Vitamin B12 Supplementation in Diabetic Neuropathy: A 1-Year, Randomized, Double-Blind, Placebo-Controlled Trial

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At a glance:

- Oral supplementation with 1000 µg vitamin B12 per day for 12 months increased B12 levels in diabetes patients taking metformin and suffering from DN (Diabetic Neuropathy) and improved neurophysiological parameters, sudomotor function, pain score and quality of life of patients.
- No adverse events related to the oral B12 supplementation were reported.

Introduction & Background

Diabetic neuropathy (DN) is one of the most common diabetic microvascular complications with a high impact on the quality of life. Vitamin B12 deficiency is very common in patients with type 2 diabetes mellitus (DM2) due to the use of metformin. It has been shown that metformin reduces the vitamin B12 absorption in the terminal ileum. This metformin-associated vitamin B12 deficiency can lead to neurological diseases, such as peripheral, autonomic (including cardiovascular), and painful neuropathy, equaling or accelerating the deterioration of DN.

The aim of this trial is to evaluate the effect of normalizing vitamin B12 levels with 1000 µg of oral vitamin B12 per day for one year in diabetes patients taking metformin and suffering from DN.

Materials & Methods

This prospective, double-blind, placebo-controlled study, randomized 90 DM2 patients who had been taking metformin for at least four years and suffered from both peripheral and autonomic DN into an active treatment group (n = 44) that received vitamin B12 and a control group (n = 46) which received a placebo. All patients had B12 levels below 400 pmol/L. Of note, it has been suggested that in particular in diabetic patients aged over 60 years, the cut-off for B12 levels that might lead to neurological disorders should be shifted from 150 to 400 pmol/L.

The following measurements were performed:

- Vitamin B12 levels
- HbA1c
- Sural Nerve Conduction Velocity (SNCV) and Sural Nerve Action Potential (amplitude) (SNAP)
- Vibration Perception Threshold (VPT)
- Cardiovascular Autonomic Reflex Tests (CARTs: mean circular resultant (MCR), Valsalva test, postural index, and orthostatic hypotension).
- Electrochemical Skin Conductance in Hands (ESCH) and Feet (ESCF)
- Michigan Neuropathy Screening Instrument Questionnaire and Examination (MNSIQ and MNSIE)
- Questionnaires: quality of life with the Diabetes Quality of Life Brief Clinical Inventory (DQOL), level of pain with the PAINDetect questionnaire (Pain Score).

Results

Vitamin B12 levels increased significantly in the active group from 232.0 ± 71.8 pmol/L at baseline to 776.7 ± 242.3 pmol/L ($p < 0.001$), whereas they did not change significantly in the placebo group ($p = 0.338$).

No significant change in blood pressure, serum lipids, and lipoproteins was detected. The glycemic control was acceptable at baseline and did not get worse during the study. There were no adverse events suspected or possibly related to the administration of vitamin B12.

Discussion & Conclusions

It is assumed that, especially in diabetics over 60 years of age, neurological dysfunction may occur even when B12 levels are above the 150 pmol/L, which is considered as the normal level. According to this assumption, vitamin B12 levels of 150–400 pmol/L should be considered as a "relative" vitamin B12 deficiency in diabetics.

In summary, this study showed that in patients with DN, treated with metformin for 4 years and longer, oral vitamin B12 supplementation with 1000 µg per day over one year increased vitamin B12 levels and improved neurophysiological parameters, sudomotor function, pain score, and patients quality of life.

Table 1 | Changes in indices from baseline to follow-up in both groups.

	Active			Placebo			
	Baseline	12 months	p[a]	Baseline	12 months	p[b]	p[c]
B12 (pmol/L)	232 ± 71.8	776.7 ± 242.3	<0.001	230.9 ± 85.9	242.8 ± 100.7	0.338	<0.001
MNSIQ	5.8 ± 2.2	5.44 ± 2.1	0.002	5.97 ± 2.1	6.17 ± 2	0.017	<0.001
SNAP (µV)	5.2 ± 4.3	7.3 ± 4.7	<0.001	5.1 ± 4.2	4.6 ± 4	<0.001	<0.001
SNCV (m/s)	28.2 ± 22.7	30.31 ± 23.2	<0.001	34.8 ± 24.6	32.9 ± 24.2	0.045	<0.001
VPT (V)	31.5 ± 14.2	23.8 ± 13.6	0.001	26.8 ± 13.7	25.8 ± 13.4	0.250	0.007
Pain Score	18.4 ± 9.7	17.1 ± 9	<0.001	19.3 ± 8.5	20.9 ± 8.5	<0.001	<0.001
ESCF (µS)	72.8 ± 10.2	74.5 ± 10.1	0.014	72.4 ± 12.3	71.2 ± 11.6	0.142	0.008

[a] For difference during follow-up in the active group; [b] for difference during follow-up in the placebo group; [c] for difference between groups adjusted for HbA1c and antidiabetic medication. Only significant changes in indices are shown. For complete information, see full publication.

Moreover, a significant difference in the change from baseline in B12 level ($p < 0.001$), MNSIQ ($p < 0.001$), DQOL ($p = 0.001$), SNAP ($p < 0.001$), SNCV ($p < 0.001$), VPT ($p = 0.007$), pain score ($p < 0.001$), and ESCF ($p = 0.008$) was observed in the active group compared to the control group. The indices of CARTS and MNSIE did not significantly improve.

None of the studied parameters improved in the placebo group. Noteworthy, MCR, MNSIQ, SNCV, SNAP and pain score even worsened significantly in the control group ($p = 0.025$, $p = 0.017$, $p = 0.045$, $p < 0.0001$, $p < 0.0001$).

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