

# RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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## Metformin and Vitamin B<sub>12</sub> deficiency

Since the publication of the United Kingdom Prospective Diabetes Study 34 (UKPDS 34) in 1998, the biguanide drug metformin has been recommended as the initial oral drug of choice for the treatment of type II diabetes, especially for obese patients.

Vitamin B<sub>12</sub> malabsorption associated with long-term treatment with metformin was first reported in 1969. Studies indicate that approximately 30% of patients taking metformin long term have reduced vitamin B<sub>12</sub> absorption. The prevalence of serum B<sub>12</sub> deficiency has been reported at 17.5% amongst patients taking an average of 3.3g of metformin daily and 5.6% amongst those taking an average of 1.8 g metformin per day. Additionally, metformin dose and duration of therapy have recently been reported to be inversely correlated with serum B<sub>12</sub> concentrations.

Although vitamin B<sub>12</sub> deficiency is a common cause of macrocytic anaemia, most elderly individuals with low serum vitamin B<sub>12</sub> do not have anaemia. The clinical significance of low vitamin B<sub>12</sub> concentrations is not always fully recognised as the clinical manifestations may be subtle. Vitamin B<sub>12</sub> deficiency may cause severe neuropsychiatric disorders such as cognitive impairment in the absence of anaemia. Due to its subtle clinical presentations, vitamin B<sub>12</sub> deficiency can go undetected for several years, during which time neuropsychiatric manifestations may become irreversible.

Recent evidence suggests that the mechanism of metformin-induced vitamin B<sub>12</sub> deficiency is via an indirect effect on B<sub>12</sub>-intrinsic factor complex which is calcium dependent. Metformin reduces the intestinal availability of free calcium ions, which are essential for absorption of vitamin B<sub>12</sub>. It is currently uncertain if calcium supplementation will reverse B<sub>12</sub> malabsorption sufficiently to prevent deficiency therefore it is not recommended that calcium supplementation should be prescribed to prevent or treat metformin-induced vitamin B<sub>12</sub> deficiency until more evidence is available.

A small study of 60 patients conducted at the RGH in 2006 found that 15% of patients taking metformin longer than 2 years had vitamin B<sub>12</sub> deficiency and one patient had developed anaemia. The dose of metformin was found to have a statistically significant negative correlation with vitamin B<sub>12</sub> concentrations. There was a trend towards patients taking metformin for a longer duration having lower vitamin B<sub>12</sub> concentrations. Neither advancing age nor the use of proton pump inhibitors and calcium supplements were found to be associated with declining vitamin B<sub>12</sub> concentrations. Not surprisingly, use of B<sub>12</sub> supplements (mainly tablets taken orally) was associated with significantly greater serum vitamin B<sub>12</sub> concentration.

Elderly patients with higher doses of metformin and potentially with longer treatment duration are at higher risk of vitamin B<sub>12</sub> deficiency and should be monitored for vitamin B<sub>12</sub> status. Vitamin B<sub>12</sub> (either injections or tablets), but not calcium supplements should be considered to prevent or correct deficiency.

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