REPLY

Reply to 'Folate Deficiency in Chronic Pancreatitis'

Joan M Braganza

Royal Infirmary. Manchester, United Kingdom

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, hyper-homocysteinaemia 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 hyper-homocysteinaemia, 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

Received June 14th, 2010
Key words Ascorbic Acid; Cystic Fibrosis; Folic Acid; Homocysteine; Methionine; Pancreatitis, Chronic
Correspondence Joan M Braganza
c/o Jenny Parr, Core technology facility, 3rd floor, 46 Grafton Street, Manchester M13 9NT, United Kingdom
Phone: +44-161.275.1191;Fax: +44-161.275.1183
E-mail: jenny.parr@manchester.ac.uk
URL http://www.serena.unina.it/index.php/jop/article/view/3638/3977

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

References

1. Rajesh G, Girish BN, Vaidyanathan K, Saumya M, Balakrishnan V. Folate deficiency in chronic pancreatitis. JOP. J Pancreas (Online) 2010; 11:409-10.

2. Braganza JM, Dormandy TL. Micronutrient therapy for chronic pancreatitis: rationale and impact. JOP. J Pancreas (Online) 2010; 11:99-112. [PMID 20208316]

3. Ko SB, Mizuno N, Yatabe Y, Yoshikawa T, Ishiguro H, Yamamoto A, et al. Corticosteroids correct aberrant CFTR localization in the duct and regenerate acinar cells in autoimmune pancreatitis. Gastroenterology 2010; 138:1988-96. [PMID 20080093]

4. Jin CX, Hayakawa T, Kitagawa M, Ishiguro H. Lactoferrin in chronic pancreatitis. JOP. J Pancreas (Online) 2009; 10:237-41. [PMID 19454813]

5. Lipecka J, Norez C, Bensalem N, Baudouin-Legros M, Planelles G, Becq F, et al. Rescue of DeltaF508-CFTR (cystic fibrosis transmembrane conductance regulator) by curcumin: involvement of the keratin 18 network. J Pharmacol Exp Ther 2006; 317:500-5. [PMID 16424149]

6. Girish BN, Vaidyanathan K, Rao NA, Rajesh G, Reshmi S, Balakrishnan V. Chronic pancreatitis is associated with hyperhomocysteinemia and derangements in transsulfuration and transmethylation pathways. Pancreas 2010; 39:e11-6. [PMID 20050230]

7. McCloy RF. Chronic pancreatitis at Manchester, UK. Focus on antioxidant therapy. Digestion 1998; 59(Suppl 4):36-48. [PMID 9832634]

8. Braganza JM, Odom N, McCloy RF, Ubbink JB. Homocysteine and chronic pancreatitis. Pancreas 2010; in press.

9. Worthington HV, Hunt LP, McCloy RF, Ubbink JB, Braganza JM. Dietary antioxidant lack, impaired hepatic glutathione reserve, and cholesterol gallstones. Clin Chim Acta 2004; 349:57-65. [PMID 15469869]

10. Verlaan M, Roelofs HMJ, van Schaik A, Wanten GJA, Jansen JMBJ, Peters WHM, et al. Assessment of oxidative stress in chronic pancreatitis patients. World J Gastroenterol 2006; 12:5705-10. [PMID 17007026]

11. Braganza JM, Schofield D, Snehalatha C, Mohan V. Micronutrient antioxidant status in tropical compared with temperate-zone chronic pancreatitis. Scand J Gastroenterol 1993; 28:1098-104. [PMID 8303214]