

Bidirectional association between diabetic peripheral neuropathy and vitamin B12 deficiency: two 9-year follow-up studies using a national sample cohort

Aims: To investigate the association among metformin use, vitamin (Vit) B12 deficiency, and occurrence of diabetic peripheral neuropathy (DPN) in diabetes.

Methods: This retrospective, propensity-matched cohort study was performed using National Health Insurance Service database - National Sample Cohort in South Korea. Study 1 analysed DPN incidence in relation to Vit B12 deficiency and study 2 analysed Vit B12 deficiency incidence in relation to the presence of DPN. Finally, the studies evaluated the impact of metformin use on the results.

Results: In study 1, DPN incidence per 10000 person-year (PY) was 179.7 and 76.6 in the Vit B12 and non-Vit B12 deficiency groups, respectively. The adjusted HR was 1.32 (95% CI; 1.21-1.44, P <0.05) and metformin increased the risk of DPN occurrence in patients with Vit B12 deficiency (HR: 5.76 (95% CI; 5.28-6.29). In study 2, Vit B12 deficiency incidence per 10000 PY was 250.6 and 129.4 in the DPN and non-DPN groups, respectively. The adjusted HR was 2.44 (95% CI; 2.24-2.66, P <0.05), however, metformin use was associated with a reduced incidence of Vit B12 deficiency in DPN patients (HR 0.68 (95% CI; 0.62-0.74, P <0.05).

Conclusions: DPN occurrence increased in presence of Vit B12 deficiency and the incidence of Vit B12 deficiency was higher in patients with DPN. However, metformin showed opposite effects in both cohorts. Further studies clarifying the causal relationship among DPN occurrence, Vit B12 deficiency, and metformin use are needed.

Comments. It is known that vitamin Vit B12 deficiency can cause peripheral neuropathy (PN), mostly via demyelination. There are studies investigating not only the therapeutic effect of Vit B12 in PN, as well as the close association between them. In type 2 diabetes (T2DM) monitoring of Vit B12 has also been recommended because its levels can decrease with long-term metformin treatment.

I will encourage readers to review the Propensity scores in Fig. 1 and Cumulative incidence in Fig. 2 of the paper. Whilst the first two conclusions are not entirely unexpected, what is interesting to note is that metformin treatment in patients with pre-existing DPN did not increase the risk of Vit B12 deficiency, but rather *reduced the risk*, although diverse interpretations need to be considered. So, whilst on one hand metformin via B12 deficiency can contribute to DPN, its role in glycaemic control might alleviate DPN in established cases.

Thus, the queries that may arise amongst Neurodiab colleagues include: (i) *How do you differentiate DPN from PN due to isolated B12 deficiency?* (ii) *Do you regularly measure Vit B12 in all your patients with T2DM on metformin?* and (iii) *if a patient with T2DM develops neuropathy associated with Vit B12 deficiency, would you stop the metformin at the expense of loss of glycaemic control?*

Limitations of this study: This is a retrospective cohort study whilst the evidence would be stronger with a prospective long-term follow-up study. Other confounders like glycaemic control, dyslipidaemia, obesity, smoking, BMI etc. have not been factored in the occurrence of DPN. Finally, population based studies have inherent observer bias due to classification and coding errors.

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Reference. Jin HY, Lee KA, Kim YJ, Gwak IS, Park TS, Yeom SW, Kim JS. Bidirectional association between diabetic peripheral neuropathy and vitamin B12 deficiency: Two longitudinal 9-year follow-up studies using a national sample cohort. *Prim Care Diabetes*. 2023 Jun 19:S1751-9918(23)00109-2. doi: 10.1016/j.pcd.2023.06.006. Epub ahead of print. PMID: 37344286.,

[https://www.primary-care-diabetes.com/article/S1751-9918\(23\)00109-2/fulltext](https://www.primary-care-diabetes.com/article/S1751-9918(23)00109-2/fulltext)