

# Abstract

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## Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy.

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**OBJECTIVE:** The severity of peripheral neuropathy in diabetic patients varies for unclear reasons. Long-term use of metformin is associated with malabsorption of vitamin B(12) (cobalamin [Cbl]) and elevated homocysteine (Hcy) and methylmalonic acid (MMA) levels, which may have deleterious effects on peripheral nerves. The intent of this study was to clarify the relationship among metformin exposure, levels of Cbl, Hcy, and MMA, and severity of peripheral neuropathy in diabetic patients. We hypothesized that metformin exposure would be associated with lower Cbl levels, elevated Hcy and MMA levels, and more severe peripheral neuropathy.

**RESEARCH DESIGN AND METHODS:** This was a prospective case-control study of patients with type 2 diabetes and concurrent symptomatic peripheral neuropathy, comparing those who had received >6 months of metformin therapy (n = 59) with those without metformin exposure (n = 63). Comparisons were made using clinical (Toronto Clinical Scoring System and Neuropathy Impairment Score), laboratory (serum Cbl, fasting Hcy, and fasting MMA), and electrophysiological measures (nerve conduction studies).

**RESULTS:** Metformin-treated patients had depressed Cbl levels and elevated fasting MMA and Hcy levels. Clinical and electrophysiological measures identified more severe peripheral neuropathy in these patients; the cumulative metformin dose correlated strongly with these clinical and paraclinical group differences.

**CONCLUSIONS:** Metformin exposure may be an iatrogenic cause for exacerbation of peripheral neuropathy in patients with type 2 diabetes. Interval screening for Cbl deficiency and systemic Cbl therapy should be considered upon initiation of, as well as during, metformin therapy to detect potential secondary causes of worsening peripheral neuropathy.

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