

## The association between the biguanide drug metformin and vitamin B<sub>12</sub> deficiency in diabetic patients: a systematic review

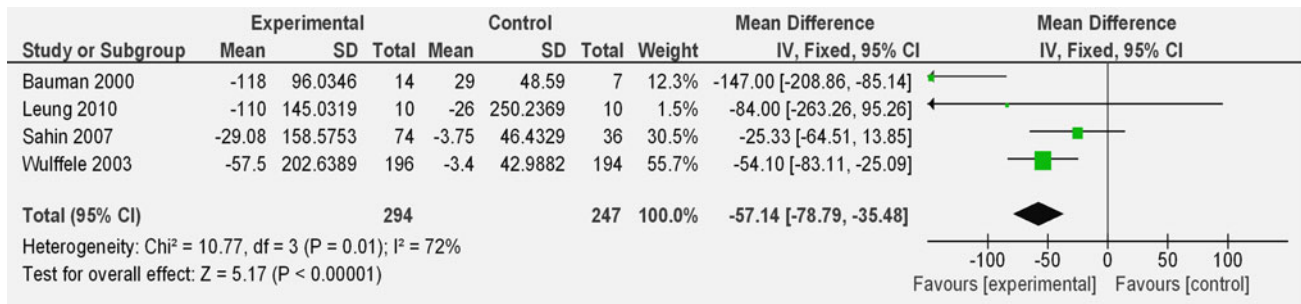
L. E. Chapman, A. L. Darling and J. E. Brown

Department of Nutritional Sciences, School of Biosciences and Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford, Surrey, UK

The prevalence of diabetes mellitus is increasing globally <sup>(1)</sup>. Metformin is the first line drug used in the treatment of Type 2 diabetes <sup>(2)</sup> and the most widely prescribed oral anti-diabetic agent. Vitamin B<sub>12</sub> deficiency can mask other conditions and is both under diagnosed and under treated. Metformin-related vitamin B<sub>12</sub> deficiency has been known for over 40 years but a systematic analysis of the data available has not been carried out. The aim of this study was to investigate by means of a systematic review, the association between diabetic patients taking metformin and vitamin B<sub>12</sub> deficiency.

An electronic database search from 1950 to June 2013 was conducted using 12 electronic databases (including the Cochrane Library). Further searching of reports of trials were conducted by examining journal articles. Expert contacts were also used to enquire about additional published/unpublished studies. Those studies included were all human studies in the English language of diabetic patients taking metformin for ≥3 years. Data was extracted in a standardised manner and the methodological quality of controlled trials was assessed using the Jadad scale and the GRADE grading system.

Twenty-six trials were included of which twenty were observational and six interventional. The majority of the studies showed statistically significantly lower vitamin B<sub>12</sub> levels in those patients on metformin but clinical outcome data was mainly limited to case reports which were not included. The lack of study data, heterogeneity and small sample sizes prevented the pooling of data to assess overall risk in the observational studies. Meta-analysis was performed on four intervention trials which demonstrated a statistically significant overall mean effect of metformin of a reduction in vitamin B<sub>12</sub> levels of 57 pmol/L after 3 months. The results of the meta-analysis are shown in the Table below.



The overall direction of evidence demonstrated an association between metformin and worsening levels of vitamin B<sub>12</sub> including frank deficiency. Further long-term randomised controlled trials are necessary to provide clearer causal evidence and to assess safety and clinical outcomes of metformin in the treatment of diabetes.

1. Lancet (2008) *The Lancet* 371, (9626) 1723.
2. Kirpichnikov D, McFarlane SI, Sowers JR (2002) *Ann Intern Med* 137, 25–33.