

Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial.

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Abstract

OBJECTIVES: To study the effects of metformin on the incidence of vitamin B-12 deficiency (<150 pmol/l), low concentrations of vitamin B-12 (150-220 pmol/l), and folate and homocysteine concentrations in patients with type 2 diabetes receiving treatment with insulin.

DESIGN: Multicentre randomised placebo controlled trial.

SETTING: Outpatient clinics of three non-academic hospitals in the Netherlands.

PARTICIPANTS: 390 patients with type 2 diabetes receiving treatment with insulin.

INTERVENTION: 850 mg metformin or placebo three times a day for 4.3 years.

MAIN OUTCOME MEASURES: Percentage change in vitamin B-12, folate, and homocysteine concentrations from baseline at 4, 17, 30, 43, and 52 months.

RESULTS: Compared with placebo, metformin treatment was associated with a mean decrease in vitamin B-12 concentration of -19% (95% confidence interval -24% to -14%; $P<0.001$) and in folate concentration of -5% (95% CI -10% to -0.4%; $P=0.033$), and an increase in homocysteine concentration of 5% (95% CI -1% to 11%; $P=0.091$). After adjustment for body mass index and smoking, no significant effect of metformin on folate concentrations was found. The absolute risk of vitamin B-12 deficiency (<150 pmol/l) at study end was 7.2 percentage points higher in the metformin group than in the placebo group (95% CI 2.3 to 12.1; $P=0.004$), with a number needed to harm of 13.8 per 4.3 years (95% CI 43.5 to 8.3). The absolute risk of low vitamin B-12 concentration (150-220 pmol/l) at study end was 11.2 percentage points higher in the metformin group (95% CI 4.6 to 17.9; $P=0.001$), with a number needed to harm of 8.9 per 4.3 years (95% CI 21.7 to 5.6). Patients with vitamin B-12 deficiency at study end had a mean homocysteine level of 23.7 micromol/l (95% CI 18.8 to 30.0 micromol/l), compared with a mean homocysteine level of 18.1 micromol/l (95% CI 16.7 to 19.6 micromol/l; $P=0.003$) for patients with a low vitamin B-12 concentration and 14.9

micromol/l (95% CI 14.3 to 15.5 micromol/l; $P < 0.001$ compared with vitamin B-12 deficiency; $P = 0.005$ compared with low vitamin B-12) for patients with a normal vitamin B-12 concentration (> 220 pmol/l).

CONCLUSIONS: Long term treatment with metformin increases the risk of vitamin B-12 deficiency, which results in raised homocysteine concentrations. Vitamin B-12 deficiency is preventable; therefore, our findings suggest that regular measurement of vitamin B-12 concentrations during long term metformin treatment should be strongly considered. Trial registration [Clinicaltrials.gov NCT00375388](https://clinicaltrials.gov/ct2/show/study/NCT00375388).