

World Journal of *Diabetes*

World J Diabetes 2024 April 15; 15(4): 575-796



EDITORIAL

- 575 Nε-carboxymethyl-lysine and inflammatory cytokines, markers and mediators of coronary artery disease progression in diabetes
Eiras S
- 579 Non-pharmacological interventions for diabetic peripheral neuropathy: Are we winning the battle?
Blaibel D, Fernandez CJ, Pappachan JM
- 586 Effect of bariatric surgery on metabolism in diabetes and obesity comorbidity: Insight from recent research
Tang HH, Wang D, Tang CC
- 591 Application and management of continuous glucose monitoring in diabetic kidney disease
Zhang XM, Shen QQ
- 598 Pancreatic surgery and tertiary pancreatitis services warrant provision for support from a specialist diabetes team
Mavroeidis VK, Knapton J, Saffioti F, Morganstein DL

REVIEW

- 606 Role of renin-angiotensin system/angiotensin converting enzyme-2 mechanism and enhanced COVID-19 susceptibility in type 2 diabetes mellitus
Shukla AK, Awasthi K, Usman K, Banerjee M

MINIREVIEWS

- 623 Are treatment options used for adult-onset type 2 diabetes mellitus (equally) available and effective for children and adolescents?
Krnic N, Sesa V, Mrzljak A, Berkovic MC

ORIGINAL ARTICLE

Retrospective Cohort Study

- 629 Prevalence and risk factors of wound complications after transtibial amputation in patients with diabetic foot
Park YU, Eim SH, Seo YW

Retrospective Study

- 638 Prevalence and risk factors of diabetes mellitus among elderly patients in the Lugu community
Zhao LZ, Li WM, Ma Y

- 645 Influence of blood glucose fluctuations on chemotherapy efficacy and safety in type 2 diabetes mellitus patients complicated with lung carcinoma

Fang TZ, Wu XQ, Zhao TQ, Wang SS, Fu GMZ, Wu QL, Zhou CW

- 654 Construction and validation of a neovascular glaucoma nomogram in patients with diabetic retinopathy after pars plana vitrectomy

Shi Y, Zhang YX, Jiao MF, Ren XJ, Hu BJ, Liu AH, Li XR

Clinical Trials Study

- 664 Effect of special types of bread with select herbal components on postprandial glucose levels in diabetic patients

Gostiljac DM, Popovic SS, Dimitrijevic-Sreckovic V, Ilic SM, Jevtovic JA, Nikolic DM, Soldatovic IA

Observational Study

- 675 Examining the association between delay discounting, delay aversion and physical activity in Chinese adults with type-2 diabetes mellitus

An YD, Ma GX, Cai XK, Yang Y, Wang F, Zhang ZL

- 686 Correlation of periodontal inflamed surface area with glycated hemoglobin, interleukin-6 and lipoprotein(a) in type 2 diabetes with retinopathy

Thazhe Poyil NJ, Vadakkekuttical RJ, Radhakrishnan C

Prospective Study

- 697 Association of age at diagnosis of diabetes with subsequent risk of age-related ocular diseases and vision acuity

Ye ST, Shang XW, Huang Y, Zhu S, Zhu ZT, Zhang XL, Wang W, Tang SL, Ge ZY, Yang XH, He MG

- 712 Associations between remnant cholesterol levels and mortality in patients with diabetes

Pan D, Xu L, Zhang LX, Shi DZ, Guo M

Basic Study

- 724 Teneligliptin mitigates diabetic cardiomyopathy by inhibiting activation of the NLRP3 inflammasome

Zhang GL, Liu Y, Liu YF, Huang XT, Tao Y, Chen ZH, Lai HL

- 735 Novel insights into immune-related genes associated with type 2 diabetes mellitus-related cognitive impairment

Gao J, Zou Y, Lv XY, Chen L, Hou XG

- 758 Long-term effects of gestational diabetes mellitus on the pancreas of female mouse offspring

Muñoz-Islas E, Santiago-SanMartin ED, Mendoza-Sánchez E, Torres-Rodríguez HF, Ramírez-Quintanilla LY, Peters CM, Jiménez-Andrade JM

- 769 Icarin accelerates bone regeneration by inducing osteogenesis-angiogenesis coupling in rats with type 1 diabetes mellitus

Zheng S, Hu GY, Li JH, Zheng J, Li YK

META-ANALYSIS

- 783** Application of three-dimensional speckle tracking technique in measuring left ventricular myocardial function in patients with diabetes

Li Z, Qian Y, Fan CY, Huang Y

LETTER TO THE EDITOR

- 793** Metabolic syndrome's new therapy: Supplement the gut microbiome

Xu YW, Tian J, Song Y, Zhang BC, Wang J

ABOUT COVER

Peer Review of *World Journal of Diabetes*, Da-Feng Liu, MD, Doctor, Professor, The First Ward of Internal Medicine, Public Health Clinical Centre of Chengdu, Chengdu 610061, Sichuan Province, China. ldf312@126.com

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJD* as 4.2; IF without journal self cites: 4.1; 5-year IF: 4.5; Journal Citation Indicator: 0.69; Ranking: 51 among 145 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Cover Editor: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Lu Cai, Md. Shahidul Islam, Michael Horowitz

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

April 15, 2024

COPYRIGHT

© 2024 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Non-pharmacological interventions for diabetic peripheral neuropathy: Are we winning the battle?

Dania Blaibel, Cornelius James Fernandez, Joseph M Pappachan

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Horowitz M, Australia; Yu M, China

Received: November 29, 2023

Peer-review started: November 29, 2023

First decision: January 16, 2024

Revised: January 18, 2024

Accepted: March 4, 2024

Article in press: March 4, 2024

Published online: April 15, 2024



Dania Blaibel, Joseph M Pappachan, Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, Preston PR2 9HT, United Kingdom

Cornelius James Fernandez, Department of Endocrinology & Metabolism, Pilgrim Hospital, United Lincolnshire Hospitals NHS Trust, Boston PE21 9QS, United Kingdom

Joseph M Pappachan, Faculty of Science, Manchester Metropolitan University, Manchester M15 6BH, United Kingdom

Joseph M Pappachan, Faculty of Biology, Medicine & Health, The University of Manchester, Manchester M13 9PL, United Kingdom

Corresponding author: Joseph M Pappachan, MD, FRCP, Academic Editor, Consultant Endocrinologist, Professor, Department of Endocrinology and Metabolism, Lancashire Teaching Hospitals NHS Trust, Sharoe Green Lane, Preston PR2 9HT, United Kingdom. drpappachan@yahoo.co.in

Abstract

Despite the advent of relatively reliable modalities of diagnosing diabetic peripheral neuropathy (DPN), such as nerve conduction studies, there is still a knowledge gap about the pathophysiology, and thus limited available interventions for symptom control and curtailing disease progression. The pharmacologic aspect of management is mainly centred on pain control, however, there are several important aspects of DPN such as loss of vibration sense, pressure sense, and proprioception which are associated with risks to lower limb health, which pharmacotherapy does not address. Furthermore, published evidence suggests non-pharmacologic interventions such as glycaemic control through dietary modification and exercise need to be combined with other measures such as psychotherapy, to reach a desired, however modest effect. Acupuncture is emerging as an important treatment modality for several chronic medical conditions including neuropathic and other pain syndromes. In their study published in the *World Journal of Diabetes* on the potential of acupuncture to reduce DPN symptoms and enhance nerve conduction parameters, Hoerder *et al* have been able to demonstrate that acupuncture improves sensory function and that this effect is likely sustained two months after treatment cessation. Although previous studies also support these findings, larger multi-center randomized control trials including a sham-controlled arm accounting for a placebo effect are required. Overall, given the satisfactory safety profile and the positive results found in these studies, it is likely that acupuncture may become an important

aspect of the repertoire of effective DPN management.

Key Words: Diabetic peripheral neuropathy; Diabetes mellitus; Pharmacotherapy; Acupuncture; Neuropathic pain; Nonpharmacological intervention

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Even with multiple studies examining the pathobiology and management options for diabetic peripheral neuropathy (DPN), especially the neuropathic pain, there are still large knowledge gaps in our understanding to effectively address this important clinical problem. Acupuncture is an important nonpharmacological option for several chronic medical conditions including pain syndromes. In their study published in the *World Journal of Diabetes*, Hoerder *et al* provide us the reasonable efficacy of acupuncture for the management of DPN, though we need larger multi-center randomized clinical trials for using this therapeutic intervention to enable more evidence-based clinical decision-making.

Citation: Blaibel D, Fernandez CJ, Pappachan JM. Non-pharmacological interventions for diabetic peripheral neuropathy: Are we winning the battle? *World J Diabetes* 2024; 15(4): 579-585

URL: <https://www.wjgnet.com/1948-9358/full/v15/i4/579.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v15.i4.579>

INTRODUCTION

Peripheral neuropathy is one of the most common and difficult-to-manage complications of diabetes mellitus (DM). Distal symmetric polyneuropathy (DSPN) is the most common form of diabetic peripheral neuropathy (DPN) which affects around 50% of individuals with type 2 DM (T2DM) with disease duration > 10 years, and approximately 20% of patients with type 1 DM (T1DM) with the disease duration > 20 years[1]. Even 10%–15% of T2DM cases may have DSPN at the time of diagnosis of DM as the metabolic derangements in T2DM might have been present for several years before the actual diagnosis. Furthermore, the lack of standardized diagnostic criteria for diabetic neuropathy in the literature creates difficulty in comparing studies, even though it is imperative to initiate early management. The reason for this is the presence of peripheral neuropathy in between 25% and 62% of patients with prediabetes, which often go on to develop chronic painful DSPN[2]. In this paper, we aim to highlight current reliable methods of diagnosing and effectively managing DPN, with a focus on acupuncture as a novel non-pharmacotherapeutic option for DPN symptom alleviation.

PATHOPHYSIOLOGY

Although there is only a limited understanding of the mechanisms of development and progression of DPN based on published evidence, there are several proposed theories based on experimental data. For instance, disintegration of the myelin sheath and Schwann cells leading to axonal degeneration has been shown in nerve biopsies from animal and human models with DPN[3]. Axonal degeneration results in disruption of impulse signalling, and conduction, and creates afferent nerve axonal loss that progresses in a length-dependent fashion[3]. This is likely why long nerve fibres such as the peroneal and sural nerves are affected early in the course of DPN. Furthermore, changes in the blood-nerve barrier (BNB) function are linked to the incidence and development of DPN. Increased permeability of the BNB results in leakage of proteins such as albumin and immunoglobulin G into the endoneurium with the development of progressive oedema and subsequent ischemic nerve damage[3,4].

There is also evidence to suggest that systemic inflammation[5] and accumulation of advanced glycation end products [6] are associated with the occurrence of DPN. It is likely that hyperglycaemia leads to the upregulation of systemic inflammation and subsequent oxidative stress. Activation of various inflammatory and oxidative pathways by a chronic hyperglycaemic state in poorly controlled DM leads to the accumulation of various reactive oxygen species which may induce neuronal damage and apoptosis leading to DPN[3].

CLINICAL PRESENTATION

Although peripheral neuropathy affects 20% to 50% of patients with DM, it is still important to distinguish DPN from other disorders of the peripheral and central nervous system associated with neuropathy, medication-induced and toxic neuropathies, various vitamin deficiency states, infective conditions such as Lyme disease, and human immunodeficiency virus disease, Guillain-Barre syndrome, compressive/entrapment neuropathy, and hereditary neuropathies. In particular, the most common presentation of DPN is an insidious symmetric sensory alteration of the distal extremities that

progresses in a “stocking and glove” pattern. While numbness and diminished vibration sense and proprioception are attributed to large-myelinated fibre neuropathy, pain and decreased pinprick sensation are due to small unmyelinated fibre damage. It is important to note that most patients with DPN often exhibit large and small fibre involvement[7].

Symptoms generally begin in the toes followed by the calves and then subsequently the fingers and forearms once the symptoms ascend above knee level. Nearly a third of patients report neuropathic pain, with other common symptoms such as hyperesthesia or allodynia also being prevalent[8]. It is also important to determine whether any concurrent autonomic symptoms are present such as orthostatic hypotension, gastroparesis, or erectile dysfunction. Distinguishing DPN from central nervous system lesions is critical by verifying about symptoms and signs such as dysarthria, cranial nerve involvement, and visual disturbances. Nerve compression or radiculopathy tends to develop in an acute asymmetrical fashion, bearing in mind that emergencies such as cauda equina syndrome need to be excluded. Furthermore, patient’s history may point towards a hereditary neuropathy if there is a report of childhood clumsiness or difficulty with shoe fitting[8].

While current guidelines recommend assessing DPN in patients with T2DM at diagnosis and patients with T1DM five years after diagnosis and then annually thereafter, it should be stressed that DPN is often underdiagnosed due to the lack of rapid, reliable, as well as highly sensitive and specific testing methods that can be done in the clinical setting[7].

DIAGNOSIS OF DIABETIC PERIPHERAL NEUROPATHY

Although diagnosing DPN often remains primarily clinical, several testing modalities can aid diagnosis which constitutes screening tools, quantitative sensory testing, as well as nerve conduction studies (NCS)[3]. The most widely used scoring method is the Douleur Neuropathique 4 (DN4)[9]. This technique allows the clinician to assess the signs and symptoms such as paraesthesia, hypoesthesia, as well as burning or shooting pain. It is a 10-item scoring system with a cut-off of 4 as an indication that the diagnosis is likely. DN4 has a reported sensitivity of 80% and a specificity of 91%, rendering this a reliable tool in assisting initial diagnosis[3]. There are other relatively dependable scoring metrics such as the Toronto Clinical Neuropathy Score, the Michigan Neuropathy Screening Instrument (MNSI), the Small Fiber Neuropathy and Symptoms Inventory Questionnaire, and the Neuropathy Disability scores. However, their sensitivity and specificity do not at present compare with that of the DN4[3]. Furthermore, the DN4 is a reasonably simple scoring tool, likely contributing to its popular use amongst clinicians.

Quantitative sensory testing is often a useful aid to sign and symptom evaluation in establishing DPN diagnosis. The evidence does suggest that combining a scoring metric in history taking, along with quantitative sensory testing such as with a tuning fork and the 10 g monofilament, reflects greater sensitivity and specificity in overall means of accurate diagnosis.

The gold standard for diagnosis of DPN however, remains NCS[3]. The test can assess myelinated α and β large fibres through velocity of nerve conduction, amplitudes, and latencies. Since DPN affects the long fibres of the lower extremities, it is the plantar, peroneal, and sural nerves that are often evaluated. The gold standard for identifying small nerve abnormalities is the intraepidermal nerve fibre density, whereby immunohistochemical testing is conducted on a distal skin biopsy and stained small nerve fibres are counted and compared to standardized values[4]. It should be noted that a systematic evaluation of DPN comprising detailed history taking, using a quantifiable scoring metric, sensory testing through a pinprick, tuning fork, and monofilament, along with NCS is more likely to yield a more accurate diagnosis.

PHARMACOTHERAPY AND ITS LIMITATIONS

Pharmacotherapy is limited in its capacity to effectively treat DPN as there is a lack of disease-modifying agents, with the sole aim of pharmacotherapy at present being pain control. Furthermore, multiple clinical trials have indicated that although achieving glycaemic control has shown some beneficial effects in ameliorating DPN in T1DM, this has not been the case for patients with T2DM[7]. There are currently four classes of drugs approved for the treatment of DPN-related pain including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentanoids, and sodium channel blockers. Unfortunately, given these medications have similar effect sizes and differences within a class are likely minimal to non-existent[7], clinicians usually prescribe according to subjective patient experience on questionnaires, while attempting to implement cost-effective and tolerable therapies.

Moreover, clinicians often have to prescribe multiple medications in order to achieve relative pain control which increases the pill burden on patients who often experience medication side effects. Recently there has been research investigating the use of sodium glucose cotransporter 2 inhibitors to treat DPN, with it showing promising effectiveness in T1DM, however, this has only been demonstrated in animal models[7,10]. With regards to topical therapy, capsaicin is the most widely studied and interestingly carries a similar effect size as oral medication. Nevertheless, given the effect size of oral and topical therapy is limited, with approximately only 1 in 7 patients with DPN reporting effective pain relief [7], treating patients should focus on starting a combination of oral and topical therapy while titrating dosages as the pain worsens with disease progression.

NON-PHARMACOTHERAPEUTIC OPTIONS

The clinical management of DPN has often focused on weight loss through dietary modification and exercise, orthotic footwear, and annual foot examinations, as well as patient education and psychological intervention. For instance, in the Look Ahead study, 5145 diabetic patients were randomized to an arm that focused primarily on weight loss as an intervention[11]. This study showed that the dietary weight loss did reflect symptom improvement on the MNSI questionnaire. Another recent observational study also showed that weight loss seems to show symptom reduction on the MNSI questionnaire[12]. Therefore, it is likely that weight loss does show a potential in managing patients symptomatically, however, weight loss needs to be combined with other interventions to achieve a disease-modifying effect. With regards to behavioural intervention, it has been demonstrated that cognitive behavioural therapy, when combined with exercise has shown potential for effective symptom management, with similar evidence reported in studies on chronic illnesses such as fibromyalgia[13].

Neuro-modulatory treatment modalities have been an important nonpharmacological therapeutic intervention for various pain syndromes in the past few decades. The basic principle of this treatment is altering the electrical signals in the pain-subserving neural pathways to increase the pain perception threshold or by stimulation of neural transmitters with pain inhibition potential. Transcutaneous electrical nerve stimulation was found to be effective in managing patients with painful DPN in the past[14]. A recent systematic review reported good efficacy of spinal cord electrical stimulation (SCS) in improving the symptoms of painful neuropathies[15]. Apart from various techniques used in SCS, dorsal root ganglion stimulation is another modality of pain control in painful DPN[16].

ACUPUNCTURE TREATMENT FOR CHRONIC CONDITIONS

Acupuncture is one of the non-pharmacotherapeutic options for the treatment of several chronic painful states including DPN. Historically, acupuncture has been used to treat various conditions such as chronic migraine, carpal tunnel syndrome, fibromyalgia, as well as other musculoskeletal pain-related conditions. The interest in acupuncture is that it is a non-invasive and cost-effective therapy, with a reasonable safety profile. In a meta-analysis of data involving 20827 patients from 39 trials, it was shown that acupuncture was superior to both the sham and no acupuncture controls for each pain condition[17]. Furthermore, the authors demonstrated that although there is a minor decrease of 15% in treatment effect after one year, the efficacy of acupuncture is maintained over time. In particular, there have been studies on the effectiveness of acupuncture on chemotherapy-induced neuropathy in cancer patients. Therefore, it is evident that acupuncture can be used as a safe means to alleviate symptoms of peripheral neuropathy across various patient populations.

ACUPUNCTURE TREATMENT FOR DPN

Acupuncture has been postulated as a safe and effective means for managing DPN. In a recent study of various systematic reviews, it has been illustrated that acupuncture improves nerve conduction and clinical symptoms[18]. These results have been echoed by another meta-analysis which has shown that most randomized controlled trials favour the use of acupuncture over the non-acupuncture control for minimizing neuropathic pain[19]. ACUDIN trial was a recent three-armed randomized placebo-controlled trial, among patients with confirmed DPN evaluated over a series of 10 consecutive weeks. The trial was able to demonstrate that acupuncture treatment improved the amplitude of the sural nerve action potential by 1.95 while only 0.5 was noticed in the placebo group[20]. Furthermore, the sural nerve conduction velocities improved significantly by a mean of 13.5 m/s in the acupuncture group compared to placebo with 3.4 m/s. This suggests that acupuncture has the potential to not only improve patient-reported outcomes on questionnaires or examination scores but also nerve conduction parameters.

In their randomized control trial published in the *World Journal of Diabetes*, Hoerder *et al*[21] focused on the use of acupuncture to manage hypesthesia, numbness, and loss of sensory function in patients with DPN. This is an especially important area for investigation as hypesthesia, numbness, and loss of sensory function are implicated in falls, foot injury, and ulceration, as well as lower limb amputation with disease progression. Immobility and reduced independence from DPN would likely have a negative impact on overall patient morbidity and mortality. Hoerder *et al*[21] have been able to demonstrate that after a series of acupuncture sessions in those with moderate to severe DPN symptoms, patients showed improved sensory function, as well as reduced dysesthesia on symptom inventory questionnaires and neurological examination scores. This was especially evident between week 8 and week 16 of treatment, whereby patients reported a reduction in numbness of about 32%[21]. Impressively the acupuncture effects seem to have lasted nearly 2 months post-treatment compared to the control group. However, a placebo effect has not been considered in this regard. This study does have a few limitations, such as nerve conduction parameters not being shown with the use of the DPN-check, the lack of blind clinical assessors, as well as a relatively small sample size. Future studies should focus on a large sample size in a double-blind randomized clinical trial (RCT), whereby NCS are employed to provide more accurate information on any change in nerve conduction following acupuncture therapy. Figure 1 shows currently available management options for DPN.

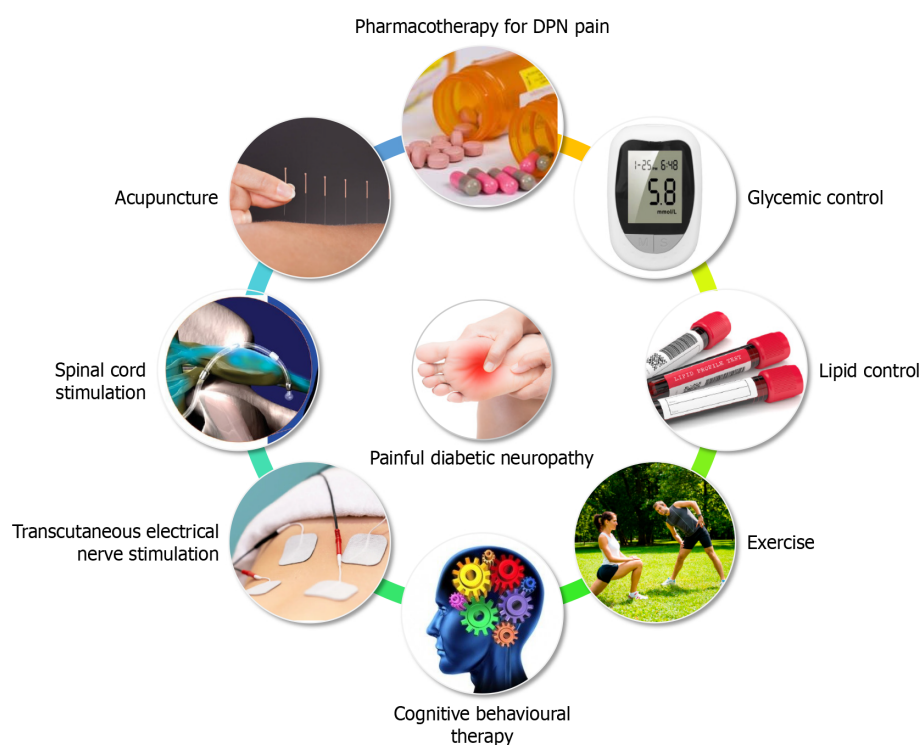


Figure 1 The therapeutic options for the management of painful diabetic neuropathy. DPN: Diabetic peripheral neuropathy.

EMERGING RESEARCH AND POTENTIAL NOVEL THERAPEUTIC OPTIONS

Historically, research on the pathogenesis of DPN has focused on the role of hyperglycaemia and hyperlipidaemia in disrupting mitochondrial function through the accumulation of reactive oxygen species, ultimately resulting in neuronal apoptosis and axonal failure[22]. However, understanding the microenvironment of the neuron during DPN development and the role of various cellular components such as Schwann cells and macrophages is critical for testing and innovating targeted therapies. For instance, novel research is now capable of deriving Schwann cells from human pluripotent stem cells that mimic the molecular features of primary Schwann cells and are capable of myelination *in vivo* and *in vitro*. Interestingly, researchers were able to demonstrate that bupropion, an antidepressant, counteracts glucotoxicity, as well as prevents sensory dysfunction and Schwann cell apoptosis in mice[23]. This method is an excellent modality for screening the effectiveness of potential drug candidates as well as studying whether certain pharmacotherapies inhibit DPN development. In addition, this will likely also lead to an enhanced understanding of the primary biochemical pathways involved in disease onset and progression.

There have also been several studies in the literature on non-pharmacological interventions to improve sensory function and reduce patient pain scores, specifically focusing on diet and physical activity. For instance, some recent studies have reported that a keto diet along with exercise has the potential to prevent and reverse the effects of DPN[24], while others have shown that switching from a diet rich in saturated fats to a diet rich in plant-based unsaturated fats and fish oil restores nerve function and counters axonal mitochondrial dysfunction[22]. Future studies must analyse various permutations of both pharmacological and non-pharmacological interventions in DPN patients. This will assist in determining the most effective holistic first-line treatments for patients, and likely therefore significantly enhance patient morbidity and mortality outcomes.

CONCLUSION

DPN is one of the most common chronic complications of diabetes affecting up to a half of the patients in their diabetes journey. It is imperative that DPN is diagnosed and managed early, in order to preserve patients' foot health and thus the quality of life. It would be interesting if future RCTs and meta-analyses investigated which combinations of quantitative testing allow for the earliest accurate diagnosis of DPN, as well as which combination of pharmacologic as well as non-pharmacologic intervention seems to be the most effective at managing symptoms and reducing disease progression. More effective pharmacologic and nonpharmacological treatments are to be developed to improve the care of patients with this crippling chronic ailment.

Future studies should also focus on randomized and sham-controlled clinical trials in order to assess the effectiveness of acupuncture on several outcomes such as neurological testing and NCS. Other endpoints should include subjective patient experience, as well as neurological examination scores. It is evident that acupuncture seems to be a safe and effective modality of improving patient symptoms as well as nerve conduction, warranting its inclusion as a potential

recommendation for the therapy of patients diagnosed with DPN. Future research targeting molecular-level disease-modifying therapy based on the pathogenic mechanisms of DPN is expected to improve our therapeutic strategies against this enigmatic disease.

ACKNOWLEDGEMENTS

We extend our sincere thanks to Dr. Marina George Kudiyirickal for helping us with the audio clip for the Core Tip.

FOOTNOTES

Author contributions: Blaibel D substantially contributed to the initial drafting of the work by performing the literature search, interpretation of relevant literature, with some broad guidance from Fernandez CJ and Pappachan JM and made revisions; Fernandez CJ also contributed to figure preparation for the manuscript; Pappachan JM conceptualised the idea, supervised the whole drafting, and revision process of the article critically for important intellectual content; All authors have read and approved the final version of the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: United Kingdom

ORCID number: Cornelius James Fernandez 0000-0002-1171-5525; Joseph M Pappachan 0000-0003-0886-5255.

S-Editor: Li L

L-Editor: A

P-Editor: Zhao S

REFERENCES

- 1 **Pop-Busui R**, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017; **40**: 136-154 [PMID: 27999003 DOI: 10.2337/dc16-2042]
- 2 **Ziegler D**, Papanas N, Vinik AI, Shaw JE. Epidemiology of polyneuropathy in diabetes and prediabetes. *Handb Clin Neurol* 2014; **126**: 3-22 [PMID: 25410210 DOI: 10.1016/B978-0-444-53480-4.00001-1]
- 3 **Galiero R**, Caturano A, Vetrano E, Beccia D, Brin C, Alfano M, Di Salvo J, Epifani R, Piacetale A, Tagliaferri G, Rocco M, Iadicicco I, Docimo G, Rinaldi L, Sardù C, Salvatore T, Marfella R, Sasso FC. Peripheral Neuropathy in Diabetes Mellitus: Pathogenetic Mechanisms and Diagnostic Options. *Int J Mol Sci* 2023; **24** [PMID: 36834971 DOI: 10.3390/ijms24043554]
- 4 **Mizisin AP**, Weerasuriya A. Homeostatic regulation of the endoneurial microenvironment during development, aging and in response to trauma, disease and toxic insult. *Acta Neuropathol* 2011; **121**: 291-312 [PMID: 21136068 DOI: 10.1007/s00401-010-0783-x]
- 5 **Kellogg AP**, Wiggin TD, Larkin DD, Hayes JM, Stevens MJ, Pop-Busui R. Protective effects of cyclooxygenase-2 gene inactivation against peripheral nerve dysfunction and intraepidermal nerve fiber loss in experimental diabetes. *Diabetes* 2007; **56**: 2997-3005 [PMID: 17720896 DOI: 10.2337/db07-0740]
- 6 **Vincent AM**, Perrone L, Sullivan KA, Backus C, Sastry AM, Lastoskie C, Feldman EL. Receptor for advanced glycation end products activation injures primary sensory neurons via oxidative stress. *Endocrinology* 2007; **148**: 548-558 [PMID: 17095586 DOI: 10.1210/en.2006-0073]
- 7 **Elafros MA**, Andersen H, Bennett DL, Savelieff MG, Viswanathan V, Callaghan BC, Feldman EL. Towards prevention of diabetic peripheral neuropathy: clinical presentation, pathogenesis, and new treatments. *Lancet Neurol* 2022; **21**: 922-936 [PMID: 36115364 DOI: 10.1016/S1474-4422(22)00188-0]
- 8 **Castelli G**, Desai KM, Cantone RE. Peripheral Neuropathy: Evaluation and Differential Diagnosis. *Am Fam Physician* 2020; **102**: 732-739 [PMID: 33320513]
- 9 **Aho T**, Mustonen L, Kalso E, Harno H. Douleur Neuropathique 4 (DN4) stratifies possible and definite neuropathic pain after surgical peripheral nerve lesion. *Eur J Pain* 2020; **24**: 413-422 [PMID: 31660676 DOI: 10.1002/ejp.1498]
- 10 **Eid SA**, O'Brien PD, Hinder LM, Hayes JM, Mendelson FE, Zhang H, Zeng L, Kretzler K, Narayanan S, Abcouwer SF, Brosius Iii FC 3rd, Pennathur S, Savelieff MG, Feldman EL. Differential Effects of Empagliflozin on Microvascular Complications in Murine Models of Type 1 and Type 2 Diabetes. *Biology (Basel)* 2020; **9** [PMID: 33105667 DOI: 10.3390/biology9110347]
- 11 **Look AHEAD Research Group**, Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, Coday M, Curtis JM, Egan C, Evans M, Foreyt J, Foster G, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jeffery RW, Johnson KC, Kitabchi AE, Knowler WC, Kriska A, Lang W, Lewis CE, Montez MG, Nathan DM, Neiberg RH, Patricio J, Peters A, Pi-Sunyer X, Pownall H, Redmon B, Regensteiner J, Rejeski J, Ribisl PM, Safford M, Stewart K, Trencle D, Wadden TA, Wing RR, Yanovski SZ. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of

- the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2016; **4**: 913-921 [PMID: [27595918](#) DOI: [10.1016/S2213-8587\(16\)30162-0](#)]
- 12 **Callaghan BC**, Reynolds EL, Banerjee M, Akinci G, Chant E, Villegas-Umana E, Rothberg AE, Burant CF, Feldman EL. Dietary weight loss in people with severe obesity stabilizes neuropathy and improves symptomatology. *Obesity (Silver Spring)* 2021; **29**: 2108-2118 [PMID: [34747574](#) DOI: [10.1002/oby.23246](#)]
- 13 **Mascarenhas RO**, Souza MB, Oliveira MX, Lacerda AC, Mendonça VA, Henschke N, Oliveira VC. Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia: A Systematic Review and Meta-analysis. *JAMA Intern Med* 2021; **181**: 104-112 [PMID: [33104162](#) DOI: [10.1001/jamainternmed.2020.5651](#)]
- 14 **Stein C**, Eibel B, Sbruzzi G, Lago PD, Plentz RD. Electrical stimulation and electromagnetic field use in patients with diabetic neuropathy: systematic review and meta-analysis. *Braz J Phys Ther* 2013; **17**: 93-104 [PMID: [23778776](#) DOI: [10.1590/S1413-35552012005000083](#)]
- 15 **D'Souza RS**, ElSaban M, Martinez Alvarez GA, Jin MY, Kubrova E, Hassett LC. Treatment of pain in length-dependent peripheral neuropathy with the use of spinal cord stimulation: a systematic review. *Pain Med* 2023; **24**: S24-S32 [PMID: [37833047](#) DOI: [10.1093/pm/pnad091](#)]
- 16 **Burkey AR**, Chen J, Argoff CE, Edgar DR, Petersen EA. Painful Peripheral Neuropathies of the Lower Limbs and/or Lower Extremities Treated with Spinal Cord Stimulation: A Systematic Review with Narrative Synthesis. *J Pain Res* 2023; **16**: 1607-1636 [PMID: [37229154](#) DOI: [10.2147/JPR.S403715](#)]
- 17 **Vickers AJ**, Vertosick EA, Lewith G, MacPherson H, Foster NE, Sherman KJ, Irnich D, Witt CM, Linde K; Acupuncture Trialists' Collaboration. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. *J Pain* 2018; **19**: 455-474 [PMID: [29198932](#) DOI: [10.1016/j.jpain.2017.11.005](#)]
- 18 **Yu B**, Li M, Huang H, Ma S, Huang K, Zhong Z, Yu S, Zhang L. Acupuncture treatment of diabetic peripheral neuropathy: An overview of systematic reviews. *J Clin Pharm Ther* 2021; **46**: 585-598 [PMID: [33511675](#) DOI: [10.1111/jcpt.13351](#)]
- 19 **Dimitrova A**, Murchison C, Oken B. Acupuncture for the Treatment of Peripheral Neuropathy: A Systematic Review and Meta-Analysis. *J Altern Complement Med* 2017; **23**: 164-179 [PMID: [28112552](#) DOI: [10.1089/acm.2016.0155](#)]
- 20 **Meyer-Hamme G**, Friedemann T, Greten J, Gerloff C, Schroeder S. Electrophysiologically verified effects of acupuncture on diabetic peripheral neuropathy in type 2 diabetes: The randomized, partially double-blinded, controlled ACUDIN trial. *J Diabetes* 2021; **13**: 469-481 [PMID: [33150711](#) DOI: [10.1111/1753-0407.13130](#)]
- 21 **Hoerder S**, Habermann IV, Hahn K, Meyer-Hamme G, Ortiz M, Grabowska W, Roll S, Willich SN, Schroeder S, Brinkhaus B, Dietzel J. Acupuncture in diabetic peripheral neuropathy-neurological outcomes of the randomized acupuncture in diabetic peripheral neuropathy trial. *World J Diabetes* 2023; **14**: 1813-1823 [PMID: [38222786](#) DOI: [10.4239/wjd.v14.i12.1813](#)]
- 22 **Ang L**, Mizokami-Stout K, Eid SA, Elafros M, Callaghan B, Feldman EL, Pop-Busui R. The conundrum of diabetic neuropathies-Past, present, and future. *J Diabetes Complications* 2022; **36**: 108334 [PMID: [36306721](#) DOI: [10.1016/j.jdiacomp.2022.108334](#)]
- 23 **Majd H**, Amin S, Ghazizadeh Z, Cesiulis A, Arroyo E, Lankford K, Majd A, Farahvashi S, Chemel AK, Okoye M, Scantlen MD, Tchieu J, Calder EL, Le Rouzic V, Shibata B, Arab A, Goodarzi H, Pasternak G, Kocsis JD, Chen S, Studer L, Fattahi F. Deriving Schwann cells from hPSCs enables disease modeling and drug discovery for diabetic peripheral neuropathy. *Cell Stem Cell* 2023; **30**: 632-647.e10 [PMID: [37146583](#) DOI: [10.1016/j.stem.2023.04.006](#)]
- 24 **Enders J**, Elliott D, Wright DE. Emerging Nonpharmacologic Interventions to Treat Diabetic Peripheral Neuropathy. *Antioxid Redox Signal* 2023; **38**: 989-1000 [PMID: [36503268](#) DOI: [10.1089/ars.2022.0158](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

