Vitamin B<sub>12</sub> in type 2 diabetic patients treated with metformin

José María Calvo Romero*, José Manuel Ramiro Lozano

Servicio de Medicina Interna, Hospital Ciudad de Coria, Coria, Cáceres, Spain

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Abstract
Objective: To test vitamin B<sub>12</sub> plasma levels in type 2 diabetic patients treated with metformin in our area.

Methods: A cross-sectional, observational study of consecutive type 2 diabetic patients on drug treatment attending an internal medicine outpatient clinic.

Results: One hundred and nine patients (81 treated with metformin) were enrolled into the study. Mean time on metformin treatment was 43.5 months and mean drug dose was 1779 mg/day. Patients treated with metformin had significantly lower vitamin B<sub>12</sub> plasma levels (393.5 vs 509 pg/mL, p = 0.0008). Seven (8.6%) of 81 patients treated with metformin and none of the 28 patients not treated with the drug had vitamin B<sub>12</sub> plasma levels lower than 197 pg/mL. No correlation was found between vitamin B<sub>12</sub> plasma levels and metformin treatment time or dosage.

Conclusions: In type 2 diabetic patients, treatment with metformin is associated to lower vitamin B<sub>12</sub> plasma levels. Vitamin B<sub>12</sub> deficiency associated with metformin is relatively common in our area.

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Introduction

Vitamin B12 deficiency is relatively common, particularly in the elderly.\textsuperscript{1,2} Its clinical signs are mainly hematological and neuropsychiatric in nature, and may sometimes be difficult to detect. Vitamin B12 deficiency is usually due to vitamin malabsorption arising from various causes, including the classical pernicious anemia (PA).\textsuperscript{1,2}

As far back as 1971 it was reported that 4 (5.6\%) out of 71 diabetic patients on long-term treatment with metformin had low plasma vitamin B12 levels due to impaired absorption.\textsuperscript{3} Various reports confirming this association have subsequently been published. However, to our knowledge (and a search on MEDLINE), no observational studies have been conducted in Spain comparing patients with type 2 diabetes treated and not treated with metformin.

Methods

An observational, cross-sectional study was conducted on consecutive patients with type 2 diabetes mellitus on drug treatment seen at two internal medicine clinics of a first level hospital in the north of the province of Cáceres. Plasma levels of vitamin B12 were measured in all patients. Vitamin B12 deficiency was defined as levels less than 197 pg/mL (the lower limit of normal in our laboratory). Patients with vitamin B12 deficiency were asked about their dietary habits and antiapartial cell and anti-intrinsic factor antibodies were measured. An upper GI tract endoscopy was also performed to rule out atrophic chronic gastritis when it was considered indicated and with the patient’s consent. PA was diagnosed based on plasma vitamin B12 levels less than 197 pg/mL, the presence of anti-intrinsic factor antibodies and/or atrophic chronic gastritis in gastric biopsies, and the response to treatment with vitamin B12 in patients with hematological or neurological evidence of PA.\textsuperscript{1,2}

Statistical analysis was performed using a Chi-square test, and a Fisher exact test when any of the expected values was less than 5, to compare proportions, and a Student’s t-test for means comparison. A value of $p < 0.05$ was considered statistically significant.

Results

The study sample consisted of 114 patients, of whom 5 (4.4\%) were excluded due to PA having been diagnosed. The characteristics of patients treated and not treated with metformin are reported in Table 1. Among the patients treated with metformin, mean treatment time was 43.5 months (range 6–200 months) and mean dose 1779 mg/day (range 425–2550 mg/day). Patients treated with metformin had significantly lower plasma vitamin B12 levels (393.5 ± 184.2 versus 509 ± 176.4 pg/mL, $p = 0.0008$). Seven (8.6\%) of the 81 patients treated with metformin and none of the 28 patients given metformin had plasma vitamin B12 levels less than 197 pg/mL. No patient with vitamin B12 deficiency (excluding those diagnosed with pernicious anemia) had macrocytic anemia, neuropathy, or cognitive impairment.

No correlation was found between metformin dose and plasma vitamin B12 levels ($r = -0.02$, $p = 0.45$) or between treatment time with metformin and plasma vitamin B12 levels ($r = 0.15$, $p = 0.78$). Among the patients treated with metformin, there was no significant difference in plasma vitamin B12 levels between those taking and not taking a proton pump inhibitor (PPI) (409.4 ± 205.3 versus 385.9 ± 174.1 pg/mL, $p = 0.58$).

Discussion

Metformin causes vitamin B12 malabsorption.\textsuperscript{2,3} The absorption of vitamin B12 bound to intrinsic factor produced from ileum is calcium-dependent. Calcium in ileal lumen enhances uptake of the vitamin B12–intrinsic factor complex by the ileal cell receptor, and metformin impairs calcium availability at ileal level.\textsuperscript{4} Various studies, including the current study, support the association of metformin therapy with decreased plasma levels of vitamin B12. A study published in 1976 reported low plasma vitamin B12 levels in 5 (16.7\%) out of 30 diabetic patients treated with metformin.\textsuperscript{5} In another retrospective study, patients treated with metformin had significantly lower plasma vitamin B12 levels (496 versus 637 pg/mL).\textsuperscript{6} In a large observational study, 5.8\% of diabetic patients over 50 years of age treated with metformin for a mean of 7 years had vitamin B12 deficiency, as compared to 2.4\% of diabetic patients not given metformin.\textsuperscript{7}

In a prospective study of patients with type 2 diabetes mellitus treated with insulin, 9.9\% of patients given metformin at doses of 2,550 mg/day for longer than 4 years had vitamin B12 levels less than 150 pmol/L (200 pg/mL), as compared to 2.7\% of patients who received placebo.\textsuperscript{8} These results may be considered similar to those of the present study.

The effect of metformin in decreasing plasma vitamin B12 levels is not transient and appears to increase with treatment duration.\textsuperscript{6,8,9} A progressive decrease over time (during more than 4 years of follow-up) in mean plasma vitamin B12 levels has been reported in patients treated with metformin.\textsuperscript{6} A case–control study showed an
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association between vitamin B12 deficiency and the dose and duration of metformin treatment.9 By contrast, our study found no correlation between metformin treatment dose and duration and plasma vitamin B12 levels. It should be noted, however, that short-term treatment with metformin already decreases vitamin B12 levels. In a 6-month study, treatment with metformin caused a mean 20 pg/mL reduction in vitamin B12 levels.10 An additional 16-week study also showed a 14% reduction in plasma vitamin B12 levels.11 The use of PPIs has also been associated with vitamin B12 deficiency. Acid secretion inhibition impairs vitamin B12 release from food. However, our study found no negative impact of treatment with PPIs on plasma vitamin B12 levels. This observation agrees with the findings in another study.9

All the patients in this study with vitamin B12 deficiency associated with metformin had so-called “asymptomatic” deficiency (defined as low plasma vitamin B12 levels with no associated macrocytic anemia, neuropathy, or cognitive impairment). However, this deficiency is not always asymptomatic. In a series of 10 patients with vitamin B12 deficiency associated with metformin, 9 patients had mild anemia and 3 had peripheral neuropathy. Isolated cases of patients with asymptomatic vitamin B12 deficiency associated with metformin have also been reported.15 There is no agreement as to whether patients with “asymptomatic” vitamin B12 deficiency should be treated.1,2 There are signs of vitamin B12 deficiency, particularly neurological signs, which are difficult to diagnose and may become irreversible. In addition, vitamin B12 deficiency is invariably associated with elevated homocysteine levels, and their potentially harmful consequences. On the other hand, one study did not show an improvement in cognitive function after vitamin B12 administration to elderly patients with mild vitamin B12 deficiency.18

An additional concept, functional vitamin B12 deficiency, is defined as the presence of normal vitamin B12 levels together with increased plasma levels of methylmalonic acid and is based on the fact that vitamin B12 deficiency invariably causes elevated methylmalonic acid levels. Such a functional deficiency has been associated with neuropathy and anemia. An increased frequency of neuropathy has recently been reported in patients with type 2 diabetes mellitus and this functional deficiency, as well as an improvement in neuropathy after the administration of vitamin B12 and the normalization of plasma levels of methylmalonic acid.19

There is no agreement regarding the convenience of regular measurements of plasma vitamin B12 levels in patients treated with metformin. Controversy also exists concerning the management of patients with vitamin B12 deficiency associated with metformin, and some authors even suggest that metformin should be discontinued. In agreement with other authors,1,18 we think it is appropriate to regularly measure plasma vitamin B12 levels in patients treated with metformin, although other authors advise against such measurements. Moreover, we think it is appropriate to continue treatment with metformin in patients with vitamin B12 deficiency and to treat such patients with oral or intramuscular vitamin B12 even if the deficiency is “asymptomatic”. In our experience (data not collected in the study) and that of other authors, plasma vitamin B12 levels easily normalized after the administration of oral or intramuscular vitamin B12. This approach is based on the benefits of metformin for patients with type 2 diabetes mellitus and on the fact that treatment with vitamin B12 is simple, inexpensive, and safe and also has potential benefits. Oral calcium supplements may reverse vitamin B12 malabsorption induced by metformin, and could be a treatment option.4

Conflicts of interest

The authors state that they have no conflicts of interest.

References


