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To: Holstein A, Stumvoll M (2005) Contraindications can damage your health—is metformin a case in point? Diabetologia 48:2454–2459

Received: 15 December 2005 / Accepted: 16 December 2005 / Published online: 25 March 2006
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To the Editor: We read with interest the review article by Holstein and Stumvoll, in which they made a strong case for revising the contra-indication to the use of metformin in the elderly [1]. While agreeing with their general line of argument, we would, however, like to highlight an issue that was not addressed in the article. Long-term use of metformin is known to be associated with reduced vitamin B₁₂ absorption, an observation first reported by Berchtold et al. in this journal more than 30 years ago [2]. However, perhaps for historical reasons related to phenformin, the focus on biguanides used to be on its association with lactic acidosis, whereas its potential effects on vitamin B₁₂ have often been neglected. In some studies, the prevalence of vitamin B₁₂ malabsorption in metformin users was estimated to be as high as 30% [3]. While this was previously thought to be due to alterations in small bowel motility, bacterial overgrowth or a direct effect on absorption [4], more recent evidence suggests that food-cobalamin malabsorption is the principal mechanism of vitamin B₁₂ deficiency associated with metformin [5]. The risk of food-cobalamin malabsorption is further exacerbated by achlorhydria, chronic *Helicobacter pylori* infection, chronic use of antacids or acid-suppression drugs or previous gastrectomy [6]. The elderly, who are already at risk of cobalamin deficiency due to poor dietary intake or pernicious anaemia, are therefore especially prone to this complication, especially after prolonged use of metformin. In a recent prospective cohort of patients with confirmed cobalamin deficiency, it was noted that 6% of cases were due to metformin use alone, with a mean age of 69 among the affected subjects. Overt evidence of cobalamin deficiency was not uncommon, with minor haematological abnormalities noted in 90% of cases and mild peripheral

neuropathy noted in 30% of subjects [5]. More severe cases resulting in symptomatic anaemia, severe megaloblastic anaemia or neurological sequelae have also been reported following metformin use [5]. Since some of the symptoms of vitamin B₁₂ deficiency can resemble those of diabetic peripheral neuropathy, this potentially treatable condition may not be recognised, causing problems that could be avoided if treated.

In addition to the potential haematological and neurological complications, low vitamin B₁₂ levels due to metformin can also lead to increased levels of homocysteine, a recognised cardiovascular risk factor. Indeed, it has been demonstrated that short-term treatment with metformin for 16 weeks can lead to a significant decrease in levels of vitamin B₁₂ and folate, resulting in raised homocysteine levels [7]. It is not known at present whether this could have a significant impact on cardiovascular outcome. However, it is conceivable that the cardiovascular benefits of metformin in improving insulin resistance may be partially offset by its effect on vitamin B₁₂ and homocysteine.

Given the above considerations, it is therefore advisable to monitor vitamin B₁₂ and folate levels among subjects who have been on metformin therapy for prolonged periods of time. Previous estimates [8] suggested that among subjects with adequate dietary intake, the time it takes to develop vitamin B₁₂ deficiency is 10 to 15 years. However, more recent data suggest that clinically detectable vitamin B₁₂ deficiency can develop in metformin users after considerably shorter periods of use, especially among elderly subjects [5]. Annual screening for cobalamin deficiency should be performed in all elderly subjects taking metformin, or in younger subjects who have received metformin at a dose of >1 g/day for 5 years or more.

For patients on metformin who are found to have vitamin B₁₂ deficiency, treatment with oral cobalamin has recently been proposed as an effective alternative to intramuscular injections [5]. Replacement should be guided by regular monitoring of B₁₂ levels. It is not clear whether metformin use should be discontinued in this situation, though a dose reduction, along with vitamin B₁₂

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replacement, seems appropriate. Clinicians should weigh up the benefits and risks of continuing metformin for each individual patient. It has been suggested that oral calcium supplementation could be effective in preventing metformin-associated vitamin B₁₂ malabsorption [9]. We agree that old age itself should not be a contra-indication to the use of metformin, though regular monitoring of vitamin B₁₂ levels is warranted in elderly users of this drug.

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