Sir,

It is well documented that metformin use may cause vitamin B12 deficiency,\(^1,2\) which may lead to hyperhomocysteinemia,\(^3\) particularly when folate deficiency, B12 deficiency or methylenetetrahydrofolate reductase (MTHFR) homozygous C677T mutation is also present, based on the metabolic pathway of homocysteine.\(^3\) It was estimated that 5.6–7.3% of diabetic patients taking metformin might develop evidence of B12 deficiency.\(^1\) Higher metformin dose and longer treatment duration as well as increased age and vegetarianism were shown to be independent risk factors of vitamin B12 deficiency.\(^2\) Other confounding factors include uncontrollable supplement of vitamins or trace elements in food or any daily elements.\(^4\)

The prevalence of MTHFR C677T homozygous mutation was reported to be 5–12% in a White population and 6–8% in Taiwanese Chinese,\(^5\) and the homozygous mutation is related to hyperhomocysteinemia when lower plasma folate level coexists, but not when plasma folate level is higher.\(^6\) Hence, it has been reported that homocysteine level may\(^3\) or may not\(^4\) increase during metformin treatment; many confounding factors result in such conflicting data. Findings in the one case report\(^7\) meant to call attention to the clinical evidence that hyperhomocysteinemia caused by a metformin-induced vitamin B12 deficiency and a MTHFR C677T homozygous mutation may serve as an additional independent risk factor for vascular thrombosis in diabetic patients, although many patients are on metformin therapy without significant problems.

**References**