ASSOCIATION BETWEEN GASTRIC CANCER AND \textit{H. pylori} WITH REFERENCE TO AGE.


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In order to assess the influence of age on association between gastric cancer and \textit{H. pylori}, a large case-control study was conducted in Kanto area of Japan. Sera were collected between 1982 and 1994 from gastric cancer patients aged 20–69 years, who were diagnosed at 10 hospitals, and from screen negatives (control) in general health check programs in the same area. Anti-\textit{H. pylori} IgG antibodies were measured using ELISA kit; Pillika-Plate G Helicobacter produced by Bionorm Co. Ltd. (CA, USA). Sera were obtained from 757 patients (65.9% males) and 1005 controls (50.9% males).

The seropositive percentage and odds ratio for association are presented in the Table, divided into five ten-year age groups. Odds ratio in all age groups was significantly elevated except the oldest. The magnitude of odds ratio was negatively related to age (p<0.01). The decrease in odds ratio with age was mainly due to an increase of the seropositive percentage in controls.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>No. of subjects</th>
<th>Seropositive (%)</th>
<th>Odds ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–29</td>
<td>20 (50.0%)</td>
<td>20 (29.8%)</td>
<td>23.5 (1.5, 103.0)</td>
</tr>
<tr>
<td>30–39</td>
<td>121 (10.3%)</td>
<td>20 (17.1%)</td>
<td>11.0 (5.8, 20.8)</td>
</tr>
<tr>
<td>40–49</td>
<td>124 (9.1%)</td>
<td>19 (9.5%)</td>
<td>11.0 (6.4, 19.4)</td>
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<tr>
<td>50–59</td>
<td>216 (14.8%)</td>
<td>20 (9.7%)</td>
<td>3.2 (1.9, 5.5)</td>
</tr>
<tr>
<td>60–69</td>
<td>216 (14.8%)</td>
<td>20 (9.7%)</td>
<td>3.2 (1.9, 5.5)</td>
</tr>
<tr>
<td>Total</td>
<td>757 (100.0%)</td>
<td>103 (13.3%)</td>
<td>4.7 (3.8, 6.1)</td>
</tr>
</tbody>
</table>

RECURRENT OF DUODENAL ULCER AFTER HELICOBACTER PILORI ERADICATION IS RELATED TO HIGH GASTRIC ACID OUTPUT

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Eradication of \textit{H. pylori} (Hp) reduces recurrence of duodenal ulcer (DU) to < 2% per annum. It is not clear why DU recurs rarely in the absence of Hp re-infection or NSAIDs. Basal (BAO), gastrin releasing peptide (GRP) and gastrin/gastrinogen (G/G) stimulated peak acid outputs (PAO1, PAO/G) are increased in Hp-ve DU and return to the range of Hp-ve controls after eradication. Does acid output in patients with recurrent DU after Hp eradication also return to the control values?

We studied 6 patients (5 men, mean age 41, range 28–53) with symptomatic and endoscopic recurrence of DU> six months (mean 18 months) after Hp eradication, and compared them with 10 Hp-ve controls with normal endoscopy (4 men, mean age 33, range 24–40), and with Hp-ve non-recurrent DU before (n=10, 7 men, mean age 37, range 22–54) and six months after (n=6, 6 men, mean age 39, range 34–58) Hp eradication. None had taken NSAIDS. Hp status was determined by urea and body histology and culture and by the 13C urea breath test, and classified as Hp-ve on any +ve result and Hp-ve on all three tests. After an overnight fast, a NG tube was passed, the stomach emptied, and the 30 min basal aspirate collected. GRP (40 pmol/kg/h) was then infused for 45 min. After a 30 min washout, Pg (6pmol/kg) was injected i.m. These 15 min aspirates were collected after each stimulus.

Acid outputs are expressed as mmol/h and normalised to 70kg body weight. BAO, PAO1, and PAO1/G were significantly (p<0.05, Mann Whitney test) higher in Hp-ve DU than Hp-ve controls, with median (range) BAO 7 (2–17) vs 2 (0.3–6) mmol/h (p<0.05), PAO1 20 (0.3–64) vs 10 (1.25) and PAO1 44 (20–79) vs 25 (12–40). Six months after Hp eradication, median (range) BAO, PAO1, and PAO1/G in DU were 3 (1–11), 14 (4–45) and 29 (6–40), respectively; all significantly (p<0.05, Wilcoxon signed rank test) lower than before Hp eradication and within the range of controls. In Hp-ve recurrent DU median (range) BAO, PAO1, and PAO1/G were 5.5 (0–15), 18.5 (2–48) and 38 (27–60), respectively; PAO1/G was significantly (p<0.05) higher than Hp-ve controls and within the range of Hp-ve DU.

In DU recurrence after Hp eradication PAO1/G remains within the Hp-ve DU range. By contrast in non-recurrent DU PAO1/G failed to the control range after Hp eradication. Our findings suggest that there may be a subset of DU who return an abnormally high response to gastrinogen.

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PARIELT CELL SENSITIVITY TO GASTRIN DISTINGUISHES \textit{H. pylori} INFECTED DU PATIENTS FROM INFECTED HEALTHY VOLUNTEERS

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It is unclear why \textit{H. pylori} produces duodenal ulceration in only a minority of infected subjects. In all subjects it increases gastrin release and the magnitude of this is similar in those with and without DU. We have investigated whether those who develop DU are more sensitive to the acid stimulatory effects of gastrin.

Patients and Methods: Fifteen \textit{H. pylori} positive healthy volunteers and six \textit{H. pylori} positive DU patients were examined. Each group was matched for age, sex and body weight. After a 30 minute basal period, Gastrin-17 was infused i.v. in increasing doses of 3, 20, and 50 pmol/kg/h over 30 consecutive 30 minute periods. Gastric juice was collected in 15 minute aliquots and acid output determined. Dose-response curves were plotted and the Gastrin 17 dose required to produce half maximal acid response (D50) calculated.

Results: None of the groups showed a statistically significant difference in maximum acid output to Gastrin-17. However, the \textit{H. pylori} positive DU patients were significantly less sensitive to gastrin than the \textit{H. pylori} negative healthy volunteers (p<0.03). In addition, the \textit{H. pylori} positive DU patients were more than twice as sensitive to gastrin compared to the \textit{H. pylori} positive healthy volunteers (p<0.004).

<table>
<thead>
<tr>
<th>Median MAO to G17 in mmol/h (range)</th>
<th>Healthy Volunteers</th>
<th>DU Patients</th>
</tr>
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<tbody>
<tr>
<td>38.5 (21.9–60.2)</td>
<td>35.1 (18.6–54.8)</td>
<td>27.7 (16.1)</td>
</tr>
</tbody>
</table>

**Median sensitivity to G17 (i.e. D50 in pmol/kg/h) (range):**

- **p<0.03** versus Hp-ve HV; **p<0.004** versus Hp+ve HV.

Summary and Conclusion: The finding that \textit{H. pylori} positive DU patients have a 2–3 fold increased parietal cell sensitivity to gastrin compared to \textit{H. pylori} positive healthy volunteers explains how acid peptic disease develops only in the latter despite the two groups having similarly elevated gastrin levels. It is unclear whether the difference in parietal cell sensitivity is an effect of \textit{H. pylori} infection or the genetic factor predisposing to DU disease.

Heliobacter pylori augments the pH-raising effect of omeprazole in duodenal ulcer patients.


** Aim:** The effect of eradication \textit{H. pylori} (HP) on baseline gastric pH and on intragastric acidid output with omeprazole therapy in duodenal ulcer (DU) patients was investigated.

**Methods:** HP infection and eradication were assessed by urease test, culture, histology, and breath test, eradication therapy and 4 to 6 weeks after stopping eradication therapy, intragastric acidity (ingolad electrode 5 cm below the cardia) was measured after a one week treatment with omeprazole (OME) 20 mg (group I; 17 DU patients) or without treatment (group II; baseline; pH; DU patients).

**Results:** Cure of bacterial infection resulted in a decrease of the gastric pH during treatment with omeprazole 20 mg od, while the baseline pH remained unchanged (Table).
PENTAGASTRIN STIMULATED GASTRIC ACID SECRETION AND POSTPRANDIAL GASTRIN PROFILES IN HELICOBACTER PYLORI (HP) POSITIVE AND NEGATIVE HEALTHY VOLUNTEERS.

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It is still established if HP infection is directly responsible for changes in acid secretion observed in duodenal ulcer (DU) patients, nor do we fully comprehend the pathophysiologic mechanisms involved. We tested the hypothesis whether the HP status influences the pentagastrin stimulated gastric acid secretion.

Method: HP-status was assessed by CLO-test and histology (2 biopsies each from the antrum and the corpus) in 9 HP positive and 14 HP negative healthy volunteers of comparable age. Acid secretion was studied by measuring 1 hour basal acid secretion (BAO) and by establishing a cumulative pentagastrin dose response curve. Pentagastrin was infused at 0.03, 0.1, 0.3, 1.0, 3.0 and 8.0 µg/kg/h. From these data 1 hour maximum acid secretion (MAO) and E15g (pentagastrin-sensitivity = PGS) was established and results compared by ANOVA. Postprandial gastrin profile (before, 1, 2 and 3 hours after standard breakfast) was performed.

Results: The dose response curves of the pentagastrin stimulated gastric acid secretion analyzed by parallel-line assay were not different between HP positive and HP negative groups. No significant difference was found between the two groups with respect to BAO (H+m@hr), MAO (H+mmol/hr), PGS (µg/kg body weight/hr) and postprandial gastrin profile (pmol/l).

Conclusion: HP does not seem to influence BAO, pentagastrin stimulated gastric acid secretion and postprandial gastrin profile in healthy volunteers. These observations are different from the findings in HP+ve DU patients. These data support the hypothesis that HP infection is not the only reason of pathophysiologic changes observed in DU disease.


Factors thought to be responsible for hypergastrinemia in H. pylori infection are local ammonium production and a decrease in the number of somatostatin cells in chronically infected antral mucosa. The aim of this study was to evaluate whether water soluble proteins (WSP) of H. pylor i may directly effect gastrin release.

Methods: Single cell suspensions of human antral biopsies were established by enzymatic pronase digestion and resuspended at 1x10^6 cells/ml. 1% of the total cell population were gastrin cells. Three different concentrations of each WSP-extract were tested. Following a 30 min. incubation period supernatants were assayed for gastrin (G-17) using a radioimmunnoassay system. Human complement was used as a positive gastrin stimulant. H. pylori styatus and gastritis grade of each patient was determined by CLO-test, IgG-antibody ELISA, H&E and Whartin-Starry histology.

Results: The addition of WSP-extracts demonstrated a dose-dependent rise in gastrin released in single cell suspensions [p<0.01, mean ± SEM, **p<0.001].

This effect was similar in both cytotoxic-positive and negative strains. Gastrin release in cell suspensions of patients with a positive or negative H. pylori status did not differ significantly. However, a trend to lower gastric release upon WSP stimulation was seen in the H. pylori negative patient population, and a higher H. pylori-gastrin grade correlated with greater release.

Control experiments using different ammonium chloride concentrations (0.1 to 100mM) did not demonstrate gastrin release.

Conclusions: For the first time this study provides considerable evidence suggesting a direct effect of water-soluble H. pylori components on gastrin release. Since bacterial adherence mediates close contact of H. pylori with gastric epithelium the above phenomenon should be considered as a possible explanatory mechanism of hypergastrinemia in H. pylori-associated disease.


Introduction: H. pylori (Hp) infection produces major changes in gastric secretory responses to gastrin–releasing peptide (GRP). This study addressed whether this is due to gastric somatostatin (SST) cells failing to respond to GRP in Hp+ individuals.

Methods: Dyspeptic non– ulcer patients, 9 Hp+ and 8 Hp– received a 3 hour intravenous infusion of GRP (14–27), 200 pmol/kg/h or vehicle alone on separate occasions. At the end of each infusion endoscopy was performed and biopsies were taken for measurement of SST and gastrin mRNAs.

Results: Plasma gastrin rose far more in the Hp+ than in Hp– patients. GRP significantly elevated antral gastrin mRNA in the Hp+ patients, but a caused significant fall in the Hp– group. GRP stimulated a significant rise in antral SST mRNA in the Hp+ group, but not in the Hp– group. Corpus SST mRNA showed similar trends but the rise in the infected group was not statistically significant.

ANTRAL SOMATOSTATIN CELL DENSITY AND HELICOBACTER PYLORI IN MAN. TCK Thomas, L Chen, N Dennison, CF Johnston, JSA Collins, JA Ardill, KD Buchanan. Dept. of Medicine, Queen’s University and Royal Victoria Hospital, Belfast, N. Ireland, U.K.

Helicobacter pylori infection may be associated with abnormalities in antral gastrin (G) and somatostatin (D) cell density.

AIM: To evaluate the effect of the eradication of H. pylori on antral G and D cell density in man.

METHODS: 25 patients with H. pylori infection (age 42±13 years; duodenal ulcer disease in 18, normal 4, oesophagitis 2, gastric ulcer 1) were studied. 9 of these had H. pylori successfully eradicated and the rest remained infected. At least 2 antral biopsies were taken, Sussa-fixed and was-embedded before and 4 weeks after H. pylori eradication therapy. Well orientated sections were immunostained for G and D cells. The number of G and D positive cells including the nucleus with positive apical and basal cytoplasm were counted per linear µm of mucosa by an investigator who was blind to the patients’ clinical details. Serum gastrin was measured at the time the biopsies were taken.

RESULTS: G cell density was unchanged with persistent H pylori infection confirming previous reports. D cell density increased after H pylori eradication (before treatment, median 50 [15-72]; after treatment 71 [39-107] cells/mm) (P<0.05) but was unchanged with persistent H pylori infection (before 32 [6-80]; after 39 [16-72] cells/mm). Serum gastrin decreased after H pylori eradication (before treatment, median 70 [45-100]; after treatment 30 [10-100] ng/l) (P<0.05) but was unchanged with persistent H pylori infection (before 80 [20-260]; after 50 [35-270] ng/l).

CONCLUSIONS: Following eradication of H. pylori, there is an increase in D cell density with no change in G cell density although there is a fall in serum gastrin. This supports the theory that H pylori infection results in a decrease in D cells and as the latter is an inhibitor of G cells, this results in an increased serum gastrin and gastric acid secretion.