

## PROPHYLAXIS USE OF VITAMIN B IN DIABETIC PATIENTS

Mais Damani<sup>\*1</sup>, Yusra Damani<sup>2</sup> and Doaa Alkhalidi<sup>3</sup><sup>1</sup>RPh – Mpharm Candidate in Clinical Pharmacy and Pharmacotherapeutic, Dubai Pharmacy College - Dubai, UAE.<sup>2</sup>MBBS – General Practitioner in Al Zahra Hospital – Dubai, UAE.<sup>3</sup>Assistant Professor in Clinical Pharmacy and Pharmacotherapeutics Department, Dubai Pharmacy College for Girls, Dubai, UAE.

Received on: 12/07/2022

Revised on: 02/08/2022

Accepted on: 22/08/2022

\*Corresponding Author

Mais Damani

RPh – Mpharm Candidate in  
Clinical Pharmacy and  
Pharmacotherapeutic, Dubai  
Pharmacy College - Dubai,  
UAE.

## ABSTRACT

**Background:** Diabetes Mellitus (DM) is considered to be a very common disorder worldwide, affecting hundreds of millions of people all over the world. Diabetes can lead to severe complications and high prevalence of morbidities if not treated. Diabetic Neuropathy (DN) is the most common complication that may affect up to fifty percent of diabetic patients. B Vitamins play an important role in maintaining healthy nervous system.<sup>[1]</sup> **Aim of the study** is identify the healthcare professionals' point of view regarding the use of Vitamin B as prophylaxis in patients with DM. **Methodology:** this is considered as a cross-sectional study in which a questionnaire survey was distributed to physicians from Al Zahra Hospital, Dubai-UAE. 80 physicians from different specialties (GP, ICU, family medicine, internal medicine, neurologist and endocrinologist) were included in our study and the distribution of the questionnaire survey was from September 2021 to October 2021. Physicians from another specialties, and patients with or without diabetes were excluded from our study. **Results:** Regarding physicians; the significant results (P<0.05) shows that vitamin B complex is the most prescribed type among specialists and neurologists, and along with it they are using pregabalin in the management of diabetic neuropathy. Regarding pharmacists; the significant results (P<0.05) shows that most of the participating pharmacists were receiving up to 50 prescriptions that includes vitamin B complex. The more experienced and female pharmacists believe that vitamin B complex will decrease progression of diabetic neuropathy and should be started for patients that experience and DM symptoms more than less experienced and male pharmacists. **Conclusion:** Our findings were demonstrating that that Overall knowledge of vitamin B uses and effect as a treatment was more than the knowledge of it as a prophylaxis. In conclusion we suggest highlighting this topic and to start getting more clinical trials on the use of vitamin B as a prophylaxis therapy in diabetic patient to avoid its complications, prevent nerve damage and development of diabetic neuropathy and its symptoms.

**KEYWORDS:** Diabetes Mellitus, Diabetic Neuropathy, type-2 diabetes mellitus, vitamin B complex, Cyanocobalamine, Pyridoxine, Thiamin.

## INTRODUCTION

Diabetes Mellitus (DM) is a heterogeneous disease that is characterized by high blood glucose levels. Its is considered to be a very common disorder worldwide and became a major public health issue, affecting hundereds of millions of people all over the world.<sup>[1]</sup>

## Signs and Symptoms of DM.

Sign and symptoms of diabetes may reflect as increased thirsty, hunger and increased urination at night. Patients may also experience blurry vission, excessive fatigue and, slow healing wounds.<sup>[1]</sup>

It was estimated that approximately 194 million people have DM in adult population in the International

Diabetes Federation (IDF) regions. Recent studies in UAE estimate that diabetes risk increase with age. 40 percent of age group 60 and above are having DM.<sup>[3]</sup>

Diabetic Neuropathy (DN) is one of the most common complication of diabetes mellitus. It can be caused by diabetes mellitus type-1 and type-2. DN incidence is more common in diabetic patients with poor control, overweight, high blood fat and uncontrolled blood pressure.

Neuropathy which is a condition where the nerves will be damaged causing symptoms like; pain which gets worsen at night, numbness, tingling and burning sensation.

Small blood vessels provides nutrients and oxygen to nerves in order for it to function. High glucose levels or uncontrolled diabetes will damage those small blood vessels thus the nerves get damaged because of insufficient nutrients and oxygen reaches the nerves. Nerves play an important role in feeling sensation, controlling heart rate, digestive system, bladder control and sexual function. Symptoms of DN may start in the feet and if left untreated it may lead to complete loss of feeling and spread to other parts of the body.

B Vitamins plays an important role in maintaining good health and well-being, it also contribute essentially to the maintainance of a healthy nervous system. It was listed that having a deficiency of vitamin B can lead to neurological problems and the use of vitamin B supplements for patients without deficiency can also contribute to show improvement in neurological function. Vitamin B usually has eight types, each has a different action and mechanism in improving and maintaining healthy body and nervous system.

Thiamin (B1) works by converting glucose into energy and improve nerve function.

Riboflavin (B2) works by producing energy and help vision and skin health. Niacin which is vitamin B3 can convert carbohydrates and fats into energy and support nervous and digestive systems. Pantothenic acid (B5) and Pyridoxine (B6) metabolise carbohydrates and fats and produce red blood cells. Biotin (B7) energy metabolism and fat synthesis. Folic acid (B9) forms red blood cells and helps in development of fetal nervous system, DNA synthesis and cell growth. Cyanocobalamine is the last type of vitamin B which is vitamin B12 it works by producing and maintaining the myelin sheath, formation of red blood cells and producing energy.<sup>[11]</sup>

In early stages of neuropathy, symptoms and pain can be relieved with vitamins but if it was left without treatment it will lead to irreversible nerves damage.<sup>[12]</sup>

## MATERIALS AND METHODS

**Study design, settings and selection criteria:** In the current study, a Cross-sectional study design was adopted. It involved a questionnaire-based survey among the Healthcare Professionals (i.e. physicians and pharmacists) who were working in a private hospital in Dubai-UAE. This study was conducted among 72 registered physicians who were belonging to any of the following specialties: GP, ICU, Family Medicine, Internal Medicine, and Neurology& Endocrinology. In addition, the study included 18 registered pharmacists as well. Physicians from another specialty, and patients with or without diabetes will be excluded from our study. Data were collected from 72 physicians in different specialties and 18 pharmacists.

**Statistical methods:** The pilot questionnaire was designed using online survey in collecting data, specifically "Google form Survey". This survey was distributed through E-mails & WhatsApp application to physicians from Al Zahra hospital, Dubai, UAE and data was analysed by (SPSS-IBM version 26) Statistical Package for Social Science.

**Data collection:** Based on previous studies mentioned in the literature review, a set of questionnaires was designed and developed. And based on those studies, 15 survey questions were made. It was formatted as an online based survey and questions were divided into; demographic information, knowledge and recommendation, satisfactions and their opinion regarding the use of vitamin B as prophylactic therapy in diabetic patients. Demographic information consisted of 6 items; Age, Gender, Nationality, Designation and specialty as well as years of experience. Knowledge will be determined by asking the physicians if all diabetic patients are at risk of developing neuropathy, if they are using Vitamin B as a **treatment** for patients already diagnosed with neuropathy and which type of vitamin B they are prescribing for diabetic neuropathy. Duration of treatment with vitamin B and to mention what are the medications prescribed for the treatment of neuropathy other than vitamin B, if they agree that the use of vitamin B as prophylaxis can reduce the risk of developing neuropathy or its symptoms, if there are any side effects that the patient may experience while using vitamin B will also be asked. The survey questions consist of 5 statements to be answered with always, often, sometimes, rarely or never. Last part of our questionnaire was about recommendation, physicians will be requested to answer if they recommend the use of vitamin B as prophylaxis for all diabetic patients even with controlled cases.

## RESULTS

A pilot test was conducted for the purpose of testing the research approach with a small number of participants before conducting our study which helped us in getting more reliable results. In order to conduct the pilot test; questionnaires surveys were randomly distributed to 20 physicians and 20 pharmacists. Then, the data collected from physicians' and pharmacists' surveys were tested by Cronbach alpha which is a measurement for internal consistency and reliability.

As in regards to the Cronbach alpha value for pharmacist questions was 0.749 and 0.635 for physician questions. And this demonstrates in good internal consistency and suitability for application among pharmacists and physicians.

### Participant's demographics and characteristics

In order to achieve the targeted sample size, 80 physicians working in Al Zahra Hospital in Dubai, UAE were approached. Out of the 80 physicians, 72 has completed the questionnaire and were enrolled in this

study, including 13 (18.1%) general practitioners, 12 (16.7%) endocrinologists, 11 (15.3%) internal medicine physicians, 8 (11.1%) family medicine physicians 9 (12.5%), intensive care unit physicians 9 (12.5%) and 19 (26.4%) neurologists. Most of the participants were specialists 40 (55.6%), 17 (23.6%) were GP, while 15 (20.8%) of the participants were consultants. The majority of the physicians were males 43(59.7%) and 29 (40.3%) females. Regarding the age group of physicians,

17 (23.6%) are between 20 to 30 years, 48 (66.7%) are between 30 to 50 years and 7 (9.7%) are above 50 years. Furthermore, 42 (58.3%) of the participants were having 6 to 10 years of experience, 23 (31.9%) were having more than 10 years' experience while only 7 (9.7%) had 1 to 5 years of experience. As for the nationality, the majority of participants 48 (66.7%) were from the Middle East countries, 18 (25%) from gulf countries and only 6 (8.3%) were from Europe.

**Table 1: Physicians’ pattern of prescribing vitamin B and other management for diabetic neuropathy among diabetic patients’ questions among the participating physicians.**

Questionnaire Item	Participants Characteristics	P Value
Please specify the type of vitamin B that you usually prescribe for your diabetic patients.	Specialty	0.040*
	Designation	0.016*
Have you ever prescribed any other medication for the management of Diabetic Neuropathy?	Specialty	0.042*

**The type of vitamin B which is prescribed by the participating physicians**

Based on Table 1, it has been shown that the specialty of the participants is significantly associated (P<0.05) with the type of vitamin B that is usually prescribed among patients as a treatment of DN. It was noticed that vitamin B complex (54.2%) is more prescribed than vitamin B 12 (45.8%) by the participating physicians (Table 2). Regarding the specialty of the participants, Neurologist (19.4%) found to be the most frequent physicians who

are prescribing vitamin B-complex for the treatment of DM in diabetic patients, followed by endocrinologist (12.5%). The designation of the participating physicians was also significantly associated (P<0.05) with the type of vitamin B that is usually prescribed among patients as a treatment of DN, where the specialists were more frequently prescribing vitamin B complex (30.6%) followed by consultants (16.7%) then general practitioners (6.9%), see (Table 3).

**Table 2: The type of vitamin B which is prescribed by the participating physicians based on their specialty.**

	GP n (%)	Endocrinologist n (%)	Internal Medicine n (%)	Family Medicine n (%)	ICU n (%)	Neurologist n (%)	Total n (%)
Vitamin B12	9(12.5%)	3(4.2%)	8 (11.1%)	3 (4.2%)	5 (6.9%)	5 (6.9%)	33(45.8%)
Vitamin B-complex	4 (5.6%)	9(12.5%)	3(4.2%)	5(6.9%)	4 (5.6%)	14 (19.4%)	39(54.2%)
Total	13(18.1%)	12(16.7%)	11(15.3%)	8(11.1%)	9(12.5%)	19 (26.4%)	72 (100%)

**Table 3: The type of vitamin B which is prescribed by the participating physicians based on their Designation.**

	GP	Specialist	Consultant	Total
Vitamin B 12	12 (16.6%)	18 (25%)	3 (4.2%)	33 (45.8%)
Vitamin B complex	5 (6.9%)	22 (30.6%)	12 (16.7%)	39 (54.2%)
Total	17 (23.6%)	40 (55.6%)	15 (20.8%)	72 (100%)

**Table 4: Type of medications for the management of Diabetic Neuropathy which is prescribed by the participating physicians based on their specialty.**

	General Practitioner n (%)	Endocrinologist n (%)	Internal Medicine n (%)	Family Medicine n (%)	ICU n (%)	Neurologist n (%)	Total
did not prescribe anything	5 (6.9%)	0 (0%)	2 (2.8%)	4 (5.6%)	0 (0%)	2 (2.8%)	13 (18%)
duloxetine	1 (1.4%)	6 (8.3%)	3 (4.2%)	2 (2.8%)	3 (4.2%)	6 (8.3%)	21(29.2%)
pregabalin	6 (8.3%)	6 (8.3%)	6 (8.3%)	2 (2.8%)	5 (6.9%)	11 (15.2%)	36 (50%)
venlafaxine	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)
Amitriptyline	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)	0 (0%)	1 (1.4%)
Total	13 (18%)	12 (16.7%)	11 (15.2%)	8 (11.1%)	9 (12.5%)	19 (26.4%)	72 (100%)

**Table 4:** Is demonstrating that the designation of participating physicians was significantly associated ( $P>0.05$ ) with the physicians' views regarding the safety of using vitamin B as treatment in diabetic neuropathy and the most common used medicine for treatment of diabetic neuropathy is pregabalin.

Pharmacists' Demographic information:	Pharmacists
Variables	N=38 / percentage (%)
<b>Designation</b>	
Clinical pharmacist	4 (10.5%)
Hospital pharmacist	27 (71.1%)
Community pharmacist	7 (18.4%)
<b>Gender</b>	
Male	13 (34.2%)
Female	25 (65.8%)
<b>Age</b>	
20-30 years	22 (57.9%)
30-50 years	16 (42.1%)
More than 50 years	0 (0.0%)
<b>Experience</b>	
Fresh graduate	1 (2.6%)
1-5 years	12 (31.6%)
6-10 years	19 (50%)
More than 10 years	6 (15.8%)
<b>Nationality</b>	
Middle east	28 (73.3%)
Gulf countries	10 (26.3%)
Europe	0 (0.0%)

**Table 5:** Pharmacists' perception toward the prophylactic use of vitamin B in diabetic neuropathy based on the pharmacists' designation, gender, age, experience, and nationality.

Questionnaire Item	Participants Characteristics	P Value
Do you think prescribing the Patient a Prophylaxis dose of Vitamin B would reduce the risk of Neuropathy development or its symptoms?	Years of Experience	0.030*
What is the monthly approximated number of prescriptions that include Vitamin B Complex?	Designation	0.000*
	Years of Experience	0.028*

**Table 5** demonstrates that years of experience is significantly associated ( $P<0.05$ ) with the pharmacists view in prescribing vitamin B as prophylaxis therapy for reducing the risk of developing neuropathy. it has been also shown that designation of participating pharmacists was significantly associated ( $P<0.05$ ) with the monthly approximated number of prescriptions that includes vitamin B therapy. It has been demonstrated in table 11

that more than half of the participating pharmacists (63.2%) were receiving up to 50 prescriptions that includes vitamin B per month, 23.7% of the pharmacists are receiving approximately more than 100 prescriptions per month and only 13.2% of the participating pharmacists are receiving less than 10 prescriptions per month.

**Table 6:** Pharmacists' point of view in recommending vitamin B for all diabetic patients, even with the controlled cases, as a prophylaxis therapy or prevention of diabetic neuropathy based on the gender.

	<i>male</i>	<i>female</i>	<i>Total</i>
Always	5 (13.2%)	15 (39.5%)	20 (52.6%)
often	4(10.5%)	10 (26.3%)	14 (36.8%)
sometimes	3 (7.9%)	0 (0%)	3 (7.9%)
rarely	1 (2.6%)	0 (0%)	1 (2.6%)
total	13 (34.2%)	25 (65.8%)	38 (100%)

**Table 7: Pharmacists' perception regarding the prophylaxis use of vitamin B therapy and reducing the risk of neuropathy development based on the years of experience.**

	Fresh graduates	1-5 years	6-10 years	More than 10 years	total
Always	1 (2.6%)	7 (18.4%)	11 (28.9%)	3 (7.9%)	22 (57.9%)
often	0 (0%)	4 (10.5%)	7 (18.4%)	2 (5.3%)	13 (34.2%)
sometimes	0 (0%)	0 (0%)	0 (0%)	1 (2.6%)	1 (2.6%)
rarely	0 (0%)	1 (2.6%)	1 (2.6%)	0 (0%)	2 (5.3%)
total	1 (2.6%)	12	19	6	38 (100%)

As demonstrated in table 6 and 7, the more experienced and female pharmacists believe that vitamin B complex will decrease progression of diabetic neuropathy and should be started for patients that experience and DM symptoms more than less experienced and male pharmacists.

## CONCLUSION

Our findings were demonstrating that that Overall knowledge of vitamin B uses and effect as a treatment was more than the knowledge of it as a prophylaxis. In conclusion we suggest highlighting this topic and to start getting more clinical trials on the use of vitamin B as a prophylaxis therapy in diabetic patient to avoid its complications, prevent nerve damage and development of diabetic neuropathy and its symptoms.

## LIMITATIONS

Our study is considered to be the first study that focuses on the prophylaxis use of vitamin B for all diabetic patients in Dubai – UAE, which in turn needs more clinical trials to confirm our results and findings. One more limitation for our study was the low sample size number where the pharmacy staff number is less and this study can be considered as preliminary study to help for further future studies.

## REFERENCES

- Li, W., Huang, E., & Gao, S. Type 1 diabetes mellitus and cognitive impairments: A systematic review. *Journal of Alzheimer's Disease*, 2017; 57(1): 29–36. <https://doi.org/10.3233/JAD-161250>.
- Boles, A., Kandimalla, R., & Reddy, P. H. Dynamics of diabetes and obesity: Epidemiological perspective. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 2017; 1863(5): 1026–1036. <https://doi.org/10.1016/j.bbadis.2017.01.016>.
- Ogurtsova, K., da Rocha Fernandes, J. D., Huang, Y., Linnenkamp, U., Guariguata, L., Cho, N. H., Cavan, D., Shaw, J. E., & Makaroff, L. E. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Research and Clinical Practice*, 2017; 128: 40–50. <https://doi.org/10.1016/j.diabres.2017.03.024>
- Boulton, A. J. M. *Diabetic neuropathy and foot complications*, 2014; 126: 97–107. Elsevier. <https://doi.org/10.1016/B978-0-444-53480-4.00008-4>
- Selvarajah, D., Kar, D., Khunti, K., Davies, M. J., Scott, A. R., Walker, J., & Tesfaye, S. Diabetic peripheral neuropathy: Advances in diagnosis and strategies for screening and early intervention. *The Lancet Diabetes & Endocrinology*, 2019; 7(12): 938–948. [https://doi.org/10.1016/S2213-8587\(19\)30081-6](https://doi.org/10.1016/S2213-8587(19)30081-6).
- Misher, A. M., Rosselli, J. L., Schumacher, C. A., & See, M. The role of the diabetes care and education specialist in caring for diabetes complications and common comorbid conditions. *ADCES in Practice*, 2021; 9(3): 30–52. <https://doi.org/10.1177/2633559X211002805>.
- Pavone, P., Di Rosa, M., Musumeci, G., Caccamo, M., Greco, F., Pavone, V., Smilari, P., Santamato, A., & Vecchio, M. Focal neuropathy mimicking focal dystonia in a child: Diagnostic and rehabilitative tools. *Journal of Functional Morphology and Kinesiology*, 2019; 4(3): 54. <https://doi.org/10.3390/jfmk4030054>.
- Hicks, C. W., & Selvin, E. (2019). Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. *Current Diabetes Reports*, 19(10): 86. <https://doi.org/10.1007/s11892-019-1212-8>
- Misra, U., Kalita, J., & Nair, P. Diagnostic approach to peripheral neuropathy. *Annals of Indian Academy of Neurology*, 2008; 11(2): 89. <https://doi.org/10.4103/0972-2327.41875>.
- Ardeleanu, V., Toma, A., Pafili, K., Papanas, N., Motofei, I., Diaconu, C. C., Rizzo, M., & Pantea Stoian, A. Current pharmacological treatment of painful diabetic neuropathy: A narrative review. *Medicina*, 2020; 56(1): 25. <https://doi.org/10.3390/medicina56010025>.
- Kennedy, D. B vitamins and the brain: Mechanisms, dose and efficacy—a review. *Nutrients*, 2016; 8(2): 68. <https://doi.org/10.3390/nu8020068>.
- Department of Biology, Drexel University, Philadelphia, PA, USA, Murphy, K. L., Bethea, J. R., Department of Biology, Drexel University, Philadelphia, PA, USA, Fischer, R., & Department of Biology, Drexel University, Philadelphia, PA, USA. *Neuropathic pain in multiple sclerosis—current therapeutic intervention and future treatment perspectives* (Department of Neural & Behavioral Sciences, Pennsylvania State University College of Medicine Hershey, Pennsylvania, USA, I. S. Zagon, P. J. McLaughlin, & Department of Neural & Behavioral Sciences, Pennsylvania State University College of Medicine Hershey,



- Pennsylvania, USA, Eds.; pp. 53–69). Codon Publications.  
<https://doi.org/10.15586/codon.multiplesclerosis.2017.ch4>, 2017.
13. Didangelos, T., Karlafti, E., Kotzakioulafi, E., Margariti, E., Giannoulaki, P., Batanis, G., Tesfaye, S., & Kantartzis, K. Vitamin b12 supplementation in diabetic neuropathy: A 1-year, randomized, double-blind, placebo-controlled trial. *Nutrients*, 2021; *13*(2): 395. <https://doi.org/10.3390/nu13020395>.
  14. Ang, C. D., Alviar, M. J. M., Dans, A. L., Bautista-Velez, G. G. P., Villaruz-Sulit, M. V. C., Tan, J. J., Co, H. U., Bautista, M. R. M., & Roxas, A. A. Vitamin B for treating peripheral neuropathy. *The Cochrane Database of Systematic Reviews*, 2008; *3*: CD004573.  
<https://doi.org/10.1002/14651858.CD004573.pub3>
  15. Martini, L. A., Catania, A. S., & Ferreira, S. R. Role of vitamins and minerals in prevention and management of type 2 diabetes mellitus: Nutrition Reviews©, Vol. 68, No. 6. *Nutrition Reviews*, 2010; *68*(6): 341–354. <https://doi.org/10.1111/j.1753-4887.2010.00296.x>.
  16. Al-Maskari, M. Y., Waly, M. I., Ali, A., Al-Shuaibi, Y. S., & Ouhtit, A. Folate and vitamin B12 deficiency and hyperhomocysteinemia promote oxidative stress in adult type 2 diabetes. *Nutrition*, 2012; *28*(7–8): e23–e26. <https://doi.org/10.1016/j.nut.2012.01.005>.
  17. Valdés-Ramos, R., Ana Laura, G.-L., Elina, M.-C. B., & Donají, B.-A. A. Vitamins and type 2 diabetes mellitus. *Endocrine, Metabolic & Immune Disorders Drug Targets*, 2015; *15*(1): 54–63. <https://doi.org/10.2174/1871530314666141111103217>.
  18. Ahmed, M. A., Muntingh, G., & Rheeder, P. Vitamin B12 deficiency in metformin-treated type-2 diabetes patients, prevalence and association with peripheral neuropathy. *BMC Pharmacology and Toxicology*, 2016; *17*(1): 44. <https://doi.org/10.1186/s40360-016-0088-3>.
  19. Gupta, K., Jain, A., & Rohatgi, A. An observational study of vitamin b12 levels and peripheral neuropathy profile in patients of diabetes mellitus on metformin therapy. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, 2018; *12*(1): 51–58. <https://doi.org/10.1016/j.dsx.2017.08.014>.
  20. Alharbi, T. J., Tourkmani, A. M., Abdelhay, O., Alkhashan, H. I., Al-Asmari, A. K., Bin Rashed, A. M., Abuhaimed, S. N., Mohammed, N., AlRasheed, A. N., & AlHarbi, N. G. The association of metformin use with vitamin B12 deficiency and peripheral neuropathy in Saudi individuals with type 2 diabetes mellitus. *PLOS ONE*, 2018; *13*(10): e0204420. <https://doi.org/10.1371/journal.pone.0204420>.
  21. Singh, A., Kumar, A., Karmakar, D., & Jha, R. Association of B12 deficiency and clinical neuropathy with metformin use in type 2 diabetes patients. *Journal of Postgraduate Medicine*, 2013; *59*(4): 253. <https://doi.org/10.4103/0022-3859.123143>.
  22. Yang, W., Cai, X., Wu, H., & Ji, L. Associations between metformin use and vitamin B<sub>12</sub> levels, anemia, and neuropathy in patients with diabetes: A meta-analysis. *Journal of Diabetes*, 2019; *11*(9): 729–743. <https://doi.org/10.1111/1753-0407.12900>.
  23. Badedi, M., Darraj, H., Hummadi, A., Solan, Y., Zakri, I., Khawaji, A., Daghreeri, M., & Budaydi, A. Vitamin b12 deficiency and foot ulcers in type 2 diabetes mellitus: A case-control study. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 2019; *12*: 2589–2596. <https://doi.org/10.2147/DMSO.S233683>.
  24. Didangelos, T., Karlafti, E., Kotzakioulafi, E., Margariti, E., Giannoulaki, P., Batanis, G., Tesfaye, S., & Kantartzis, K. Vitamin b12 supplementation in diabetic neuropathy: A 1-year, randomized, double-blind, placebo-controlled trial. *Nutrients*, 2021; *13*(2): 395. <https://doi.org/10.3390/nu13020395>.
  25. Yao, H., Feng, J., Zheng, Q., Wei, Y., Yang, G., & Feng, W. Comparison of the effects of prophylactic and therapeutic administrations on peripheral neuropathy in streptozotocin-diabetic rats with gliclazide or methylcobalamin. *Experimental and Clinical Endocrinology & Diabetes*, 2020; *128*(10): 635–643. <https://doi.org/10.1055/a-0635-0672>.
  26. Sawangjit, R., Thongphui, S., Chaichompu, W., & Phumart, P. Efficacy and safety of mecobalamin on peripheral neuropathy: A systematic review and meta-analysis of randomized controlled trials. *The Journal of Alternative and Complementary Medicine*, 2020; *26*(12): 1117–1129. <https://doi.org/10.1089/acm.2020.0068>.
  27. T. Julian, R. Syeed, N. Glasgow, E. Angelopoulou, and P. Zis, “B12 as a Treatment for Peripheral Neuropathic Pain: A Systematic Review,” *Nutr. 2020*; *12*: 8. doi: 10.3390/NU12082221.
  28. B. Jayabalan and L. L. Low, “Vitamin B supplementation for diabetic peripheral neuropathy,” *Singapore Med. J.*, 2016; *57*(2): 55–59. doi: 10.11622/SMEDJ.2016027.
  29. L. M. Miles, E. Allen, R. Clarke, K. Mills, R. Uauy, and A. D. Dangour, “Impact of baseline vitamin B12 status on the effect of vitamin B12 supplementation on neurologic function in older people: secondary analysis of data from the OPEN randomised controlled trial,” *Eur. J. Clin. Nutr.* 2017 *71*10, 2017; *71*(10): 1166–1172. Feb., doi: 10.1038/ejcn.2017.7.
  30. J. Shi, X. Mo, and Z. Sun, “Content validity index in scale development,” *J. Cent. South Univ. (Medical Sci.)*, 2012; *37*(2): 152–155. doi: 10.3969/J.ISSN.1672-7347.2012.02.007.
  31. House, A. A., Eliasziw, M., Cattran, D. C., Churchill, D. N., Oliver, M. J., Fine, A., Dresser, G. K., & Spence, J. D. Effect of b-vitamin therapy on progression of diabetic nephropathy: A randomized controlled trial. *JAMA*, 2010; *303*(16): 1603.

- <https://doi.org/10.1001/jama.2010.490>.
32. Tassone, D. M., Boyce, E., Guyer, J., & Nuzum, D. Pregabalin: A novel  $\gamma$ -aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. *Clinical Therapeutics*, 2007; 29(1): 26–48. <https://doi.org/10.1016/j.clinthera.2007.01.013>.
  33. Lesser, H., Sharma, U., LaMoreaux, L., & Poole, R. M. Pregabalin relieves symptoms of painful diabetic neuropathy: A randomized controlled trial. *Neurology*, 2004; 63(11): 2104–2110. <https://doi.org/10.1212/01.WNL.0000145767.36287.A1>.
  34. Altun, I., & Kurutaş, E. Vitamin B complex and vitamin B<sub>12</sub> levels after peripheral nerve injury. *Neural Regeneration Research*, 2016; 11(5): 842. <https://doi.org/10.4103/1673-5374.177150>.
  35. Aldossari, K. K., Al-Ghamdi, S., Alzahrani, J., Al Turki, M. S., Almuhareb, M., Alanazi, Z. G., Alshahrani, Z. M., & Wong, J. Physicians' perception about use of vitamin b12 in the treatment or prevention of diabetic neuropathy: A cross-sectional survey in saudi arabia. *Current Diabetes Reviews*, 2022; 18(2): e021021191310. <https://doi.org/10.2174/1573399817666210211095610>
  36. Didangelos, T., Karlafti, E., Kotzakioulafi, E., Margariti, E., Giannoulaki, P., Batanis, G., Tesfaye, S., & Kantartzis, K. Vitamin b12 supplementation in diabetic neuropathy: A 1-year, randomized, double-blind, placebo-controlled trial. *Nutrients*, 2021; 13(2): 395. <https://doi.org/10.3390/nu13020395>