CMV infection may be a risk factor for venous thromboembolism and prophylaxis of this should be considered.

Conflicts of interest
None.

References

Received 22 November 2005; accepted 6 December 2005

Metformin-related vitamin B12 deficiency

Kin Wah Liu, Lok Kwan Dai, Woo Jean

Medical and Geriatric Unit, Shatin Hospital, New Territories, Hong Kong, China

Address correspondence to: Kin Wah Liu. Email: kwliuhk@yahoo.com

Abstract
Metformin is an invaluable hypoglycaemic agent. We report two cases who had symptomatic vitamin B12 deficiency related to metformin use; the mechanisms are discussed. The clinician must be aware of the possibility of metformin-associated B12 deficiency in users who suffer cognitive impairment, peripheral neuropathy, subacute combined degeneration of the cord or anaemia.

Keywords: Metformin, elderly, Vitamin B12 deficiency

Introduction
The UK Prospective Diabete study Group 34 showed metformin to be an effective hypoglycaemic agent with less weight gain, and decreased hypoglycaemia, myocardial infarction, stroke and death [1]. Gastrointestinal side-effects and lactic acidosis related to metformin are commonly recognised; however, the associated vitamin B12 deficiency is less well known. Two cases illustrate the problem.

Case report 1
An 82-year-old Asian non-vegetarian had type 2 diabetes mellitus for 20 years. Medications included metformin 1 g BD for many years and famotidine for gastritis. She presented with memory loss and progressive leg weakness. Her legs were hypotonic with decreased power, absent reflexes and bilateral extensor plantar reflexes. Vibration and proprioception sense were impaired. The gait was atactic with a positive Romberg’s test. Mini mental state...
examination (MMSE) was 9/30. Her haemoglobin level was 10.3 g/dl with mean corpuscular volume (MCV) 99.7 fl. Vitamin B12 level was 97 pmol/l with normal folate level and negative anti-intrinsic factor antibodies. Vitamin B12-deficient subacute combined degeneration of cord and cognitive impairment related to metformin was suspected. Metformin was stopped, diabetes was stabilised on sulfonylurea and insulin, and she was given vitamin B12 1000 μg on alternate days for five doses followed by vitamin B12 1000 μg on a monthly basis. This led to improvements in gait, lower limb power, MMSE (20/30) and haematological abnormalities.

**Case report 2**

A non-vegetarian diabetic patient had taken over the counter metformin for 8 years, with diarrhoea for 2 years. Her haemoglobin level was 9.4 g/dl (MCV 104 fl) and B12 level was 125 pmol/l. Anti-parietal cell and anti-intrinsic factor antibodies were negative. Upper gastrointestinal endoscopy and small bowel enema were normal. Schilling test showed intestinal malabsorption. The diarrhoea and haematological abnormalities resolved on stopping the metformin and replacing the B12 in the similar manner as patient in case report 1.

**Discussion**

These two patients had B12 deficiency associated with metformin therapy.

Vitamin B12 deficiency affects approximately 20% of elderly people [2], although the prevalence varies greatly depending on population studied and B12 cut-off used.

Many factors contribute to the deficiency including diet, gastrointestinal pathology, autoimmune disease and medications.

Several studies have screened outpatients taking biguanides for B12 deficiency. Thirty per cent of 46 patients undergoing biguanide therapy developed B12 malabsorption, which resolved in half on stopping the drug [3]. In 71 metformin patients, 21 had low B12 absorption, and four had low B12 levels [4]. Fifty-four of 600 patients on long-term biguanides had B12-related megaloblastic anaemia [5].

**What is the mechanism?**

Diabetic people may have slow intestinal transit causing bacterial overgrowth and B12 malabsorption; however, metformin does not alter oral–caecal transit time [6], and there was no evidence of bacterial overgrowth related to metformin in a controlled trial [7]. The B12-intrinsic factor complex uptake by ileal cell membrane receptors is known to be calcium-dependent, and metformin affects calcium-dependent membrane action. The resulting B12 deficiency can be reversed by administering calcium [7], and this seems to be the clearest mechanism.

Diabetes is associated with neuropathy, cognitive impairment, several causes of anaemia and is on everyone’s list of causes of absent ankle reflexes with upgoing plantars; however, it is vital to consider co-existent B12 deficiency, particularly if taking metformin.

The value of routine screening for B12 deficiency (recommended by some [5]) is unknown, but the clinician must be aware of this association. The optimum management of such patients is uncertain; although some withdraw metformin and fully investigate the patient, others take a more pragmatic approach to continue the metformin, a valuable drug which may not be the cause of the deficiency, and to replace the B12 with hydroxycobalamin.

**Key point**

- The clinician must be aware of the possibility of metformin-related B12 deficiency in diabetic older patients and test accordingly.

**References**