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**Ghrelin and Helicobacter pylori**

We read with interest the article by Nwokolo et al reporting raised serum ghrelin levels following Helicobacter pylori eradication (Gut 2003;52:637–40). There are some exceptions to the interpretation of the data that we would take.

The authors state that the increase in ghrelin levels seen in their study “leads support to the view that ghrelin could be involved in the long term regulation of body weight”. While there is growing evidence to support this in the literature, this study does not present any such data and is not methodologically geared towards addressing this question. The proposal that eradication of *H pylori* leads to an increase in ghrelin levels, which in turn leads to an increase in obesity, is also without foundation. The only known situation in which hyper-ghrelinaeemia is associated with obesity is in Prader-Willi syndrome. In all other studies ghrelin levels correlate inversely with measures of body fat and activity, and are altered in a compensatory manner by changes in body weight. To suggest therefore that *H pylori* eradication leads to a hyper-ghrelinaeemic state that drives increased appetite is not physiologically feasible as any transient appetite increase would be expected to be countered by any increase in adiposity, which in turn would suppress ghrelin levels.

The authors’ proposal that “children with *H pylori* may have relatively low ghrelin concentrations contributing to growth retardation” is also without foundation. A recent study has shown *H pylori* status to have no effect on ghrelin levels. The role of ghrelin on the growth of children remains unclear.

Ghrelin is an endogenous ligand to the growth hormone secretagogue receptor (GHS-R), and potently stimulates growth hormone release. It may indeed have a role to play in growth, as in patients with a genetic growth hormone releasing hormone deficiency nocturnal enhancement of growth hormone secretion remains, an effect that may be mediated by ghrelin.

One other proposal of the authors is that *H pylori* eradication increases 24 hour gastric acidity by a ghrelin dependent mechanism. While central and peripheral ghrelin administration has been shown to increase stomach acidity when given to rats, data are lacking in humans. The small but statistically significant increase in acidity seen here would be expected after *H pylori* eradication, and is likely to be secondary to parietal cell recovery following resolution of inflammation. The suggestion that hypergastrinaemia leads to lower ghrelin levels, and vice versa, is not supported in the literature.

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**References**


**Authors’ reply**

We would like to draw the attention of Drs Murry and Emmanuel to the objectives set by the authors. The authors refer to “physiological feasibility” and therefore miss the point that *Helicobacter pylori* infected stomachs exhibit distortion of normal physiological mechanisms. For example, the tight reciprocal relationship between gastrin and intragastric acidity seen in *H pylori* negative patients is modified in *H pylori* positive subjects. We believe that a *H pylori* infected stomach produces less ghrelin, leading to decreased appetite and food intake. The physiological response should be that the resulting weight loss leads to a compensatory increase in ghrelin, increased appetite, and weight gain, and so on. We believe that this “physiological” mechanism is altered by the presence of *H pylori*, possibly by resetting a putative “ghrelin thermostat” at a lower level, allowing thinness and hypothalamic appetite centres to occur together. Proof will come only from further experimentation.

The authors cite a study comparing spot measurements of plasma ghrelin in women with and without *H pylori* gastritis; this does not amount to a robust challenge to our hypothesis on *H pylori*, ghrelin, and children. The authors repeat the widely held although unproven belief that the increase in intragastric acidity after *H pylori* cure can be attributed to recovery of parietal cells from inflammation. They ignore our observation of a positive correlation between *H pylori* and 24 hour intragastric acidity. We accept that the relationship between gastrin and ghrelin is unproven in humans but this emphasises the paucity of human data and the need for more studies.

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**Reference**


**Helicobacter pylori, ghrelin, and obesity**

Nwokolo et al have demonstrated that following eradication of *Helicobacter pylori* from asymptomatic patients, plasma ghrelin “increases profoundly” (*Gut* 2003;52:637–40). Although we find these results interesting, we cannot agree with the conclusion that this may be causally linked to epidemiological observations of the rising incidence of obesity and oesophageal adenocarcinoma in Western populations. In particular, the present study in fact demonstrates that after *H pylori* eradication, ghrelin merely returns to levels detected in non-obese control patients using the same hormone assay. It would seem likely that *H pylori* infection, leading to oxyntic gland atrophy, is associated with at most a mild suppression of plasma ghrelin, which recovers after treatment. This seems unlikely to have a profound effect on appetite, particularly as obese patients have a lower mean plasma ghrelin concentration than matched non-obese controls. While it is possible, although unproven, that the virtual ablation of plasma ghrelin seen after roux-en-Y gastric bypass surgery may contribute to the paradoxical reduction in hunger...
observed in these patients, it is simplistic to suggest that the moderate reduction in ghrelin, as seen in the H pylori infected group in this study, is protective against the development of obesity and its associated conditions.

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References

2 Date Y, Kajima M, Hosoda H, et al, Ghrelin, a novel hormone stimulating appetite and food intake, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. Endocrinology 2000;141:4255–61

Author’s reply

Macadam et al have rightly questioned whether our novel observation is merely epiphenomenal or of pathophysiological significance. Their “gut feeling” is that it is the former as the changes are “mild” and ghrelin concentrations after Helicobacter pylori cure are no different from those seen in a non-obese Western population. They also suggest that the “moderate” reduction of ghrelin in H pylori positive subjects (which they attribute to oesophageal gland atrophy) is unlikely to protect these individuals from obesity.

There is no doubt that cure of H pylori increases plasma ghrelin in “healthy subjects”. The real questions are: whether plasma ghrelin concentrations are higher in H pylori negative individuals and, if so, whether the higher ghrelin concentrations cause weight gain, and whether any weight gained exacerbates gastro-oesophageal acid reflux enough to induce Barrett’s oesophagus and cancer. There are no satisfactory answers to these questions based on first class evidence but in our discussion, we considered some indirect evidence. Firstly, populations with a high prevalence of H pylori have a relatively high proportion of thin children and adults, and those with a low prevalence have a higher proportion of obese individuals; we acknowledge the numerous other confounding factors in our paper.

Secondly, Furuta et al showed that patients cured of H pylori may gain weight.1 Lane et al, continuing their reporting of the large Bristol Helicobacter project, showed that at the end of six months, individuals who received treatment for H pylori increased their weight by 0.6 kg over and above a matched group that received placebo.2 Finally, in the only published study of its kind, infusion of ghrelin into healthy subjects was associated with increased appetite and food intake.1

In the presence of H pylori, abnormalities in the function of the gastric neuroendocrine cell population can be detected long before gastric atrophy occurs. “Inappropriate” hypergastrinaemia and disturbances in D cell function have been described; these are fully reversible, returning to normal soon after H pylori cure.4 Similarly, gastric atrophy which is irreversible in the short term is unlikely to be the mechanism that mediates hypergastrinaemia in H pylori positive subjects, given that reversion to normal non-obese concentrations occurred 6–12 weeks after cure, which was the time course of our study. Also, the median age of our subjects was 36 years; the fact that they had normal gastric concentrations and 24 hour intragastric acidity makes it unlikely that they had significant gastric atrophy.

In general, single factors rarely account for large epidemiological trends. We do not believe that everything can be explained by ghrelin; that would really be simplistic. However, we believe that H pylori positive subjects with low ghrelin may have decreased appetite and food intake and are thinner than their H pylori negative counterparts in the Western world. Their poor nutritional status would be exaggerated by coexisting dyspepsia due to peptic ulceration, concurrent infection, and poor diet. They would have relatively lower intragastric acidity. Taken together, these factors could protect these individuals from gastro-oesophageal reflux disease (GORD). Conversely, having normal ghrelin, a good appetite, and normal intragastric acidity could make GORD more likely, possibly leading to Barrett’s oesophagus and oesophageal adenocarcinoma.

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References


In the paper by Feinle-Bisset et al (Gut 2003; 52:1414–18), an author was missing from the author list, listing only three of the authors as C Feinle-Bisset, B Meier and M Fried. In fact, there was a fourth co-author, C Beglinger, based at University Hospital Basle, Switzerland.

CORRECTION

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Ghrelin and *Helicobacter pylori*

C D R Murray and A V Emmanuel

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