

Insulin-like growth factor-I in *Helicobacter pylori* gastritis and response to eradication using bismuth based triple therapy

A S Taha, G Beastall, R Morton, R H R Park, A D Beattie

Abstract

Aims—To measure insulin-like growth factor-I (IGF-I) concentrations in the presence and absence of *Helicobacter pylori* infection and in response to eradication of the organism.

Methods—An enzyme linked immunosorbent assay was used to measure gastric and fasting serum concentrations of IGF-I in 17 patients with and 11 without *H pylori* infection. Repeat assessments were performed in the infected patients six weeks after they received a two week course of bismuth chelate, metronidazole, and amoxicillin.

Results—IGF-I was detected at very low concentrations in gastric juice and in mucosal incubates. The median serum IGF-I concentration was 88 µg/l in the patients infected with *H pylori* compared with 90 µg/l in the non-infected controls; IGF-I concentrations dropped to 77 µg/l following eradication therapy ($p = 0.014$).

Conclusion—The similarity in baseline IGF-I concentrations in the presence and absence of *H pylori* suggests that their subsequent drop after treatment is more likely to be due to the treatment.

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week of endoscopy. Ten microlitres of fasting venous blood was taken and the serum was immediately separated and stored frozen at -70°C pending analysis. Endoscopy was performed using 5-10 mg midazolam for sedation. Gastric antral and body biopsy specimens were taken to test for *H pylori* infection by histology (two specimens), culture (one specimen) and urease activity (CLO-test; one specimen). Patients with *H pylori* in any or all of these specimens were regarded as positive, and those lacking *H pylori* in all specimens were considered negative. Specimens of fasting gastric juice were taken and frozen, and gastric antral biopsy specimens incubated overnight in RPMI 1640 prior to IGF-I measurements.

Gastritis was classified according to the Sydney system and its activity graded on a scale from 0 to 3 as follows: 0 = normal; 1 = mild; 2 = moderate; and 3 = severe, depending on the intensity of neutrophilic infiltration.

In patients infected with *H pylori* all assessments were repeated six weeks after completion of a two week eradication regimen, comprising metronidazole (400 mg three times daily), amoxicillin (500 mg three times daily) and bismuth chelate (De-Nol; 120 mg four times daily). IGF-I concentrations were measured using an enzyme linked immunosorbent assay, with a sensitivity of 10 µg/l, and using an antibody that does not cross-react with insulin, pro-insulin, or IGF-II.

Statistical analyses included the Mann-Whitney U test and the Wilcoxon's test for unpaired and paired data, respectively. Informed consent was obtained from all patients and all specimens were coded prior to analysis. The study was approved by the local Ethics Committee.

Results

Twenty nine patients were studied, 18 of whom were positive and 11 negative for *H pylori* infection. In the infected group the triple therapy regimen failed to eradicate *H pylori* in five patients. The baseline serum sample of one *H pylori* positive patient was lost during processing, and another patient refused triple therapy altogether. This left 28 patients (17 positive and 11 negative for *H pylori*) with baseline specimens and 11 patients with specimens taken both before and after eradication therapy.

The biochemical basis of the increased gastric mucosal cell proliferation observed in *Helicobacter pylori* gastritis¹ remains poorly understood. The action of *H pylori* on the expression of insulin-like growth factor-I (IGF-I), an anabolic and mitogenic protein which has a key role in growth and development, is a possible cause of this increase in proliferation.² The purpose of the present study, therefore, was to measure gastric and serum concentrations of IGF-I in patients with and without *H pylori* infection, and following eradication therapy.

Methods

Adult patients were included if they were scheduled for upper gastrointestinal endoscopy, and excluded if they had any systemic illness, malignancy, gastric surgery, or if they had taken anti-ulcer drugs or antibiotics within one

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Table 1 Patient characteristics

	Patients	
	<i>H pylori</i> positive	<i>H pylori</i> negative
Number	17	11
Male:female ratio	9:8	5:6
Age (years)*	48 (43–57)	54 (40–63)
Smokers	10	7
Alcohol drinkers	10	8
Duodenal ulcer	2	0
Gastric ulcer	1	1
Grade of gastritis activity		
0 (normal)	1	8
1 (mild)	7	3
2 (moderate)	6	0
3 (severe)	3	0

*Median (interquartile range).

The characteristics of patients are shown in table 1. Patients were comparable with respect to their sex, age, smoking and drinking habits, and endoscopic findings. All but one of the *H pylori* positive patients had varying degrees of active gastritis, while eight (73%) of 11 *H pylori* negative subjects had normal gastric histology. IGF-I was detectable only at a very low concentrations in gastric juice and tissue incubates and, therefore, statistical comparison was not possible in these specimens.

Serum IGF-I concentrations in the presence or absence of *H pylori* are shown in fig 1A, and were similar in both groups. The effect of successful *H pylori* eradication on serum IGF-I concentrations is shown in fig 1B. Post-triple therapy values are significantly lower than those at baseline. No significant change in IGF-I concentrations was noted in patients with persistent *H pylori* infection, probably due to poor compliance with therapy, and these were excluded from statistical analysis. It is also worth noting that the successfully treated group (n = 11) included four patients with grade 1, five with grade 2, and two with grade 3 gastritis at baseline, compared with 10 patients with normal gastric histology (grade 0) and one patient with mild gastritis (grade 1) after successful eradication of the infection.

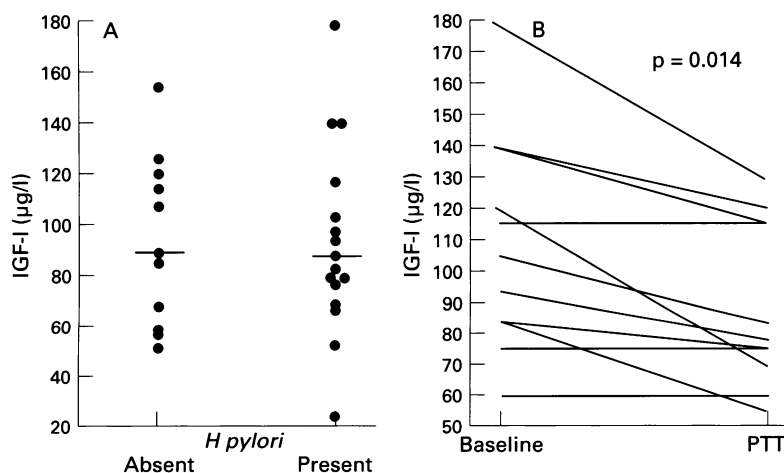


Figure 1 (A) IGF-I fasting serum concentrations in *H pylori* positive patients and their negative counterparts. (B) A significant drop in IGF-I concentrations was observed six weeks post triple therapy (PTT) following successful eradication.

Discussion

This study shows that fasting serum IGF-I concentrations are not influenced by the presence of *H pylori* gastritis, although they did fall significantly in response to a two week course of bismuth based triple therapy.

With the increasing evidence linking *H pylori* with gastric mucosal cell proliferation,¹ one could not exclude the possibility that IGF-I concentrations might be influenced by the presence of this organism. This was not confirmed by our study and suggests the involvement of other factors in *H pylori* related mucosal cell proliferation.¹

The similarity in IGF-I concentrations in patients with and without *H pylori* infection, with different grades of gastritis, suggests that it is unlikely that IGF-I is expressed in measurable amounts by the neutrophils *in vivo*, given the role of the neutrophils as an index of the activity of gastritis. This also explains the absence of high concentrations of IGF-I in gastric juice or tissue, as assessed in the present study.

There are two possible explanations for the drop in serum IGF-I concentrations following eradication of *H pylori*. The first relates to the normalisation of gastric histology. This, however, does not reconcile the differences in the activity of gastritis in patients with and without *H pylori* infection given the similarity in baseline IGF-I concentrations in these patients. The second, and probably the more likely explanation, is a direct inhibitory effect of bismuth based triple therapy on IGF-I production. This might explain another effect of triple therapy, thought to be independent of *H pylori*: it has been found that gastric mucosal cell proliferation decreased—that is, returned to normal four weeks after the intake of triple therapy, irrespective of the patient's *H pylori* status.¹ It will therefore be interesting, should ethical approval be forthcoming, to investigate the effect of triple therapy on *H pylori* negative subjects when the consequences of eradication are studied.

The pathophysiological properties of IGF-I and the ability to produce it by recombinant DNA techniques have led to extensive testing of its "endocrine" activities. IGF-I stimulates glucose disposal in a manner similar to insulin and can increase insulin sensitivity,³ raising the possibility of an application in insulin resistant syndromes.⁴ In catabolic subjects, intravenous IGF-I reverses nitrogen loss,⁵ whereas recovery from both ischaemic renal necrosis⁶ and dermal wounding⁷ can be accelerated by subcutaneous or local administration. However, IGF-I has also been linked to the development of a variety of neoplastic diseases including those of the breast, stomach, liver, and colon.^{8,9} To date, no agent has been shown to suppress IGF-I production, and this highlights the therapeutic potential of our findings.

In conclusion, *H pylori* infection does not seem to alter IGF-I concentrations despite the differences in the activity of gastritis in patients with and without *H pylori* infection. Fasting serum IGF-I concentrations are, however, sup-

pressed by bismuth based triple therapy and this might have therapeutic implications.

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