

REPLY

Reply to 'Some More Comments on Folate Deficiency in Chronic Pancreatitis'

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Dear Sir,

We appreciate the interest shown by Wagner [1]. His comments highlight the complex interrelationship between folate, methyl group metabolism and choline metabolism.

Folate and betaine independently serve as methyl donors for homocysteine remethylation to methionine. Recently, Christensen *et al.* have demonstrated that increased utilization of betaine for homocysteine remethylation in folate deficiency may lead to steatosis by disrupting choline metabolism [2].

While betaine has been used in the treatment of homocystinuria due to cystathionine-beta-synthase deficiency, other approaches to homocystinuria include vitamin B₆ supplementation (in the responsive or milder phenotypic variant) and methionine restriction in addition to folate and vitamin B₁₂ supplementation. In our study, we demonstrated the defects in the trans-sulfuration pathway (cysteine and glutathione deficiency) in patients with chronic pancreatitis [3]. However, we did not estimate vitamin B₆ levels or cystathionine-beta-synthase activity which are important components of the trans-sulfuration pathway. In the case of isolated remethylation disorders such as methylenetetrahydrofolate reductase (MTHFR) deficiency, the very rare methionine synthase reductase (CbIE) and methionine synthase (CbIG) defects, and the recently identified CbID-variant-1 defect, the use of both oral folate and betaine supplements have been shown to have a favorable outcome when used in the early of treatment [4]. Of course, such rare primary single

defects are a poor analogy for a complex disease, such as chronic pancreatitis.

Recently, Lee *et al.* have demonstrated among the participants of the Framingham Offspring Study that, while higher choline and betaine intakes were associated with lower concentrations of both fasting and post-methionine load homocysteine, especially in those with low folate and vitamin B₁₂ levels; the inverse association between choline and betaine intake with homocysteine concentrations was no longer present after folate fortification [5].

Thus, betaine supplementation as suggested by Wagner [1] may well have possible benefits in chronic pancreatitis but should probably be attempted in those with normal folate levels. We have recently demonstrated zinc deficiency in patients with chronic pancreatitis and have shown that this correlated with exocrine and endocrine insufficiency [6]. Interestingly, a recent study showed that zinc supplementation reduced serum homocysteine and increased vitamin B₁₂ and folate concentrations in type 2 diabetic patients with microalbuminuria [7]. In conclusion, recent literature suggests the need for developing a holistic view; additional studies are needed to establish evidence-based guidelines for the supplementation of antioxidants, methyl donors and lipotropes in patients with chronic pancreatitis.

Conflict of interest The authors have no potential conflict of interest

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