

REPLY

Reply to 'Folate Deficiency in Chronic Pancreatitis'

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Dear Sir,

We appreciate the comments of Rajesh *et al.* published in the present issue of JOP. J Pancreas (Online) [1] in respect of our review on 'Micronutrient therapy for chronic pancreatitis' [2] and thank you for the opportunity to respond.

The authors address two points in particular.

i) Premorbid micronutrient insufficiency (especially of methionine and ascorbic acid) compromises the delivery of methyl and thiol moieties that facilitate exocytosis from acinar cells and leaves the exocrine pancreas vulnerable to other consequences of persistent electrophilic stress. These problems underlie chronic pancreatitis, such that micronutrient therapy affords first-line treatment and gives an opportunity for prophylaxis in individuals/communities at high risk of the disease.

ii) A full complement of the cystic fibrosis transmembrane conductance regulator protein (CFTR) in the luminal membrane of both acinar and ductal cells is essential for pancreatic homeostasis. Functional loss of the protein under conditions of electrophilic stress is equivalent to the reduced protein quota caused by *CFTR* mutation, which is strongly associated with idiopathic chronic pancreatitis [2].

As Rajesh *et al.* observe, the second tenet is underlined by the new observation that CFTR is mislocalised to the cytoplasm of ductal cells in patients with autoimmune pancreatitis [3]. The further finding that this was also true in the few studied patients with other forms of the disease [3] suggests that electrophilic stress is linked to the phenomenon, in that the antioxidant lactoferrin is a major antigen in autoimmune pancreatitis [4]. Moreover, the antioxidant curcumin has been shown to rescue DF508-CFTR

localisation and residual function in cell lines by remodelling the keratin 18 network [5], which is vulnerable to electrophilic stress.

In regard to the first tenet, Rajesh and colleagues draw attention to their interesting recent paper [6], which showed that in patients with alcoholic or idiopathic chronic pancreatitis in Kerala, South India, hyperhomocysteinaemia was a feature, accompanied by subnormal plasma methionine, cysteine, and folic acid - the last low in erythrocytes too. They proposed that hyperhomocysteinaemia may be a risk factor for chronic pancreatitis [6], and now call for long-term studies of folic acid supplementation in treatment because folic acid is known to be a methyl donor.

We have been interested in homocysteine metabolism for some time, recognizing that the therapeutic benefit from methionine/vitamin C supplementation could be offset by treatment-induced hyperhomocysteinaemia - if transmethylation (via folic acid-vitamin B12, and betaine-choline shuttles) and/or transsulphuration pathways (via two vitamin B6-dependant enzymes) of homocysteine removal do not function at least at par [7]. In 14 Manchester patients with mainly idiopathic disease, baseline hyperhomocysteinaemia was accompanied by subnormal plasma vitamin B6 concentration but normal folic acid and vitamin B12 [8]: we also noted the same degree of hyperhomocysteinaemia, but without chronic pancreatitis, in our patients with gallstones [9] or severe coronary artery disease [8]. In relation to alcoholic chronic pancreatitis, a report from the Netherlands showed normal plasma homocysteine but subnormal cysteine [10], whilst hyperhomocysteinaemia in patients at Soweto, South Africa, was accompanied by elevated plasma folic acid but subnormal vitamin B12 and normal vitamin B6 (I Segal *et al.*, unpublished observations; paper submitted).

Thus we conclude that hyperhomocysteinaemia is an epiphenomenon of chronic pancreatitis but nonetheless potentially significant to the development of local vascular complications. We routinely checked baseline plasma folic acid and vitamin B12 levels prior to antioxidant therapy in our patients, so that either or both could be further investigated and added to the

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regimen, if warranted. Today we would also check vitamin B6 status and especially that of choline. A deficiency of this methyl donor could hold the key to pancreatic 'reductive stress', and its correction would reduce the load of reactive oxygen species generated thereby, whilst also facilitating the removal of xenobiotic intermediate metabolites generated via induced pancreatic cytochromes P450 [2]. As to the particular conditions in patients at Kerala, there is an urgent need to examine ascorbic acid status [11]. This bioactive form of vitamin C is easily destroyed by frying vegetables at high temperature as in that region; it interacts in the folic acid-vitamin B12 pathway for reconstitution of methionine; and it substitutes for methionine-derived glutathione to protect vulnerable protein thiols as in CFTR [2].

Conflict of interest The author has no potential conflict of interest

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