



OVERVIEW OF DIABETIC NEUROPATHY

Ali Nasser Mansour Shammakhi^{1*}, Tareq Ahmed Ali Khormi², Ghason Ali A Torki³, Mohammed Ali Hussein Alhazmi⁴, Ibraheem Sindi Shetifi⁵, Majed Hameed Alharbi⁶, Abualgassam Nasseer Mohammed Zwogan⁷, Khaled Mossa Mohsen Mashi⁸, Nahla Shaker Saati⁹, Saleh Mohammed Shami¹⁰, Feher Mohammed Alturkistani¹¹, Ahmed Sameer Munshi¹², Mosaad Abdullah Alqarni¹³, Adel Hamad Khardali¹⁴

^{1*,2,3,4,5,7,8,14} Eradah Hospital For Mental Health – Jazan – Saudi Arabia

^{11,12,13} King Abdulaziz Hospital - Jeddah– Saudi Arabia

⁶ General Directorate Of Health Affairs – Medina– Saudi Arabia

⁹ Alwafaa Primary Healthcare – Jeddah– Saudi Arabia

¹⁰ Eradah And Mental Health Complex – Jeddah– Saudi Arabia

***Corresponding Author:** Ali Nasser Shammakhi

*****Eradah Hospital For Mental Health – Jazan – Saudi Arabia

Abstract:

Background: Diabetic neuropathy, impacting both type 1 and type 2 diabetes patients, stems from prolonged high blood sugar damaging nerves, leading to diverse symptoms like discomfort and numbness. Various physiological mechanisms, including hyperglycemia and prediabetes, contribute to its development, while psychological factors also impact patients' quality of life. Diagnosis involves comprehensive evaluations, including nerve conduction studies and skin biopsy. Prevention strategies focus on strict glycemic control, lifestyle adjustments, and early intervention, with exercise, neurostimulation devices, and nutraceuticals showing promise in managing neuropathic pain. Pharmaceutical treatments alleviate symptoms but may cause adverse effects. Herbal remedies, like flavonoids, offer alternative therapeutic options with potential benefits in reducing inflammation and oxidative stress, presenting a multifaceted strategy for diabetic neuropathy management.

Aim: to understand diabetic neuropathy, covering its causes, symptoms, pathophysiology, diagnosis, control and prevention, and treatment options to improve treatment outcomes.

Methods: a comprehensive review of Diabetic neuropathy and therapy. The PUBMED and Google Scholar search engines were the main databases used for the search process, with articles collected from 2007 to 2022.

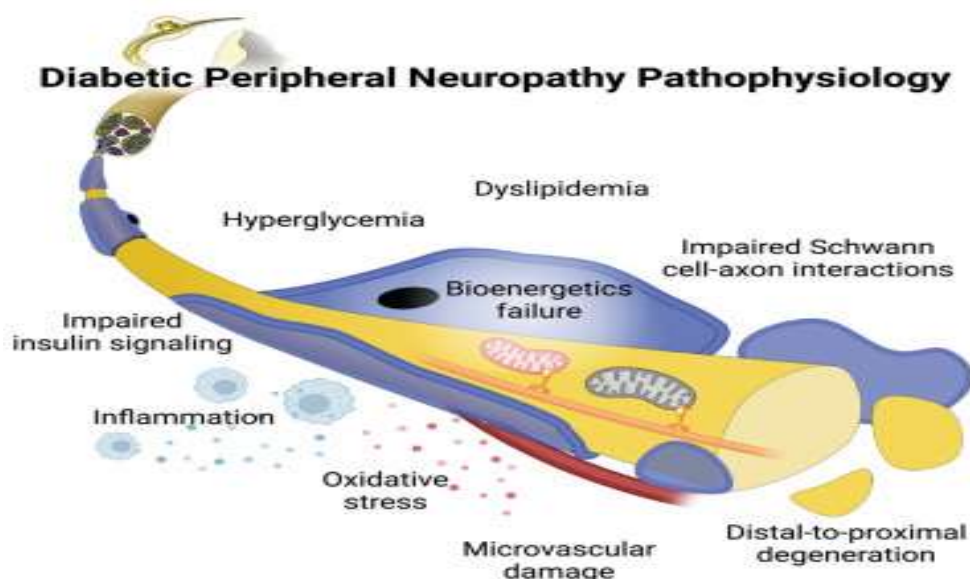
Conclusion: Diabetic neuropathy, prevalent in both type 1 and type 2 diabetes, results from prolonged high blood glucose levels damaging nerves. Symptoms vary from discomfort to numbness and autonomic issues. Prediabetes is also linked to neuropathy, stressing early detection. Pathophysiologically, factors like glycemic dysregulation and oxidative stress contribute to nerve damage. Diagnosis involves nerve conduction studies and clinical evaluation, though early detection challenges persist. Prevention emphasizes glycemic control, lifestyle adjustments, and emerging therapies like neurostimulation. Medications offer symptom relief, while herbal remedies and flavonoids show promise. Managing diabetic neuropathy requires a multifaceted approach integrating

traditional and emerging treatments for improved patient outcomes and quality of life.

Keywords: Diabetic neuropathy, Pathophysiology, Diagnosis, Prevention, and control.

Introduction:

Diabetic neuropathy, a condition frequently found in individuals with diabetes mellitus, is a prevailing complication that can greatly disrupt one's quality of life. This condition is characterized by damage to the nerves resulting from prolonged periods of heightened glucose levels circulating in the bloodstream; surprisingly, diabetic neuropathy does not differentiate between individuals with type 1 or type 2 diabetes, as it can impact both groups equally. The manifestations of this condition can vary greatly, impacting nerve function and integrity throughout the entire body (1) besides, Diabetes shows significant influence on the nervous system, ultimately resulting in the development of neuropathy through a complex interplay of various physiological mechanisms. The circumstance of hyperglycemia occurs as a vital aspect in the evolution of diabetic neuropathy, playing a prominent role in the early stages and advancement of nerve damage (2). In addition, it is crucial to highlight that prediabetes, which can be described as a state preceding the emergence of type 2 diabetes, has been identified to be closely linked with neuropathy. Countless research experiments have illustrated a notable relationship between prediabetes and neuropathy, particularly concerning peripheral neuropathy. The incident of peripheral neuropathy has been documented to fluctuate between 11.2% and 25.8% in individuals with impaired glucose tolerance, emphasizing the importance of early detection and intervention of prediabetes to prevent the onset of neuropathic complications (3). Also, Gender discrepancies in diabetic neuropathy do not exhibit statistically significant variations, as evidenced by the absence of noticeable differences in terms of age at diagnosis, duration of diabetes, or glycemic control among male and female patients. This absence of notable differentiation implies a degree of gender neutrality in the development and advancement of diabetic neuropathy, underscoring the necessity of taking into account additional variables beyond gender when examining this disease (4). Moreover, The prevailing symptoms of diabetic neuropathy include discomfort, lack of feeling, prickling, burning feelings, weakness, and unusual feelings like pins and needles. Painful polyneuropathy, which impacts a substantial proportion of individuals with polyneuropathy, has the potential to materialize as shooting, squeezing, or burning pain, specifically in the feet. Individuals may undergo a commencement of sensory diminishment originating in the lower extremities and extending toward the fingers and hands. The sensation of tingling emerges as a frequently reported grievance, succeeded by the occurrence of a burning sensation among those afflicted by diabetic neuropathy. Moreover, autonomic symptoms such as constipation and episodes of lightheadedness may additionally be noticeable in individuals with diabetic neuropathy (5). Additionally, The Symptoms linked with diabetic polyneuropathy are diverse. They can be classified into two primary categories: negative symptoms, encompassing feelings of numbness and weakness in affected areas, and positive symptoms, distinguished by feelings of tingling and pain encountered by individuals with this condition (6). Besides, The evolution of diabetic neuropathy may culminate in the emergence of hypoesthesia, a condition distinguished by diminished sensitivity to stimuli, eventually causing the degeneration of nerve fibers [figure 1], which could potentially lead to the necessity for lower limb amputation. This drastic measure may become necessary due to the affected individual's inability to perceive trauma or mechanical stimuli, thereby posing a significant risk to their overall health and well-being (7). Moreover, Psychological factors, including pain catastrophizing, depression, anxiety, and sleep disturbances, are understood to play a significant role in the overall quality of life experienced by patients with Peripheral Diabetic Neuropathy (PDN). These aspects are important in foreseeing and establishing the extent to which persons with PDN might confront constraints and challenges in their everyday tasks and overall health (8). Also, Those with diabetes nerve pain (DN) may observe a decrease in their health-related quality of life (HRQoL). This decline is influenced by various factors such as the severity of neuropathy, lack of physical activity, abnormal results in nerve conduction studies, as well as the duration of diabetes. These aspects are factors in the worsening of HRQoL in individuals diagnosed with diabetic neuropathy (9).

Figure (1): nerve fiber degeneration (10).**Pathophysiology:**

The etiology of diabetic neuropathy is identified by a diverse interplay of multiple mechanisms. The deregulation of glycemic control sets off the initiation of complex pathways like the polyol, aldose reductase, and protein kinase C pathways. This activation ultimately results in initiating inflammatory responses and generating oxidative stress (11). In addition, it is vital to consider that atypical Na^+ channels, TRPA1, TRPV1, and T-type Ca^{2+} channels are supplementary elements that significantly influence the advancement and continuation of peripheral pain experienced in diabetic neuropathy (12). Moreover, it is crucial to acknowledge that many factors, such as mitochondrial irregularities, endoplasmic reticulum pressure, and diminished blood flow, all play a vital role in advancing axonal breakdown and the demise of nerve cells (13). Also, The damage to the nerves in diabetic neuropathy could arise from diverse origins, like the adverse effect of oxidative stress on nerve cells, sorbitol in the nervous system, and the formation of advanced glycation end products. These procedures might collectively contribute to the impairment and malfunction of the peripheral nervous system in individuals with diabetes (14). Moreover, it is essential to stress that diabetic neuropathies possess the potential to occur in multiple forms, including polyneuropathy, mononeuropathy, and autonomic neuropathy, ultimately leading to the manifestation of foot lesions, vulnerability to infections, and in severe circumstances, the necessity for surgical interventions. Besides, The possibility of familial history affecting factors such as genetic variations connected to the creation of reactive oxygen species and changes in protein glycosylation, which impact the pathophysiology of diabetic neuropathy (DN), is very low. These hereditary aspects, which cover various variations in DNA sequences, have been implicated in the development and progression of DN. Besides genetic factors, environmental influences like glycemic dysregulation and inflammation also play a role in the complex interaction of mechanisms that contribute to the development of DN. The combination of genetic predispositions and environmental exposures creates a multifaceted landscape in which the development of DN occurs, highlighting the intricate nature of this debilitating condition (15). Moreover, Bone marrow-derived cells expressing proinsulin and $\text{TNF}\alpha$ have been observed to undergo a process of fusion with neurons within the biological system, thereby instigating a series of events leading to dysfunction and ultimately resulting in apoptosis. This unique phenomenon sheds light on a previously unidentified pathogenic mechanism, providing valuable insights into the intricate interplay between different cell types and their impact on neuronal health and viability (16). Nevertheless, Multiple elements, including metabolic processes, vascular health, immunological responses, and genetic predispositions, collectively contribute to the notable impact on the formation and advancement of diabetic peripheral neuropathy (17).

Diagnosis:

Evaluation of diabetic neuropathy involves employing a variety of tests to assess the functionality of nerves in the person. Within this diagnostic process, nerve conduction studies play a pivotal role in determining large, myelinated fibers, providing valuable insights into their performance. Additionally, the conduction studies are complemented by the indispensable skin biopsy procedure, which serves as a critical method for evaluating the integrity of small nerve fibers. Furthermore, the screening process for diabetic distal symmetric polyneuropathy (DSP) entails a comprehensive approach that involves the identification of various risk factors, examination of foot deformities, assessment of impaired protective sensation, and observation of manifestations associated with the involvement of both small and large nerve fibers. Clinical evaluation is a meticulous process that gradually enhances the accuracy of estimating the probability of a disease, wherein uncomplicated screening techniques and measurement tools play a significant role in determining a diagnosis (18). Besides, Machine learning models that use microcirculatory parameters such as post-occlusion reactive hyperemia (PORH) have demonstrated the ability to diagnose diabetic peripheral neuropathy accurately. Within these models, the percentage of recovery flow to peak flow (RF_PF%) following PORH has been identified as a crucial predictor in determining the presence of this condition (19). Electrophysiological studies, such as nerve conduction studies (NCS), are essential for pinpointing subclinical stages and the underlying pathology affecting the nerves. These diagnostic methods involve many techniques, such as neurophysiological tests, sensory assessment, and imaging methods like ultrasonography and MRI. These modalities are lauded for their exceptional sensitivity and specificity in recognizing nerve lesions, thereby supporting the precise diagnosis and management of nerve-related conditions. Moreover, it is critical to note that regional thermal hyperemia (LTH), a biological response characterized by an augmentation in regional blood flow and skin temperature, along with transcutaneous oxygen pressure (TcPO₂), a gauge reflecting the oxygen tension at the skin level, have both been recognized as essential and informative parameters in the assessment and identification of diabetic peripheral neuropathy. Moreover, High-resolution ultrasonography, an innovative imaging technique that employs sound waves to produce detailed images of the body's internal structures, and magnetic resonance neurography, a sophisticated imaging method that concentrates on visualizing nerves, are also underscored as highly efficient approaches for the timely identification of peripheral nerve irregularities in people diagnosed with diabetes (20). Also, Accounting for a patient's background is highly significant in detecting diabetic neuropathy, a condition that impacts many. Numerous studies conducted in the field have unequivocally demonstrated that various factors, including but not limited to a familial background of diabetes mellitus, levels of fasting blood sugar, one's ethnicity, and gender, all play a crucial and undeniable role in determining the timing of neuropathy incidence. Additionally, there is evidence suggesting that amidst individuals with type 2 diabetes, those aged above 66 years, individuals with a documented history of hypertension, specific levels of certain blood cells, HbA1c concentrations surpassing the threshold of 7.7%, and FT3 levels exceeding the value of 4.4 pmol/L, are all viewed as highly significant predictive elements that impact the overall prevalence of diabetic peripheral neuropathy (DPN) (21). In addition, It has been recognized that individuals who have been dealing with diabetes for an extensive time are unlikely to undergo a raised level of severity in their peripheral neuropathy symptoms when compared to those with a shorter diabetes history. It has been observed that individuals who have had diabetes for a prolonged period are likely to encounter a heightened level of severity in their peripheral neuropathy symptoms in comparison to those with a briefer diabetes history (22). Nevertheless, Diagnosing neuropathy in individuals with diabetes poses numerous difficulties that must be carefully considered. One of the main hurdles is the accuracy that early-stage neuropathy can often be asymptomatic, making it harder to detect and diagnose promptly. Moreover, the clinical signs of neuropathy may show noticeable variances from one individual to another, thus introducing an additional layer of intricacy to the diagnostic process. It is vital to address the early intervention requirement to prevent further complications.

Furthermore, the presence of heterogeneity in manifestations involving both small and large nerve fiber types further complicates the accurate diagnosis of neuropathy in diabetic individuals. This

diversity in symptoms and presentations underscores the importance of a thorough evaluation by healthcare professionals. Moreover, it is important to establish a clear differentiation between the various subcategories of diabetes, specifically type I and type II, given that their corresponding epidemiology and pathophysiology manifest notable distinctions that may influence the selection of treatment strategies and management approaches (23).

Prevention and control :

To prevent and control diabetic neuropathy, it is imperative to implement a series of key strategies. These strategies encompass maintaining strict control over glycemic levels, making necessary adjustments to one's lifestyle, ensuring proper foot care practices, and the prompt identification of any potential issues. This system's intent is firmly established in the utilization of stringent blood sugar regulation, with a specific emphasis on attaining a target HbA1c level below 6% for individuals with type 1 diabetes and between 7.0 and 7.9 for those with type 2 diabetes. This loose oversight of blood sugar levels, in addition to lifestyle alterations, is a central component in the general handling of diabetic neuropathy. Furthermore, the implementation of enhanced glycemic control measures and Personalized dietary plans and exercise regimens has been identified as a highly effective intervention in preventing and potentially reversing diabetic neuropathy. Furthermore, the incorporation of cutting-edge methods like neurostimulation gadgets and the use of nutraceuticals as emerging therapeutic choices shows substantial potential in the efficient handling of neuropathic discomfort linked with diabetic neuropathy (24, 25). Moreover, Research underscores and highlights the significant and advantageous influence that engaging in physical exercise has on the overall health and functionality of the human body's vascular and neuronal systems. This research sheds light on the promising and encouraging outcomes that such physical activity can have, specifically in the realm of managing and warding off the development of diabetic neuropathy. Additionally, there is substantial evidence in favor of utilizing a blend of endurance exercises and sensorimotor training as the most advantageous approach for managing diabetic peripheral neuropathy, particularly emphasizing the critical role of sensorimotor training in addressing chemotherapy-induced peripheral neuropathy. Lifestyle modifications present a highly appealing and low-risk therapeutic alternative for individuals with diabetic neuropathy, with increasingly emerging data indicating their potential efficacy in individuals already diagnosed with neuropathic conditions (26). Additionally, It is necessary to appreciate the importance of current medications in diabetic neuropathy management. Pharmaceuticals such as anticonvulsants, SNRIs, and tricyclic antidepressants are extensively used in clinical environments. Also, there is an importance placed on the use of medications that regulate the incretin system, particularly glucagon-like peptide-1 agonists, which have displayed considerable potential in the treatment of peripheral diabetic neuropathy. However, despite the various treatment options that are currently available to patients, it is atypical for individuals to frequently receive doses that are below optimal, ultimately causing inadequate symptom control and subsequent treatment cessation. The medications that have received the green light from the FDA for the treatment of painful diabetic neuropathy include duloxetine, pregabalin, tapentadol, and capsaicin. Even though these pharmaceutical agents have exhibited effectiveness in alleviating symptoms, it should be noted that they could also lead to adverse reactions, prompting additional clinical studies to be implemented to discover more potent and secure treatment alternatives. In conclusion, the current pharmaceutical treatments accessible to patients are designed to relieve symptoms. Yet, there is still a requirement for improving dosage schedules and investigating new therapies for better management of diabetic nerve pain (27). Moreover, the prevalence of herbal remedies is increasing as they are increasingly favored for their perceived diminished adverse effects in contrast to traditional pharmaceuticals, thereby presenting a promising substitute for individuals searching for more organic treatment alternatives (28). In addition, The utilization of various therapeutic interventions, including but not limited to the combination of Astragali Radix–Cinnamomi Ramulus herb-pair (ACP), Berberine (BR), and vitamin E (TOC), has exhibited considerable potential in the amelioration of inflammatory processes, enhancement of neurological performance, and mitigation of sensory discomfort (29). Moreover, flavonoids like quercetin, rutin, and kaempferol are known to offer several positive influences, such

as antioxidant, anti-inflammatory, and anti-glycation traits. These plants are vital in the prevention and management of diabetic neuropathy. By exerting their antioxidant effects, flavonoids help decrease oxidative stress and shield nerve cells from harm. Furthermore, their anti-inflammatory characteristics may assist in reducing nerve inflammation. At the same time, their anti-glycation traits could hinder the development of advanced glycation end products that contribute to nerve damage in diabetes. The varied advantages of flavonoids designate them as hopeful choices for the adjunctive care of diabetic neuropathy (30). Overall, These organic treatments denote a comprehensive and integrative technique for the management of neuropathy, covering a vast array of modalities and methods that deviate from the traditional emphasis on medication-based interventions commonly used in the treatment of individuals suffering from diabetic neuropathy.

Conclusion:

Diabetic neuropathy, prevalent in both type 1 and type 2 diabetes, results from prolonged high blood glucose levels damaging nerves. Symptoms vary from discomfort to numbness and autonomic issues. Prediabetes is also linked to neuropathy, stressing early detection. Pathophysiologically, factors like glycemic dysregulation and oxidative stress contribute to nerve damage. Diagnosis involves nerve conduction studies and clinical evaluation, though early detection challenges persist. Prevention emphasizes glycemic control, lifestyle adjustments, and emerging therapies like neurostimulation. Medications offer symptom relief, while herbal remedies and flavonoids show promise. Managing diabetic neuropathy requires a multifaceted approach integrating traditional and emerging treatments for improved patient outcomes and quality of life.

References

1. Said GJNcpN. Diabetic neuropathy—a review. 2007;3(6):331-40.
2. Sharma P, Rani N, Gangwar A, Singh R, Kaur R, Upadhyaya K. Diabetic Neuropathy: A Repercussion of Vitamin D Deficiency. *Current Diabetes Reviews*. 2023;19(6):80-91.
3. Varma A, Sharma K, Sharma S. Evaluation of Diabetic Neuropathies. 2022;2(1):9-14.
4. Assunção A, Campos D, Marques R, Cunha I, Santos P, Martins A, et al. The impact of demographic and clinical characteristics on diabetic painful neuropathy %J *Romanian Journal of Internal Medicine*. 2020;58(1):13-9.
5. Mawaddah M, Susmiati S, Lenggogeni DPJRiNJ. Gambaran Karakteristik Pasien Dengan Neuropati Diabetik Pada Diabetes Melitus Tipe 2. 2022;5(3):207-13.
6. Khan MD, Yousaf H, Umar M, Zaib MS, Qazi S, Irshad K, et al. Impact of diabetes mellitus on nerves. *International Journal of Research in Medical Sciences*. 2020;8(10):3453-6.
7. Fujita Y, Murakami T, Nakamura A. Recent Advances in Biomarkers and Regenerative Medicine for Diabetic Neuropathy. 2021;22(5):2301.
8. Mushabab A, Lukman FO, Bappa A, Magaji GT, Abubakar J, Mohammed A, et al. Disease-specific quality of life in patients with diabetic neuropathy. *Saudi Medical Journal*. 2022;43(4):408.
9. Davoudi M, Rezaei P, Rajaeiramsheh F, Ahmadi SM, Taheri AA. Predicting the quality of life based on pain dimensions and psychiatric symptoms in patients with Painful diabetic neuropathy: a cross-sectional prevalence study in Iranian patients. *Health and Quality of Life Outcomes*. 2021;19(1):49.
10. Eid SA, Rumora AE, Beirowski B, Bennett DL, Hur J, Savelieff MG, et al. New perspectives in diabetic neuropathy. *Neuron*. 2023;111(17):2623-41.
11. Singh A, Kukreti R, Saso L, Kukreti S. Mechanistic Insight into Oxidative Stress-Triggered Signaling Pathways and Type 2 Diabetes. 2022;27(3):950.
12. Alles SRA, Smith PA. Peripheral Voltage-Gated Cation Channels in Neuropathic Pain and Their Potential as Therapeutic Targets. 2021;2.
13. Kang SMJTJoKD. Pathogenesis and Treatment of Diabetic Peripheral Neuropathy. 2022;23(4):222-9.

14. Mahmood F, Ahmad SJSJAMS. Pathophysiology and Pharmacotherapeutics of Diabetic Neuropathy: A Review. 2022;12:2096-102.
15. Jankovic M, Novakovic I, Nikolic D, Mitrovic Maksic J, Brankovic S, Petronic I, et al. Genetic and Epigenomic Modifiers of Diabetic Neuropathy. 2021;22(9):4887.
16. Katagi M, Terashima T, Okano J, Urabe H, Nakae Y, Ogawa N, et al. Hyperglycemia induces abnormal gene expression in hematopoietic stem cells and their progeny in diabetic neuropathy. 2014;588(6):1080-6.
17. Witzel I-I, Jelinek HF, Khalaf K, Lee S, Khandoker AH, Alsafar HJFie. Identifying common genetic risk factors of diabetic neuropathies. 2015;6:141587.
18. Chiaramonte R, Romano M, Vecchio M. A Systematic Review of the Diagnostic Methods of Small Fiber Neuropathies in Rehabilitation. 2020;10(9):613.
19. Koçer A. How to diagnose neuropathy in diabetes mellitus? The European Research Journal. 2018;4(2):55-69.
20. Goyal M, Mittal A, Samuel AJJJoDMIoMSU. Diagnostic methods used in patients with diabetic peripheral neuropathy: With special importance on radiological methods. 2022;17(2):472-8.
21. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa MJNEJoM. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. 1995;333(2):89-94.
22. Rad MM, Soheilipour FS, Baradaran HR, Rimaz SR, Marvasti SK, Taslimi H, et al. The influence of diabetic family history on the development of neuropathy in type 2 diabetic patients: a survival analysis. 2020;27(1):25-33.
23. Ansari P, Hannan JMA, Azam S, Jakaria M. Challenges in Diabetic Micro-Complication Management: Focus on Diabetic Neuropathy. 2021;1(3):175-86.
24. Gandhi M, Fargo E, Prasad-Reddy L, Mahoney KM, Isaacs DJDiC. Diabetes: how to manage diabetic peripheral neuropathy. 2022;11.
25. Smith S, Normahani P, Lane T, Hohenschurz-Schmidt D, Oliver N, Davies AH. Prevention and Management Strategies for Diabetic Neuropathy. 2022;12(8):1185.
26. Zilliox LA, Russell JW. Physical activity and dietary interventions in diabetic neuropathy: a systematic review. Clinical Autonomic Research. 2019;29(4):443-55.
27. Qureshi Z, Ali MN, Khalid M. An Insight into Potential Pharmacotherapeutic Agents for Painful Diabetic Neuropathy. Journal of Diabetes Research. 2022;2022:9989272.
28. Arora K, Tomar PC, Mohan V. Diabetic neuropathy: an insight on the transition from synthetic drugs to herbal therapies. Journal of Diabetes & Metabolic Disorders. 2021;20(2):1773-84.
29. Chung G, Kim SK. Therapeutics for Chemotherapy-Induced Peripheral Neuropathy: Approaches with Natural Compounds from Traditional Eastern Medicine. 2022;14(7):1407.
30. Asgary S, Naderi GA, Sarraf-Zadegan N, Vakili R. The Inhibitory Effects of Pure Flavonoids on in Vitro Protein Glycosylation. Journal Of Herbal Pharmacotherapy. 2002;2(2):47-55.