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Vitamin B12 and risk of diabetic foot ulcers: a new paradigm

About 40–50% of patients with diabetes experience peripheral neuropathy within ten years of disease onset [1]. Peripheral neuropathy associated with diabetes is one of the most important reasons for foot ulceration among these patients, finally leading to amputation [2, 3]. Diabetic foot ulcers (DFU) are one of the leading causes of mortality and morbidity worldwide [4].

Recent studies have shown that vitamin B12 deficiency plays an important role in developing peripheral neuropathy, especially in patients with a prolonged history of diabetes [2, 5]. Vitamin B12 plays a key functional role in the metabolism of fatty acids, which are crucial for maintaining the nerve myelin [6]. Furthermore, vitamin B12 is a cofactor in many intracellular enzymatic reactions necessary for correct central nervous system functions in healthy individuals [6]. Lengthy vitamin B12 insufficiency or deficiency can lead to neuronal degeneration and severe neurological damages, including peripheral neuropathy [7].

Patients with diabetes usually use antihyperglycemic drugs for regulating blood glucose levels. Metformin is the most widely prescribed antihyperglycemic agent for the treatment of type 2 diabetes [8]. Previous studies have reported that metformin induces vitamin B12 deficiency in patients with diabetes [8]. However, there are controversies in the metformin mechanism of action in the induction of vitamin B12 deficiency. The best-proposed mechanism is that metformin, through its biguanide hydrophobic tail binds to the hydrocarbon core of the cell membrane [9]. Then, metformin biguanide groups become positively charged and give their positive charge to the cell membrane. This positive charge can displace divalent cations like calcium and magnesium. It is well known that vitamin B12 uptake in the ileum is a calcium-dependent process; therefore, it can be impaired by metformin [9, 10].

Considering the high rates of patients with diabetes consuming metformin and the sequential vitamin B12 deficiency and following neuropathy, it is vital to monitor diabetic patients' vitamin B12 levels to prevent costly and devastating DFU in the future.

Conflict of interest

None declared.

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REFERENCES:

1. Partanen J, Niskanen L, Lehtinen J, et al. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med. 1995; 333(2): 89–94, doi: 10.1056/NEJM199507133330203, indexed in Pubmed: 7777034.
2. Sun Yu, Lai MS, Lu CJ. Effectiveness of vitamin B12 on diabetic neuropathy: systematic review of clinical controlled trials. Acta Neurol Taiwan. 2005; 14(2): 48–54, indexed in Pubmed: 16008162.
3. Yarahmadi A, Mostafavi-Pour Z, Modaghegh MHS, et al. Association between serum vitamin D, hs-CRP, and prooxidant-antioxidant balance with anthropometric and biochemical parameters in patients with diabetic foot ulcers. Clinical Diabetology. 2021; 10(1): 138–143, doi: 10.5603/dk.2020.0064.

4. Yarahmadi A, Saeed Modaghegh MH, Mostafavi-Pour Z, et al. The effect of platelet-rich plasma-fibrin glue dressing in combination with oral vitamin E and C for treatment of non-healing diabetic foot ulcers: a randomized, double-blind, parallel--group, clinical trial. Expert Opin Biol Ther. 2021; 21(5): 687–696, doi: 10.1080/14712598.2021.1897100, indexed in Pubmed: 33646060.
5. Yang W, Cai X, Wu H, et al. Associations between metformin use and vitamin B levels, anemia, and neuropathy in patients with diabetes: a meta-analysis. J Diabetes. 2019; 11(9): 729–743, doi: 10.1111/1753-0407.12900, indexed in Pubmed: 30615306.
6. Scalabrino G, Buccellato FR, Veber D, et al. New basis of the neurotrophic action of vitamin B12. Clin Chem Lab Med. 2003; 41(11): 1435–1437, doi: 10.1515/CCLM.2003.220, indexed in Pubmed: 14656022.
7. Ahmed MA. Metformin and Vitamin B12 Deficiency: Where Do We Stand? J Pharm Pharm Sci. 2016; 19(3): 382–398, doi: 10.18433/J3PK7P, indexed in Pubmed: 27806244.
8. Niafar M, Hai F, Porhomayon J, et al. The role of metformin on vitamin B12 deficiency: a meta-analysis review. Intern Emerg Med. 2015; 10(1): 93–102, doi: 10.1007/s11739-014-1157-5, indexed in Pubmed: 25502588.
9. Bauman WA, Shaw S, Jayatilleke E, et al. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care. 2000; 23(9): 1227–1231, doi: 10.2337/diacare.23.9.1227, indexed in Pubmed: 10977010.
10. Raizada N, Jyotsna VP, Sreenivas V, et al. Serum Vitamin B12 Levels in Type 2 Diabetes Patients on Metformin Compared to those Never on Metformin: A Cross-sectional Study. Indian J Endocrinol Metab. 2017; 21(3): 424–428, doi: 10.4103/ijem.IJEM_529_16, indexed in Pubmed: 28553599.