Diabetic Peripheral Neuropathy

Subjects: Pathology

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Diabetic peripheral neuropathy (DPN) is the most common complication of both type 1 and 2 diabetes. As a result, neuropathic pain, diabetic foot ulcers and lower-limb amputations impact drastically on quality of life, contributing to the individual, societal, financial and healthcare burden of diabetes.

Keywords: diabetes ; neuropathy ; peripheral neuropathy ; distal sensory polyneuropathy ; diabetic neuropathy ; diabetic peripheral neuropathy ; early detection ; screening ; diagnostics ; point-of-care

1. Introduction

The International Diabetes Federation (IDF) estimated the global prevalence of diabetes is 425 million people in 2017 and is predicted to rise to 628 million by 2045 [1]. This has been accompanied by an increase in the burden of diabetic complications [2][3]. Diabetic neuropathy affects 10–50% of people with type 1 (T1D) and type 2 diabetes mellitus (T2D) [4][5][6][7]. In the US, the annual cost for managing DPN and foot ulceration with lower limb amputation is estimated to be between $4.6–13.7 billion [8]. Diabetic peripheral neuropathy (DPN) has a predilection for small unmyelinated or thinly myelinated C and Aδ nerve fibres [9], which mediate temperature and pain perception, tissue blood flow and sweating, all of which are key factors for foot ulceration [10]. Small fibre deficits are considered to precede large fibre involvement in DPN [5][11]. Furthermore, small fibre degeneration occurs in prediabetes suggesting early subclinical pathology before the onset of overt T2D [12][13]. Indeed, small fibres are the earliest to degenerate and have the greatest potential for repair as shown in studies with normalisation of hyperglycaemia through pancreatic transplantation in T1D and weight loss following lifestyle intervention in prediabetes [14][15][16].

2. Economic and Functional Consequences of Small Fibre Degeneration

Degeneration of small sensory nerve fibres occurs in painful DPN (pDPN) which is present in up to one-third of patients with diabetes [17][18][19]. Neuropathic pain has a profound impact on quality of life, physical and emotional health and affects both functionality and sleep [20][21][22]. Chronic intractable pain is associated with anxiety and depression and is often refractory to current therapies [21][23]. Consequently, people with pDPN are more likely to be unemployed and loss of working time in a U.S. population cost ~$3.65 billion each year [24][25]. Furthermore, people suffering severe chronic pain have an increased ten-year mortality [26].

DPN is significantly underdiagnosed leading to missed opportunities for preventing progression to severe DPN and foot ulceration, which has a dreadful 5-year mortality [27][28][29]. Indeed, DPN is a major cause of foot ulceration and is implicated in 50–75% of all non-traumatic amputations [30][31]. Mortality, one and five-years after lower limb amputation in people with diabetes ranges from 10–50%, to 30–80% respectively [32][33][34] with the latter mortality rate comparable to lung cancer [35]. DPN and amputation represent a devastating impact on the individual leading to a loss of function, quality of life and financial stability [36][37]. In the UK, the National Health Service (NHS) spent £639 million on diabetic foot ulcers and £662 million on lower limb amputations, accounting for £1 in every £150 spent out of the NHS healthcare budget [38].

3. Pathogenesis

Whilst there has been progress in identifying the pathophysiology of DPN, a complete understanding of this process remains elusive [39]. DPN is associated with hyperglycaemia, hyperlipidaemia, insulin resistance and protein catabolism [6][40]. Hyperglycaemia-induced oxidative stress and reactive oxygen species result in peripheral nerve injury [41][42]. Experimental data have demonstrated nitro-oxidative stress in dorsal root ganglia, axons and Schwann cells with nerve conduction impairment, neurovascular dysfunction, apoptosis and sensory deficits [43][44][45][46]. There is also activation of poly (ADP-ribose) polymerase, polyol, hexosamine and protein kinase C (PKC) pathways and accumulation of advanced glycation end products culminating in axonal dysfunction and damage [44][47][48][49][50][51]. Increased flux through the polyol

pathway leads to accumulation of sorbitol and fructose, myo-inositol depletion and a reduction in Na^+K^+-ATPase activity. Endoneurial microvascular deficits result in hypoxia and ischaemia, generation of reactive oxygen species (oxidative stress), activation of the redox-sensitive transcription factor NFκB, and increased activity of PKC [52][53].

4. Evidence in Favour of Early Intervention for DPN

The incidence of DPN is associated with hyperglycaemia and also cardiovascular risk factors such as raised cholesterol, triglycerides, hypertension, obesity and smoking [54]. Indeed, all of these risk factors can be modulated by early intervention. In a large longitudinal study of 1441 people with T1D in the Diabetes Control and Complications trial (DCCT), intensive insulin treatment reduced the risk of developing DPN by 60% [55][56]. In fact, a continuous beneficial effect after intensive insulin treatment was observed in participants of the DCCT trial after 10 years of follow-up in the Epidemiology of Diabetes Interventions and Complications (EDIC) trial [57]. Furthermore, a Cochrane Systematic Review found enhanced glucose control significantly reduced the risk of developing DPN in participants with T1D compared to standard of care [58]. However, whilst tight glucose control reduces the incidence of DPN in T2D, this reduced risk was not statistically significant [58] and in T2D, DPN has greater multifactorial causality due to the heterogeneous nature of the disease. For instance, obesity and hypertriglyceridemia are significant risk factors of DPN for people with T2D, independent of glucose control [59]. It follows that treatment of hypertension in people with T2D is associated with a significant reduction in the incidence of DPN and improvements in people with mild DPN [60][61][62]. Furthermore, a small randomised, double-blind, placebo-controlled Phase IIa study of participants with T2D and early DPN, found that reduction of low-density lipoprotein (LDL) cholesterol and triglycerides using rosuvastatin improved the neuropathy score and nerve conduction parameters [63]. Individualised diet and aerobic and resistance exercise regimens are important in the reversal of early DPN changes and the prevention of progression to DPN [15][64][65]. Thus, a multifactorial approach is required for the prevention and early treatment of DPN of people with T2D. A key underpinning of multifactorial treatment is an accurate, reiterative diagnostic modality for the screening of people with diabetes to reliably detect early DPN.

5. Current Clinical Assessment of Neuropathy

The signs and symptoms of DPN are insidious and current screening programmes rely on subjective tests of large nerve fibre dysfunction [66][67]. NICE recommends vibration perception testing using a 128 Hz tuning fork together with a 10 g (Semmes-Weinstein) monofilament for the screening of DPN [67]. However, these tests identify DPN at a late, irreversible, pre-ulcerative stage [68][69][70]. Thus, an abnormal monofilament test is associated with a 3-year relative risk of 15% (95% CI 9.0 to 26.0) for foot ulceration or lower limb amputation [71]. Despite, early and progressive injury to small fibres in diabetes, small nerve fibre assessment is not included in annual diabetic foot screening programmes [11][72].

In direct contrast, diabetic retinopathy and diabetic kidney disease have effective screening programmes which detect early sub-clinical pathology, enabling early interventions [73] which has led to a reduction in blindness [73] and end stage renal failure [74]. In fact, largely due to the success of diabetic retinopathy screening, it is no longer the leading cause of sight loss in western society [75]. Early, multifactorial risk factor modification may reduce the risk of foot ulceration and amputation [76][77]. The Toronto Diabetic Neuropathy Expert Group and American Diabetes Association (ADA) [6][78] have recommended the early detection and monitoring of DPN, but have recommended monofilament or crude neurological testing. Clearly, there is a need for robust screening methods capable of diagnosing subclinical DPN. This article aims to critically appraise commonly used research and clinical diagnostic tools to evaluate their potential role in screening for early DPN.

6. Methods

Electronic database searches were undertaken in Google Scholar, EMBASE, PubMed, OVID and Cochrane CENTRAL to identify the included articles. Reference lists of relevant articles were searched and in addition, studies were identified by authors with expertise in DPN. Studies published from initial curation of the electronic database to November 2020 were identified and those felt not relevant by authors were excluded with the guidance of the senior author (U.A.).

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