorbidity had similar healthcare utilization. However, Type 1 patients had higher charges than those with any other diabetes-related complication or comorbidity, with a significant impact on healthcare charges and utilization.

Discussion

This systematic review aimed to inform evidence through a reappraisal of current literature on impact and burden of DPN as an illness and the findings provide a multidimensional impact of DPN on individual in terms of physical and psychosocial influences; on the society in terms of work-related disability and healthcare utilization costs; and to the nation in terms of public health burden.

This review was not originally aimed to perform meta-analysis through data pooling of individual studies since it was well known of the inevitable heterogeneity in terms of diagnostic criteria of DPN; the evaluation tools used; and types of impact evaluated; and, methods of evaluating impact and burden.

Future population-based cohort studies are essential to imply practice-based recommendations and to extrapolate the findings of evidence into routine practice.

The globally rising prevalence of DPN, with its wide range of treatment options including medical,[31] physiotherapeutic,[32] neurodynamic,[33] surgical[34] and acupuncture,[35] indicate that future controlled clinical trials should focus on burdensomeness as an outcome measure in research studies of effects, efficacy and effectiveness of interventions.

Future evidence-informed clinical practice guidelines henceforth should emphasize the multidisciplinary biopsychosocial perspective to evaluation and management of patients with DPN addressing the multidimensional burden to the individuals and their caregivers.[36]

Conclusion

DPN has a multidimensional impact on the person, society and nation, and is a physical, physiological, psychological and psychosocial burden for patients and their caregivers. A strong interdisciplinary collaborative working relationship is essential to combat the consequences of this disorder so that interventions might be aimed along a symptom control to quality of life continuum.

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