



Peripheral Neuropathy in Diabetes: Burden, Lifestyle and Pharmacological Interventions for Prevention and Treatment

**Maryam Fairag^{1*}, Abdulrahman Akbar², Abdulrahman Ghasib²,
Faisal Alagbari², Saleh Alzahrani², Hussein Alshegifi²,
Abdulmajeed Alamoudi², Mohammed Awad³, Rahaf Aljohani²
and Hend Althobaiti²**

¹Family Medicine Specialist, Ministry of Health, Makkah, Saudi Arabia.

²Medical intern, College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia.

³Medical intern, College of Medicine, Umm Al Qura University, Al Qunfudhah, Saudi Arabia.

Authors' contributions

This work was carried out in collaboration among all authors. Author MF designed the study, wrote the protocol, and reviewed the final draft of the manuscript. Authors AA, AG, FA and SA wrote the first draft of the manuscript. Author HA and AA contributed to the literature search and wrote a section in the discussion. Authors HA, RA, and Ma managed the literature searches, contributed and reviewed the first draft of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i49B33373

Editor(s):

(1) Dr. Giuseppe Murdaca, University of Genoa, Italy.

(2) Dr. Sawadogo Wamtinga Richard, Ministry of Higher Education, Scientific Research and Innovation, Burkina Faso.

(3) Dr. Vasudevan Mani, Qassim University, Saudi Arabia.

Reviewers:

(1) Terry Jeremy Ellapen, Tshwane University of Technology, South Africa.

(2) Alba López Bravo, Reina Sofía Hospital, Aragon Health Institute, Spain.

Complete Peer review History: <https://www.sdiarticle4.com/review-history/77108>

Received 08 September 2021

Accepted 13 November 2021

Published 13 November 2021

Systematic Review

ABSTRACT

Diabetes mellitus (DM) is a very common comorbidity worldwide, and it is associated with a wide variety of complications. Diabetic peripheral neuropathy (DPN) is one of these complications that increases the morbidity and mortality of these patients. Multiple studies indicated that lifestyle modifications are very beneficial for these patients in terms of decreasing the symptoms or preventing the progression of the disease. Therefore, a thorough search was conducted to study and shed light on the effects of lifestyle interventions, such as physical exercise, and

pharmacological treatment on DPN. A total of 100 studies were found and 32 were selected based on whether or not they support the aim of the study. It was concluded that lifestyle interventions such as regular exercise, healthy diet and weight loss, which will all in turn improve the patient's glycemic control, play a major role in controlling the disease and preventing its complications. Moreover, the aim of pharmacological interventions is a 30% reduction in pain intensity, however pharmacological interventions are limited in DPN, up till now the FDA approved only three medications that help in the reduction of the pain intensity. These medications are antidepressant duloxetine, anticonvulsant pregabalin, and the opioid-like analgesic tapentadol.

Keywords: Peripheral neuropathy; diabetes mellitus; DM; lifestyle interventions; exercise.

ABBREVIATIONS

DM : Diabetes mellitus
DPN: Diabetic peripheral neuropathy
US : United States
UK : United Kingdom
AAN: American Academy of Neurology
ALA : Alpha-lipoic acid
FDA : Food and Drug Administration

1. INTRODUCTION

By 2017, approximately 451 million adults were affected by Diabetes Mellitus (DM) worldwide, and this huge number is expected to increase up to around 690 million adults by 2045 [1,2]. Diabetic peripheral neuropathy (DPN) is the commonest complication of diabetes and it affects almost 50% of all patients with both types of DM [3]. Moreover, the prevalence of DPN among adults in the United States (US) is approximately 28% [4,5]. DPN is defined as “the presence of signs and/or symptoms of peripheral nerve dysfunction in diabetic patients after exclusion of other causes” [4]. Symptoms of this disease include neuropathic pain and reduced sensation which in turn will lead to a lot of complications that would eventually impair and restrict the daily life of the patients [6,7]. Symmetrical DPN is the most common form of the disease, and the lower limbs are most commonly affected [8,9]. DPN, especially the aforementioned type, has a major impact on morbidity and mortality since it hugely increases the risk of developing ulcers, amputation, and disability [8,9]. In fact, DM is considered the most common cause of non-traumatic lower limb amputation in the United Kingdom (UK) [10]. Besides, it also poses a tremendous financial burden on hospitals and healthcare systems, since the total annual cost required to manage DPN symptoms and its complications such as amputation in the US is approximately between \$4.6 and \$13.7 billion [11].

It has been proven in multiple studies that nerve function in DM patients is improved with better glycemic control [8,12]. Additionally, strict glycemic control was shown to be effective in reducing the risk of acquiring DPN in type 1 diabetes patients, and it may decrease the risk in type 2 DM [13]. In fact, in type 1 DM the risk is dramatically decreased with improved glycemic control (78% relative risk reduction), while slight risk reduction is achieved through better glycemic control in type 2 DM (5%-9% relative risk reduction) [14,15]. Lifestyle modifications are extremely important for the treatment and control of DPN such as physical activity, healthy diet, and weight loss [16]. Regular physical exercise has been shown to be effective in relieving the pain associated with DPN as well as improving the neural function [16,17]. Moreover, multiple studies concluded that combined resistance and aerobic exercise training drastically decreases neuropathic pain, improves walking and balance, and strengthens the muscular fibers [17,18]. As for diet and weight loss, a long-term intensive program about lifestyle modifications and interventions targeted to achieve and maintain weight loss led to a significant reduction in questionnaire based DPN in overweight as well as obese patients with DM [19,20].

Knowing how huge the burden of DPN is, shows just how important the prevention of such issue is as well as the importance of controlling the disease and preventing its complications. The main aim of this study is to determine the effects and impact of lifestyle interventions such as better glycemic control, physical exercise, healthy diet, and weight loss on diabetic peripheral neuropathy and the importance of these changes in controlling the disease and preventing its complications.

2. MATERIALS AND METHODS

A comprehensive search was carried out by five co-authors independently on Pubmed using the

following MeSH terms: "Diabetes mellitus", "Diabetic peripheral neuropathy", "DM", "DPN", "Lifestyle interventions". Then, search results were filtered based on the title, abstract, study included humans only, and availability in English language as well as availability of full texts. A total of 100 articles were found and based on the previously mentioned criteria and whether or not they provide benefit towards achieving the aim of the study, 32 were selected.

3. RESULTS AND DISCUSSION

3.1 Prevalence of Diabetic Peripheral Neuropathy

The most common complication of diabetes is DPN as it affects about half of all cases with diabetes mellitus [3]. Furthermore, diabetes is the most common cause of neuropathy all over the world [21]. In fact, 66% of insulin dependent diabetes mellitus patients had some form of neuropathy as per a population-based cohort study done by Dyck PJ et al. [3]. According to Patricia Kluding et al. in their study about DPN, it is present in about one third of diabetic patients aged 40 or older in the US [17]. Moreover, the primary symptom in one third of DPN patients is pain [17]. Furthermore, according to a study done by Rayan Sendi et al. regarding DPN among Saudi diabetic patients, the prevalence of DPN among type 2 diabetic patients was 30.1%, while the prevalence among type 1 diabetic patients was 25.9% [22]. As per the aforementioned study, the overall prevalence of DPN is estimated to be 29.1% [22]. Moreover, the most common signs and symptoms were tingling (26.7%), hypoesthesia to touch (23.3%), and pins and needles (23%) [22]. This shows how prevalent the condition is among diabetic patients which is considered the most common cause of neuropathy worldwide.

3.2 Morbidity and Prognosis of DPN

Symmetrical distal degeneration of peripheral nerves is the most common form of DPN associated with pain and sensory loss due to both large and small nerve fibers being affected [17]. This eventually leads to gait and balance abnormalities which can precipitate lower limb injuries and potentially amputations [17]. Furthermore, this balance impairment can easily lead to falls in diabetic patients especially if it was associated with diabetic retinopathy [15]. In fact, patients with diabetic distal symmetrical polyneuropathy have 2-3 times higher risk of falls

compared to those with diabetes without neuropathy [15]. Additionally, falls leading to fractures occur in approximately 25% of diabetics above 65 years of age [23]. Amputations are one of the most deleterious complications of this disease since it affects the patient's quality of life tremendously with a 15-fold increase in amputation risk in diabetic patients [15]. Additionally, neuropathic pain associated with this condition is quite troublesome and it approximately develops in 10%-20% of all diabetic patients and in 40%-60% of those with neuropathy [15]. However, these numbers are thought to be underestimated since it was found that 12% of patients with DPN did not tell their doctors about it [24]. Unfortunately, the quality of life of DPN patients are affected in other important aspects as well such as excessive anxiety, sleep disturbance and depression which are reported by 43% of the patients and the impact of these factors on the quality of life should not be underestimated [25]. All these factors and more would eventually affect the employment status of patients since according to a study done by Thomas Tolle et al. 35% - 43% of DPN patients have their employment affected in a way or another [25]. As for the economic burden of this condition, according to a study about the health care costs of diabetic peripheral neuropathy in the US, one fourth of the total costs of diabetes patients' care is due to neuropathy and its complications [11]. It is undoubtable how significant the magnitude of DPN is and how a patient's condition and quality of life can deteriorate consequently.

3.3 Management and Prevention of DPN

DPN management is centered around various principles that aim to slow or prevent the progression of the disease and its complications [6]. As per Brian Callaghan et al. in their study about prevention and treatment of DPN, glycemic control is not an effective way of reducing the symptoms of DPN [15]. However, according to two other studies regarding the same topic, better glycemic control is associated with improved nerve function in diabetic patients leading eventually to less symptoms [8,12]. Generally, the first step in the management and prevention of DPN is glycemic control [26]. Regular physical activity has an impactful role in the prevention of DPN in diabetic patients by significantly improving the most important three risk factors which are glucose control, obesity, and dyslipidemia [1]. A clinical trial done by Patricia Kluding et al. involving 17 subjects with

diabetic neuropathy concluded after 10 weeks of aerobic and strengthening exercise program that there is significant improvement in terms of pain and neuropathic symptoms [17]. Moreover, intraepidermal nerve fiber branching was found to be increased and HbA1c significantly improved [17]. On the other hand, no significant changes in nerve conduction studies and quantitative sensory testing were found [17]. Exercise as well as diet counseling can reduce the incidence of type 2 diabetes according to The Diabetes Prevention Program [27]. A significant randomized controlled pilot study conducted in May 2015 about dietary intervention for chronic diabetic neuropathy pain concluded that a low fat-based diet had potential improvement in regard to some clinical and pain measures [28]. Additionally, alpha-lipoic acid (ALA) is a type of dietary supplementation that has characteristic antioxidant properties [29]. It has been proven according to a study trial known as SYDNEY 1 trial that ALA reduces neuropathic pain [29]. However, further studies are required to test the effectiveness of ALA in reducing the symptoms of DPN and preventing its progression, since SYDNEY 1 was a short-term study [29]. Although vitamin B12 deficiency is implemented to be one of the main causes of peripheral neuropathy, there is no evidence supporting the use of vitamin B12 supplementation in DPN [19]. There is emerging evidence that dietary and physical modifications prevent the development of diabetic neuropathy in type 2 diabetes mellitus subjects by the effect on biochemical pathways that improve muscle function and affect other organ systems like peripheral nerves, however, data from randomized controlled trials are needed [1]. Therefore, as per these different studies and more, lifestyle interventions including physical activity and diet as well as improved glycemic control are very important aspects in the management of DPN.

Furthermore, pain management is a very important aspect in the management of this disease. A 30% reduction in pain intensity, regardless of the baseline pain score, is considered a purposeful and considerable reduction in patients with DPN [30]. Only three pain-relieving medications have secured FDA approval regarding their usage in DPN patients which are; the antidepressant duloxetine, the anticonvulsant pregabalin, and the opioid-like analgesic tapentadol [30]. Pregabalin and duloxetine are considered the initial and most appropriate choices for the management of neuropathic pain in diabetic patients [4].

Pregabalin is an effective medication for neuropathic pain in DPN and has a rapid onset of action [31]. According to the American Academy of Neurology (AAN) guidelines, pregabalin is the preferred treatment for patients with DPN (Level A) [30]. Duloxetine is also effective and has been found to improve neuropathy-related quality of life [32]. Venlafaxine, amitriptyline, gabapentin, valproate, opioids (i.e., morphine sulfate, tramadol, and oxycodone), and topical capsaicin are “probably effective” and should be considered for these patients (Level B) [30].

4. CONCLUSION

In conclusion, diabetic peripheral neuropathy is the most common complication of diabetes mellitus and is a major factor in increasing morbidity and mortality in these patients. Quality of life is majorly affected by DPN and its complications that can eventually lead to amputation. Furthermore, this condition exerts a huge economic burden to the whole healthcare system. Lifestyle modifications such as regular physical activity and healthy diet are major factors in managing the disease as well as preventing its complications. Pain and glycemic control are essential aspects that should not be overlooked during the management. All in all, DPN is a very common complication of DM that should be managed thoroughly in order to control the disease and prevent its debilitating complications.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Zilliox LA, Russell JW. Physical activity and dietary interventions in diabetic neuropathy: a systematic review. *Clin Auton Res* [Internet]. 2019;29(4):443–55. Available:<http://link.springer.com/10.1007/s10286-019-00607-x>
2. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* [Internet]. 2018;138:271–81. Available:<https://linkinghub.elsevier.com/retrieve/pii/S0168822718302031>
3. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, et al. The prevalence by

- staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: The rochester diabetic neuropathy study. *Neurology* [Internet]. 1993;43(4):817–817. Available: <http://www.neurology.org/cgi/doi/10.1212/WNL.43.4.817>
4. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic neuropathy: A position statement by the american diabetes association. *Diabetes Care* [Internet]. 2017;40(1):136–54. Available: <http://care.diabetesjournals.org/lookup/doi/10.2337/dc16-2042>
 5. Gregg EW, Gu Q, Williams D, de Rekeneire N, Cheng YJ, Geiss L, et al. Prevalence of lower extremity diseases associated with normal glucose levels, impaired fasting glucose, and diabetes among U.S. adults aged 40 or older. *Diabetes Res Clin Pract* [Internet]. 2007;77(3):485–8. Available: <https://linkinghub.elsevier.com/retrieve/pii/S016882270700040X>
 6. Hicks CW, Selvin E. Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. *Curr Diab Rep* [Internet]. 2019;19(10):86. Available: <http://link.springer.com/10.1007/s11892-019-1212-8>
 7. Vileikyte L, Leventhal H, Gonzalez JS, Peyrot M, Rubin RR, Ulbrecht JS, et al. Diabetic peripheral neuropathy and depressive symptoms: The association revisited. *Diabetes Care* [Internet]. 2005;28(10):2378–83. Available: <http://care.diabetesjournals.org/cgi/doi/10.2337/diacare.28.10.2378>
 8. Ghavami H. Effect of lifestyle interventions on diabetic peripheral neuropathy in patients with type 2 diabetes, result of a randomized clinical trial. *Ağrı - J Turkish Soc Algol* [Internet]. 2018;30(4):165–70. Available: <http://www.agridergisi.com/jvi.aspx?pdire=agri&plng=eng&un=AGRI-45477>
 9. Timar B, Timar R, Gaiță L, Oancea C, Levai C, Lungeanu D. The impact of diabetic neuropathy on balance and on the risk of falls in patients with type 2 diabetes mellitus: A cross-sectional study. *Santanelli, di Pompeo d'Ilasi F, editor. PLoS One* [Internet]. 2016;11(4):e0154654. Available: <https://dx.plos.org/10.1371/journal.pone.0154654>
 10. Selvarajah D, Kar D, Khunti K, Davies MJ, Scott AR, Walker J, et al. Diabetic peripheral neuropathy: Advances in diagnosis and strategies for screening and early intervention. *Lancet Diabetes Endocrinol* [Internet]. 2019;7(12):938–48. Available: <https://linkinghub.elsevier.com/retrieve/pii/S2213858719300816>
 11. Gordois A, Scuffham P, Shearer A, Oglesby A, Tobian JA. The health care costs of diabetic peripheral neuropathy in the U.S. *Diabetes Care* [Internet]. 2003;26(6):1790–5. Available: <http://care.diabetesjournals.org/cgi/doi/10.2337/diacare.26.6.1790>
 12. Graf RJ. Glycemic control and nerve conduction abnormalities in non-insulin-dependent diabetic subjects. *Ann Intern Med* [Internet]. 1981;94(3):307. Available: <http://annals.org/article.aspx?doi=10.7326/0003-4819-94-3-307>
 13. Peltier A, Goutman SA, Callaghan BC. Painful diabetic neuropathy. *BMJ* [Internet]. 2014;348:g1799–g1799. Available: <https://www.bmj.com/lookup/doi/10.1136/bmj.g1799>
 14. Linn T, Ortac K, Laube H, Federlin K. Intensive therapy in adult insulin-dependent diabetes mellitus is associated with improved insulin sensitivity and reserve: A randomized, controlled, prospective study over 5 years in newly diagnosed patients. *Metabolism* [Internet]. 1996;45(12):1508–13. Available: <https://linkinghub.elsevier.com/retrieve/pii/S0026049596901808>
 15. Callaghan BC, Cheng HT, Stables CL, Smith AL, Feldman EL. Diabetic neuropathy: Clinical manifestations and current treatments. *Lancet Neurol* [Internet]. 2012;11(6):521–34. Available: <http://www.ncbi.nlm.nih.gov/pubmed/22608666>
 16. Seyedizadeh SH, Cheragh-Birjandi S, Hamedia Nia MR. The effects of combined exercise training (Resistance-Aerobic) on serum kinesin and physical function in type 2 diabetes patients with diabetic peripheral neuropathy (randomized controlled trials). *J Diabetes Res* [Internet]. 2020;2020:1–7. Available: <https://www.hindawi.com/journals/jdr/2020/6978128/>
 17. Kluding PM, Pasnoor M, Singh R, Jernigan S, Farmer K, Rucker J, et al. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy.

- J Diabetes Complications [Internet]. 2012;26(5):424–9.
Available:<http://www.ncbi.nlm.nih.gov/pubmed/22717465><http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3436981><http://linkinghub.elsevier.com/retrieve/pii/S1056872712001614>
18. Tan S, Li W, Wang J. Effects of six months of combined aerobic and resistance training for elderly patients with a long history of type 2 diabetes. *J Sports Sci Med* [Internet]. 2012;11(3):495–501.
Available:<http://www.ncbi.nlm.nih.gov/pubmed/24149359>
 19. Tesfaye S, Sloan G. Diabetic polyneuropathy – Advances in diagnosis and intervention strategies. *Eur Endocrinol* [Internet]. 2020;16(1):15.
Available:<https://www.touchendocrinology.com/person-centred-obesity-care-techniques-thresholds-tools-and-targets/>
 20. Look AHEAD Research Group. Effects of a long-term lifestyle modification programme on peripheral neuropathy in overweight or obese adults with type 2 diabetes: the Look AHEAD study. *Diabetologia* [Internet]. 2017;60(6):980–8.
Available:<http://link.springer.com/10.1007/s00125-017-4253-z>
 21. Liu X, Xu Y, An M, Zeng Q. The risk factors for diabetic peripheral neuropathy: A meta-analysis. *PLoS One* [Internet]. 2019;14(2):e0212574.
Available:<http://www.ncbi.nlm.nih.gov/pubmed/30785930>
 22. Sendi R, Mahrus A, Saeed R, Mohammed M, Al-Dubai SR. Diabetic peripheral neuropathy among Saudi diabetic patients: A multicenter cross-sectional study at primary health care setting. *J Fam Med Prim Care* [Internet]. 2020;9(1):197.
Available:<http://www.jfmpc.com/text.asp?2020/9/1/197/276811>
 23. Yang Y, Hu X, Zhang Q, Zou R. Diabetes mellitus and risk of falls in older adults: a systematic review and meta-analysis. *Age Ageing* [Internet]. 2016 Nov;45(6):761–7.
Available:<https://academic.oup.com/ageing/article-lookup/doi/10.1093/ageing/afw140>
 24. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. *Diabet Med* [Internet]. 2004;21(9):976–82.
Available:<https://onlinelibrary.wiley.com/doi/10.1111/j.1464-5491.2004.01271.x>
 25. Tölle T, Xu X, Sadosky AB. Painful diabetic neuropathy: A cross-sectional survey of health state impairment and treatment patterns. *J Diabetes Complications* [Internet]. 2006;20(1):26–33.
Available:<https://linkinghub.elsevier.com/retrieve/pii/S1056872705001509>
 26. Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA, et al. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. *Diabetes Care* [Internet]. 2006;29(2):340–4.
Available:<http://care.diabetesjournals.org/cgi/doi/10.2337/diacare.29.02.06.dc05-1549>
 27. Orchard TJ, Temprosa M, Goldberg R, Haffner S, Ratner R, Marcovina S, et al. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: The diabetes prevention program randomized trial. *Ann Intern Med* [Internet]. 2005;142(8):611.
Available:<http://annals.org/article.aspx?doi=10.7326/0003-4819-142-8-200504190-00009>
 28. Bunner AE, Wells CL, Gonzales J, Agarwal U, Bayat E, Barnard ND. A dietary intervention for chronic diabetic neuropathy pain: a randomized controlled pilot study. *Nutr Diabetes* [Internet]. 2015;5(5):e158–e158.
Available:<http://dx.doi.org/10.1038/nutd.2015.8>
 29. Ametov AS, Barinov A, Dyck PJ, Hermann R, Kozlova N, Litchy WJ, et al. The sensory symptoms of diabetic polyneuropathy are improved with -Lipoic acid: The Sydney trial. *Diabetes Care* [Internet]. 2003;26(3):770–6.
Available:<http://care.diabetesjournals.org/cgi/doi/10.2337/diacare.26.3.770>
 30. Cohen K, Shinkazh N, Frank J, Israel I, Fellner C. Pharmacological treatment of diabetic peripheral neuropathy. *P T* [Internet]. 2015;40(6):372–88.
Available:<http://www.ncbi.nlm.nih.gov/pubmed/26045647>
 31. Dworkin RH, Jensen MP, Gammaitoni AR, Olaleye DO, Galer BS. Symptom profiles differ in patients with neuropathic versus non-neuropathic pain. *J Pain* [Internet]. 2007;8(2):118–26.
Available:<https://linkinghub.elsevier.com/retrieve/pii/S1526590006008959>
 32. Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, et al. A randomized controlled trial of duloxetine in

diabetic peripheral neuropathic pain.
Neurology [Internet]. 2006;67(8):1411–20.

Available:<http://www.neurology.org/cgi/doi/10.1212/01.wnl.0000240225.04000.1a>

© 2021 Fairag et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

*The peer review history for this paper can be accessed here:
<https://www.sdiarticle4.com/review-history/77108>*