LETTER TO THE EDITOR

Metformin, B12 and Homocysteine Levels: The Plausible Cause or Effect?

Kashif Musarrat, Dhanya Kalathil, George I. Varughese*

Sir,

In the September 2007 issue of the *Journal of the Formosan Medical Association*, Lin et al highlighted an important point that is well described but less well recognized in clinical practice.[1] Indeed, they have categorically emphasized the role of metformin and vitamin B12 deficiency as the plausible cause of the deep vein thrombosis in their patient, although the patient was proven to have a homozygous C677T mutation of the *MTHFR* gene which seemed to have been the cause of the hyperhomocysteinemia.[1] This conclusion based on one case report is a hypothesis that has to be interpreted cautiously, given the lack of definitive evidence to support this notion in the literature.[2–4]

Recent data have suggested that the evidence to support the role of metformin therapy in affecting homocysteine levels is insufficient. For example, homocysteine levels were unaffected by metformin treatment in pregnant and non-pregnant women with polycystic ovarian syndrome.[2] A previous study from Thailand suggested that although metformin may have caused low vitamin B12 levels, there were no significant changes to homocysteine levels.[3] It has also been demonstrated that other dietary factors such as fruit and vegetable consumption in diabetic patients are strong independent determinants of homocysteine levels.[4]

We are aware of only one large randomized controlled trial over a period of 16 weeks that has demonstrated metformin-related B12 deficiency and a modest rise in homocysteine levels, the clinical significance of which remains unknown.[5] A much smaller study over a duration of 6 months showed that the effect of metformin therapy on homocysteine levels, if any, is likely to be small.[6] Interestingly, it has recently been reported that metformin increased levels of homocysteine and rosiglitazone conversely decreased homocysteine levels over a 6-week period in diabetic subjects, the clinical significance of which again remains unknown.[7]

It is therefore important to remember that *association does not mean causation* and a large number of diabetic patients are on metformin therapy without significant problems. The clinical implications and exact mechanisms of metformin-related B12 deficiency remains contentious in the absence of large randomized controlled trials over longer time intervals,[2–7] hence the need for reminding clinicians of the caveats to be aware of within the large scheme of things in people with diabetes mellitus.

In order to inform the debate on this subject, further studies involving a far greater number of patients over a much longer time period is warranted, especially when other plausible causes such as hypochlorhydria could explain the mechanism.[8,9] However, such anecdotal case reports are helpful for signal generation and help to remind clinicians of a potential side effect with metformin

Department of Diabetes and Endocrinology, Diabetes Centre, Queen's Hospital, Burton-upon-Trent DE13 0RB, United Kingdom.

***Correspondence to:** Dr Kashif Musarrat, Department of Diabetes and Endocrinology, Diabetes Centre, Queen's Hospital, Burton-upon-Trent DE13 0RB, United Kingdom.
E-mail: kashif.musarrat@gmail.com

therapy that is less commonly perceived in routine daily clinical practice.

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Competing Interest

All the authors work in the specialty of diabetes and endocrinology and are currently involved in managing patients with diabetes mellitus and polycystic ovaries on metformin therapy in routine daily clinical practice.