Hypomagnesaemia due to malabsorption is not always responsive to oral magnesium oxide supplementation alone

We read with interest the Gut File report by Dr Ross and colleagues of hypomagnesaemia due to malabsorption, eventually responding to oral magnesium oxide supplementation (Gut 2001;48:857–8). Our experience however has been different. For the past seven years we have managed a 65 year old woman with short bowel syndrome (right hemicolectomy and ileal diversion). She has been able to manage (after excluding infection, secretory diarrhea and pregnancy) gastrin releasing peptide (GRP) mediated gastric acid secretion despite dietary and pharmacological modifications. Clinical signs of hypomagnesaemia and hypocalcaemia ensued. An initial trial with magnesium glycerophosphate (September 1992 to December 1993) was insufficient to sustain her serum magnesium levels requiring frequent “top ups” of intravenous magnesium. In December 1993, she was switched to magnesium oxide supplementation but despite this the frequency of intravenous magnesium “top ups” were not reduced. Compliance was not deemed to be an issue with our patient.

Since then we have managed this woman while still taking magnesium oxide supplements with almost 3–6 monthly (fig 1) intravenous magnesium replacement through a peripheral line and have avoided insertion of a Hickman line and all its associated complications. While we agree that a trial of magnesium oxide is prudent and until the pharmacokinetics are better understood, this preparation may not be sufficient, especially in patients with extensive resection of the small bowel, as demonstrated in our patient.

Although the authors stated that alteration of somatostatin secretion is unlikely to explain the acid inhibitory action of BIM26226 because the GRP antagonist did not alter somatostatin mRNA levels. They also argued that the lack of change of gastrin mRNA supported the physiological data showing no alteration in gastrin secretion. While we agree, in longer term studies such as these, it is incorrect to assume mRNA levels reflect peptide secretion rates. Indeed, previous studies with GRP infusion in humans have shown that although secretion of gastrin peptide was enhanced, gastrin mRNA levels were actually decreased. Thus it would be unwise to exclude the possibility of any peptide having a role in this dynamic system.

The authors also state that muscarinic receptor activation inhibits somatostatin secretion from D cells. This is correct for fundic but incorrect for antral D cells. Muscarinic activation actually stimulates somatostatin release from antral D cells. This would be more compatible with the mechanisms suggested by the authors: GRP enhanced neural acetylcholine release and this reduced fundic somatostatin mediated inhibition of histamine and acid secretion; in the antrum, stimulation of somatostatin release would then impair the gastrin response and could contribute to the lack of gastrin response seen in the current experiments.

The authors felt that previous in vitro studies of G cells were difficult to assess but they appear to have overlooked detailed studies of cultured human G cells. Squires and colleagues demonstrated two receptors of the GRP family in antral tissue, namely GRPR (BB1) and BRS-3 (BB3). BRS-3 is an orphan receptor that does not functionally respond to bombesin/GRP except at very high concentrations. Single cell microfluorometry clearly showed antral G cells responding to bombesin with an increase in intracellular calcium, thus suggesting that human antral G cells express physiologically functional GRP receptors. In the light of these data, the results of Hildebrand et al are very interesting and the current study should stimulate interest in the ever evolving understanding of gastric secretory function. Further studies with BIM26226 under different conditions, to more fully describe the pathophysiological role of GRP, are awaited with interest.

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References

Regulation of gastric function by gastrin releasing peptide

Hildebrand et al reported data suggesting that gastrin releasing peptide (GRP) may be a physiological regulator of pre- and postprandial gastric acid secretion (Gut 2001;49:23–8). Interestingly, these effects were independent of gastrin and the authors appropriately questioned the physiological role of gastrin in regulating gastric secretion. Several aspects of the authors’ conclusions deserve further clarification and discussion.

The authors concluded that alteration of somatostatin secretion is unlikely to explain the acid inhibitory action of BIM26226 because the GRP antagonist did not alter somatostatin mRNA levels. They also argued that the lack of change of gastrin mRNA supported the physiological data showing no alteration in gastrin secretion. While we agree, in longer term studies such as these, it is incorrect to assume mRNA levels reflect peptide secretion rates. Indeed, previous studies with GRP infusion in humans have shown that although secretion of gastrin peptide was enhanced, gastrin mRNA levels were actually decreased. Thus it would be unwise to exclude the possibility of any peptide having a role in this dynamic system.

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References

Figure 1 Serum magnesium levels in our patient over the course of treatment with magnesium oxide supplements and intravenous magnesium replacement.


www.gutjnl.com
Osteoporosis is not a specific complication of primary biliary cirrhosis (PBC)

Newton et al (Gut 2001;49:282–7) described a retrospective study on bone mineral density (BMD) in a large cohort of patients with primary biliary cirrhosis (PBC). The authors concluded that osteoporosis is not a specific complication of PBC, but certain weaknesses in the study design do not support this conclusion.

(A) The authors did not include age and sex matched controls from the general population, or control groups with different types of liver disease.

(B) A proper methodological design comparing osteoporosis in PBC and in a normal population should calculate the standardised incidence ratio of osteoporosis for the two cohorts by comparing the observed incidence versus the expected incidence. The calculation should include 95% confidence intervals according to exact Poisson limits.

Thus we agree with Newton et al that osteoporosis in PBC should be revisited. In fact, analysis of the literature enables the following conclusions to be drawn. There are several osteoporosis risk factors common to liver disease, aging processes, or genetic variability, as well as cholestasis related risk factors, that are obviously not specific for PBC (table 1). The pathogenesis of osteoporosis is multifactorial, increasing with advancing age, and influenced by genetic factors, and it may be that liver disease accelerates bone resorption through various mechanisms.

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References

Authors’ reply
We read with interest the letter of Professor Floreani in which she agrees that it is timely to revisit the perceived dogma that patients with primary biliary cirrhosis (PBC) are predisposed to osteoporosis. It was pleasing to note that our findings compare favourably with work from her group. We would also like to take this opportunity to draw attention to two further studies which have been presented in abstract form since the submission of our manuscript, which confirm that there is no increase in prevalence of osteoporosis’ and no increase in fracture risk in PBC populations taken as a whole compared with appropriately matched normal controls.’ A further study has also been published recently describing bone mineral density in a selected series of patients with PBC in whom the prevalence of osteoporosis (defined by T score) was comparable with that seen in our series. We were pleased to note that in this prospective series other risk factors for osteoporosis were examined. They concur with our finding that increased age is an independent risk factor, although they do not present mean Z score data (bone mineral density data controlled for both sex and age). Their group, we would argue, was younger and had more severe disease than patients in our series, whom we would regard as more representative of the whole PBC population.

In our study we demonstrated that although 85/272 (31%) patients had osteoporosis, as defined by the WHO (T score) at the time of their first DEXA scan, mean Z score at the neck of femur was −0.1 and at the lumbar spine 0.1. As Z scores represent bone mineral density compared with an age and sex matched population, this suggests the prevalence of osteoporosis seen in PBC is a reflection of the fact that this is predominantly a disease of postmenopausal women who show a generalised increased prevalence of osteoporosis. The use of Z scores implicitly controls our data for age and sex norms. We agree with Professor Floreani that readdressing the question of osteoporosis prevalence in other chronic liver diseases (both cholestatic and non-cholestatic) would be of interest but we feel that this is not relevant to the current study.

Given the very real problems experienced by some PBC patients as a result of osteoporotic fracture (particularly in the early post-transplant period), further study of the aetiology is appropriate (although the retrospective nature of the current study makes the suggested logistic regression analysis inappropriate). The message that we (and more recently others) have been communicating is that the search for risk factors for osteoporosis should not be focused on liver disease specific factors but could more usefully be directed at more generalised population risk factors.

Table 1 Risk factors for osteoporosis in liver diseases

<table>
<thead>
<tr>
<th>Common risk factors</th>
<th>Cholestasis related risk factors</th>
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<tbody>
<tr>
<td>• Cirrhosis</td>
<td>• Calcium malabsorption</td>
</tr>
<tr>
<td>• Female sex</td>
<td>• Vit D malabsorption</td>
</tr>
<tr>
<td>• Old age</td>
<td>• Hypophosphatemia</td>
</tr>
<tr>
<td>• Alcohol consumption</td>
<td>• Cholestyramine therapy</td>
</tr>
</tbody>
</table>

BMI, body mass index; VDR, vitamin D receptor.
Expression of isoforms of nitric oxide synthase in collagenous colitis

We read with interest the study by Perner et al (Gut 2001;49:387–94) investigating expression of various isoforms of nitric oxide synthase (iNOS, eNOS, and nNOS) in non-inflamed colon, collagenous colitis, and ulcerative colitis. Inducible NOS (iNOS) was identified by immunohistochemical analysis in the epithelium of patients with non-inflamed colon. The authors concluded that this might be a result of bowel preparation with bisacodyl. Increased synthesis of nitric oxide has been observed in collagenous colitis. The reason for iNOS expression in normal colon is not yet clear. Nitric oxide production may aid maintenance of the epithelial barrier by preventing bacterial translocation or by inducing apoptosis. It is also possible that its presence represents a link between dietary or other luminal factors and the development of colorectal cancer, as hypothesised by Cameron et al, although high iNOS expression in collagenous colitis is not associated with an increased risk of malignancy.

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References

Authors’ reply
We thank Cameron et al for their comment on our recent publication and important observations that suggest physiological expression of inducible nitric oxide synthase (iNOS) in histologically normal human colon. As we observed subtle iNOS labelling in colonic mucosal biopsies from our group of controls with non-inflamed bowel, we have subsequently studied whether bowel preparation with bisacodyl or polyethylene glycol prior to sigmoidoscopy might induce iNOS expression. Ten healthy non-smoking male subjects were investigated. Mucosal biopsies were taken from the sigmoid colon prior to bowel preparation and again 12 hours after rectal administration of an enema consisting of bisacodyl (100 mg) or polyethylene glycol 3000 (6.4 g in 100 ml of water) in randomised order. Expression of iNOS protein was quantified by western blot analysis and localised by immunohistochemistry.

iNOS was expressed in the colonic mucosal biopsies from all subjects and localised in epithelial cells, particularly at the luminal border of the epithelial cells and more pronounced in the crypt epithelium. Expression of iNOS was unaffected by bowel preparation with bisacodyl or polyethylene glycol (fig 1).

Hence we agree with Cameron et al that expression of iNOS in epithelial cells is possibly a result of physiological expression of iNOS rather than a secondary phenomenon as a result of the bowel preparation per se or the effect of the secretagogue laxative bisacodyl. For the reasons given above, we also agree that nitric oxide may be important in maintaining the epithelial barrier and may represent a link between dietary or other luminal factors and the development of colorectal cancer, as hypothesised by Cameron et al, although high iNOS expression in collagenous colitis is not associated with an increased risk of malignancy.

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References

Figure 1 Expression of inducible nitric oxide synthase in mucosal biopsies from the unprepared (Unprep) sigmoid colon and 12 hours following bowel preparation with bisacodyl (Bis) or polyethylene glycol 3000 (PEG), analysed by western blotting and quantified by densitometry relative to a reference. Values in individual subjects are represented by circles and connected by lines. OD, optical density.
meeting on 31 August to 4 September 2002 in
Glasgow, UK. The organisers anticipate 300
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mation: Mrs Pat Howard, Honorary Secretary,
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Postgraduate Gastroenterology
This course will be held on 15–18 September
2002 in Oxford, UK. The course has been
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ing those who do not specialise in gastroenter-
ology. Topics will include: Barrett’s Oesoph-
agus; The Case for Endoscopic Surveillance
Debate; Liver Disease; Bacteria and the Gut;
IBD Therapeutics, Gastrointestinal Bleeding,
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3rd World Chinese Congress of
Digestology
This congress will take place on 23–25 Septem-
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5th International Workshop on
Pathogenesis and Host Response
in Helicobacter Infections
This will be held on 4–7 July 2002 in
Helsingør, Denmark. Further information: Dr
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