Endocrinol Nutr. 2012;59(8):487–490

ENDOCRINOLOGÍA Y NUTRICIÓN

www.elsevier.es/endo

ORIGINAL ARTICLE

Vitamin B_{12} 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

Received 11 April 2012; accepted 11 June 2012
Available online 6 November 2012

KEYWORDS
Cobalamin;
Diabetes mellitus;
Metformin;
Vitamin B_{12}

Abstract
Objective: To test vitamin B_{12} 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_{12} 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_{12} plasma levels lower than 197 pg/mL. No correlation was found between vitamin B_{12} plasma levels and metformin treatment time or dosage.
Conclusions: In type 2 diabetic patients, treatment with metformin is associated to lower vitamin B_{12} plasma levels. Vitamin B_{12} deficiency associated with metformin is relatively common in our area.

PALABRAS CLAVE
Cobalamina;
Diabetes mellitus;
Metformina;
Vitamina B_{12}

Vitamina B_{12} en pacientes diabéticos tipo 2 en tratamiento con metformina

Resumen
Objetivo: Estudiar los niveles plasmáticos de vitamina B_{12} en pacientes diabéticos tipo 2 tratados con metformina en nuestro medio.
Métodos: Estudio observacional transversal de pacientes consecutivos con diabetes mellitus tipo 2 en tratamiento farmacológico atendidos en consulta de Medicina Interna.
Resultados: Se estudiaron 109 pacientes (81 en tratamiento con metformina). El tiempo medio en tratamiento con metformina fue 43,5 meses y la dosis media fue 1.779 mg/día. Los pacientes tratados con metformina tuvieron unas concentraciones plasmáticas de vitamina B_{12} significativamente menores (393,5 frente a 509 pg/ml, p = 0,0008). Siete (8,6%) de 81 pacientes tratados

☆ Please cite this article as: Calvo Romero JM, Ramiro Lozano JM. Vitamina B_{12} en pacientes diabéticos tipo 2 en tratamiento con metformina. Endocrinol Nutr. 2012;59(8):487–90.
* Corresponding author.
E-mail address: jm.calvo@orangemail.es (J.M. Calvo Romero).

2173-5093/$ – see front matter

con metformina y ninguno de los 28 no tratados con metformina tuvieron unas concentraciones plasmáticas inferiores a 197 pg/ml. No hubo correlación entre las concentraciones de vitamina B_{12} y el tiempo en tratamiento con metformina o la dosis de metformina.
Conclusiones: En pacientes diabéticos tipo 2, el tratamiento con metformina se asocia a concentraciones plasmáticas de vitamina B_{12} más bajas. El déficit de vitamina B_{12} asociado a metformina es relativamente frecuente en nuestro medio.

Introduction

Vitamin B_{12} deficiency is relatively common, particularly in the elderly.[1,2] Its clinical signs are mainly hematological and neuropsychiatric in nature, and may sometimes be difficult to detect. Vitamin B_{12} deficiency is usually due to vitamin malabsorption arising from various causes, including the classical pernicious anemia (PA).[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 B_{12} levels due to impaired absorption.[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 B_{12} were measured in all patients. Vitamin B_{12} deficiency was defined as levels less than 197 pg/mL (the lower limit of normal in our laboratory). Patients with vitamin B_{12} deficiency were asked about their dietary habits and antiparietal 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 B_{12} 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 B_{12} in patients with hematological or neurological evidence of PA.[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 B_{12} 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 B_{12} levels less than 197 pg/mL. No patient with vitamin B_{12} deficiency (excluding those diagnosed with pernicious anemia) had macrocytic anemia, neuropathy, or cognitive impairment.

No correlation was found between metformin dose and plasma vitamin B_{12} levels ($r = -0.02$, $p = 0.45$) or between treatment time with metformin and plasma vitamin B_{12} levels ($r = 0.15$, $p = 0.78$). Among the patients treated with metformin, there was no significant difference in plasma vitamin B_{12} levels between those taking and not taking a proton pump inhibitor (PPI) (409.4 ± 205.3 versus 385.5 ± 174.1 pg/mL, $p = 0.58$).

Discussion

Metformin causes vitamin B_{12} malabsorption.[2,3] The absorption of vitamin B_{12} bound to intrinsic factor produced from ileum is calcium-dependent. Calcium in ileal lumen enhances uptake of the vitamin B_{12}-intrinsic factor complex by the ileal cell receptor, and metformin impairs calcium availability at ileal level.[4] Various studies, including the current study, support the association of metformin therapy with decreased plasma levels of vitamin B_{12}. A study published in 1976 reported low plasma vitamin B_{12} levels in 5 (16.7%) out of 30 diabetic patients treated with metformin.[5] In another retrospective study, patients treated with metformin had significantly lower plasma vitamin B_{12} levels (496 versus 637 pg/mL).[6] In a large observational study, 5.8% of diabetic patients over 50 years of age treated with metformin for a mean of 5 years had vitamin B_{12} deficiency, as compared to 2.4% of diabetic patients not given metformin.[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 B_{12} levels less than 150 pmol/L (200 pg/mL), as compared to 2.7% of patients who received placebo.[8] These results may be considered similar to those of the present study.

The effect of metformin in decreasing plasma vitamin B_{12} levels is not transient and appears to increase with treatment duration.[6,8,9] A progressive decrease over time (during more than 4 years of follow-up) in mean plasma vitamin B_{12} levels has been reported in patients treated with metformin.[6,8] A case–control study showed an

Table 1 Characteristics of patients with and without metformin treatment.

	With metformin (n = 81)	Without metformin (n = 28)	*p*
Age	71.6 ± 12.4	75.4 ± 8.3	NS
Sex (female)	56 (69.1%)	16 (57.1%)	NS
BMI (kg/m^2)	30.4 ± 5.4	29.3 ± 3.2	NS
Treatment with PPIs	27 (33.3%)	16 (57.1%)	0.02
Treatment with insulin	17 (21%)	11 (39.3%)	NS
HbA_{1c} (%)	7 ± 1.3	6.9 ± 0.9	NS

HbA_{1c}: glycosylated hemoglobin; PPIs: proton pump inhibitors; BMI: body mass index; NS: no statistically significant ($p \geq 0.05$).

association between vitamin B_{12} 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 B_{12} levels. It should be noted, however, that short-term treatment with metformin already decreases vitamin B_{12} levels. In a 6-month study, treatment with metformin caused a mean 20 pg/mL reduction in vitamin B_{12} levels.[10] An additional 16-week study also showed a 14% reduction in plasma vitamin B_{12} levels.[11] The use of PPIs has also been associated with vitamin B_{12} deficiency.[12] Acid secretion inhibition impairs vitamin B_{12} release from food.[13] However, our study found no negative impact of treatment with PPIs on plasma vitamin B_{12} levels. This observation agrees with the findings in another study.[9]

All the patients in this study with vitamin B_{12} deficiency associated with metformin had so-called ''asymptomatic'' deficiency (defined as low plasma vitamin B_{12} levels with no associated macrocytic anemia, neuropathy, or cognitive impairment).[1,2] However, this deficiency is not always asymptomatic. In a series of 10 patients with vitamin B_{12} deficiency associated with metformin, 9 patients had mild anemia and 3 had peripheral neuropathy.[14] Isolated cases of patients with symptomatic vitamin B_{12} deficiency associated with metformin have also been reported.[15] There is no agreement as to whether patients with ''asymptomatic'' vitamin B_{12} deficiency should be treated.[1,2] There are signs of vitamin B_{12} deficiency, particularly neurological signs, which are difficult to diagnose and may become irreversible.[2] In addition, vitamin B_{12} deficiency is invariably associated with elevated homocysteine levels[8,11] and their potentially harmful consequences.[16,17] On the other hand, one study did not show an improvement in cognitive function after vitamin B_{12} administration to elderly patients with mild vitamin B_{12} deficiency.[18]

An additional concept, functional vitamin B_{12} deficiency, is defined as the presence of normal vitamin B_{12} levels together with increased plasma levels of methylmalonic acid and is based on the fact that vitamin B_{12} deficiency invariably causes elevated methylmalonic acid levels.[19–21] Such a functional deficiency has been associated with neuropathy and anemia.[19–21] 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 B_{12} and the normalization of plasma levels of methylmalonic acid.[21]

There is no agreement regarding the convenience of regular measurements of plasma vitamin B_{12} levels in patients treated with metformin.[8,9,14,15,22] Controversy also exists concerning the management of patients with vitamin B_{12} deficiency associated with metformin, and some authors even suggest that metformin should be discontinued. In agreement with other authors,[3,8] we think it is appropriate to regularly measure plasma vitamin B_{12} levels in patients treated with metformin, although other authors advise against such measurements.[22] Moreover, we think it is appropriate to continue treatment with metformin in patients with vitamin B_{12} deficiency and to treat such patients with oral or intramuscular vitamin B_{12} even if the deficiency is ''asymptomatic''. In our experience (data not collected in the study) and that of other authors,[14] plasma vitamin B_{12} levels easily normalized after the administration of oral or intramuscular vitamin B_{12}. This approach is based on the benefits of metformin for patients with type 2 diabetes mellitus and on the fact that treatment with vitamin B_{12} is simple, inexpensive, and safe and also has potential benefits.[1,2] Oral calcium supplements may reverse vitamin B_{12} 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

1. Dali-Youcef N, Andrès E. An update on cobalamin deficiency in adults. QJM. 2009;102:17–28.
2. Stabler SP, Lindenbaum J, Allen RH. Vitamin B-12 deficiency in the elderly: current dilemmas. Am J Clin Nutr. 1997;66:741–9.
3. Tomkin GH, Hadden DR, Weaver JA, Montgomery DA. Vitamin-B12 status of patients on long-term metformin therapy. BMJ. 1971;2:685–7.
4. Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. Diabetes Care. 2000;23:1227–31.
5. Carpentier JL, Bury J, Luyckx A, Lefebvre P. Vitamin B 12 and folic acid serum levels in diabetics under various therapeutic regimens. Diabete Metab. 1976;2:187–90.
6. Kos E, Liszek MJ, Emanuele MA, Durazo-Arvizu R, Camacho P. The effect of metformin therapy on vitamin D and B12 levels in patients with diabetes mellitus type 2. Endocr Pract. 2012;18:179–84.
7. Reinstatler L, Qi YP, Williamson RS, Garn JV, Oakley Jr GP. Association of biochemical B12 deficiency with metformin therapy and vitamin B12 supplements: the national health and nutrition examination survey, 1999–2006. Diabetes Care. 2012;35:327–33.

8. de Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010;340:c2181.
9. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B(12) deficiency in patients receiving metformin. Arch Internal Med. 2006;166:1975–9.
10. Sahin M, Tutuncu NB, Ertugrul D, Tanaci N, Guvener ND. Effects of metformin or rosiglitazone on serum concentrations of homocysteine, folate, and vitamin B12 in patients with type 2 diabetes mellitus. J Diabetes Complications. 2007;21:118–23.
11. Wulffelé MG, Kooy A, Lehert P, Bets D, Ogterop JC, Borger van der Burg B, et al. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B12 in type 2 diabetes mellitus: a randomized, placebo-controlled trial. J Internal Med. 2003;254:455–63.
12. McColl KE. Effect of proton pump inhibitors on vitamins and iron. Am J Gastroenterol. 2009;104 Suppl. 2:5–9.
13. Varughese GI, Scarpello JH. Metformin and vitamin B12 deficiency: the role of H2 receptor antagonists and proton pump inhibitors. Age Ageing. 2007;36:110–1.
14. Andrès E, Noel E, Goichot B. Metformin-associated vitamin B12 deficiency. Arch Internal Med. 2002;162:2251–2.
15. Liu KW, Dai LK, Jean W. Metformin-related vitamin B12 deficiency. Age Ageing. 2006;35:200–1.
16. Smulders YM, Blom HJ. The homocysteine controversy. J Inherit Metab Dis. 2011;34:93–9.
17. Khanna S, Kapoor P, Pillai KK, Vohora D. Homocysteine in neurological disease: a marker or a cause? CNS Neurol Disord Drug Targets. 2011;10:361–9.
18. Eussen SJ, de Groot LC, Joosten LW, Bloo RJ, Clarke R, Ueland PM, et al. Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: a randomized, placebo-controlled trial. Am J Clin Nutr. 2006;84:361–70.
19. Solomon LR. Disorders of cobalamin (vitamin B12) metabolism: emerging concepts in pathophysiology, diagnosis and treatment. Blood Rev. 2007;21:113–30.
20. Turner MR, Talbot K. Functional vitamin B12 deficiency. Pract Neurol. 2009;9:37–41.
21. Solomon LR. Diabetes as a cause of clinically significant functional cobalamin deficiency. Diabetes Care. 2011;34: 1077–80.
22. Vidal-Alaball J, Butler CC. Reduced serum vitamin B-12 in patients taking metformin. BMJ. 2010;340:c2198.