Eradication of *Helicobacter pylori* May Be Beneficial in the Management of Chronic Open-Angle Glaucoma

Jannis Kountouras, MD, PhD; Nikolaos Mylopoulos, MD, PhD; Dimitrios Chatzopoulos, MD; Christos Zavos, MD; Panagiota Boura, MD, PhD; Anastasios G. P. Konstas, MD, PhD; John Venizelos, MD, PhD

**Background:** We have documented a high prevalence of *Helicobacter pylori* infection in patients with glaucoma.

**Objective:** To evaluate the effect of *H pylori* eradication on the 2 most commonly used glaucoma parameters: intraocular pressure and visual field.

**Methods:** A total of 41 patients with glaucoma and 30 age-matched anemic controls underwent upper gastrointestinal endoscopies and gastric mucosal biopsies to detect the presence of *H pylori* infection by histologic analysis and rapid urease test (CLOtest; Delta West, Draper, Utah). Saliva samples were also tested by CLOtest. Serum anti–*H pylori*–specific IgG was analyzed by enzyme-linked immunosorbent assay. *Helicobacter pylori*–positive patients received a triple eradication regimen (omeprazole, clarithromycin, and amoxicillin treatment), and all patients were observed for 2 years while remaining under the same antiglaucoma therapy.

**Results:** *Helicobacter pylori* was detected in 88% of glaucoma cases and in 47% of controls (*P* < .001). *Helicobacter pylori* eradication was successful in 83% of treated patients. At the 2-year clinical end point, glaucoma parameters (mean intraocular pressure and mean visual field parameters) were improved in the subgroup of patients where *H pylori* eradication was successful (*P* < .001 for intraocular pressure; *P* ≤ .01 for visual field parameters), but not in the other patients.

**Conclusion:** *Helicobacter pylori* eradication may positively influence glaucoma parameters, suggesting a possible causal link between *H pylori* and glaucoma.

Arch Intern Med. 2002;162:1237-1244
PATIENTS AND METHODS

PATIENTS

This was a 2-part study. Part 1 was designed to evaluate the prevalence of *H pylori* infection in chronic OAG. Forty-one patients with documented chronic OAG and 30 age-matched anemic controls were included in this part of the study. The control subjects were undergoing upper and lower GI endoscopy to investigate mild iron-deficiency anemia, but their endoscopy findings were normal. After a detailed history was taken from all patients and their first-degree relatives, 26 (63%) patients with glaucoma were found to have intermittent symptoms of dyspepsia (defined as pain, discomfort, or other symptoms believed to originate from the upper GI tract), heartburn, or a history of upper GI tract bleeding. All patients with glaucoma (36 *H pylori*-infected patients who received the *H pylori* eradication regimen and 5 *H pylori*-negative patients who did not receive eradication therapy) were subsequently observed in the second part of the study, which evaluated the effect of administration of *H pylori* eradication regimen on intraocular pressure and visual field parameters over a 2-year follow-up period.

Patients were enrolled in the study if they met the following criteria: (1) an untreated intraocular pressure of 21 mm Hg or higher; (2) typical glaucomatous optic nerve head changes (including saucerization, rim thinning or notching in the inferior or superior temporal area of the optic nerve head, or total glaucomatous cupping); and/or (3) typical glaucomatous visual field loss (including a paracentral, arcuate, or Seidel scotoma or a nasal step). Seven of the patients enrolled were legally blind in the contralateral eye due to end-stage glaucoma. To reduce the possible bias of age, all participants were older than 45 and younger than 70 years. Exclusion criteria included all eye diseases other than glaucoma, diabetes mellitus, and a myopic refractive error exceeding –8 diopters. In addition, patients were excluded if they had taken H₄-receptor antagonists, proton pump inhibitors, antibiotics, bismuth compounds, or nonsteroidal anti-inflammatory drugs in the preceding 4 weeks (excluding low doses of aspirin [ie, 80 mg 2-3 times daily]). Patients were also excluded if they had undergone previous gastric surgery; were receiving antiocoagulant therapy; were alcohol abusers; had allergy to penicillin or macrolides; had gastric cancer or other neoplasms; or had severe cardiac, pulmonary, kidney, or liver disease.

All patients signed a consent form prior to enrollment, and the study protocol was approved by the local ethics committee. The intraocular pressure was measured with a calibrated Goldmann applanation tonometer by the same ophthalmologist. The visual field parameters were measured with the G1 Octopus program (Octopus 500EZ G1; Luterzeg AG, Zurich, Switzerland) by the same perimetrist. The ophthalmologist and the perimetrist were masked to the *H pylori* status of the patient. All patients had prior experience with automated perimetry. The parameters assessed included corrected loss variance (CLV), mean defect (MD), and short-term fluctuation (SF) of both eyes. The G1 program evaluates the threshold at 59 points within the central 30° of the visual field. Normal intraocular pressure generally varies between 12 and 20 mm Hg. The normal spread of the visual field parameters are SF, 0 to 2 dB; CLV, 0 to 4 dB; and MD –2 to +2 dB. The SF describes the intratest variation of the retinal sensitivity and may be affected by test-retest experience. The CLV shows the nonuniform variation from the expected hill of vision minus the effect of the SF. The MD represents the average decibel defect per location from the expected norm and may be influenced by refraction, the pupil size, and media opacities. It should be emphasized that no definite rules exist to indicate whether a patient’s condition is progressing or is stable.

Only topical glaucoma treatment was used in the 41 patients included in this study. The details of their treatment have been reported previously. None of the patients in this study received oral drugs that could influence intraocular pressure (eg, carbonic anhydrase inhibitors). All patients with glaucoma received the same topical eye regimen during the 2-year follow-up period of this study.

The control subjects had been recently diagnosed as having mild iron-deficiency anemia. The diagnosis of anemia was based on history and the GI investigation, and none of the subjects had received any treatment (eg, ferrous sulfate) prior to the diagnosis. Details of their blood profile and the causes of iron-deficiency anemia have been reported previously.

All 71 participants (41 patients with glaucoma, 30 anemic controls) underwent elective upper GI endoscopy combined with diagnostic biopsies at baseline. In addition, all patients with glaucoma underwent the same endoscopic procedure 3 months after *H pylori*-eradication treatment. Patients with peptic ulcer disease who agreed to undergo repeated elective follow-up endoscopies with biopsies were followed up with elective endoscopic procedures at 6 and 12 months to rule out *H pylori* reinfection.

STUDY DESIGN

Subjects reported for the procedures at 9 AM after a 12-hour fast. Intravenous sedation was given, and standard upper GI endoscopy was performed with a forward-viewing videoscope (Olympus CE 0197; Opto-Electronics Co Ltd, Tokyo, Japan) for evaluation of any macroscopic abnormalities. Simultaneously, 3 biopsy specimens were obtained from the antral region within 2 cm of the pyloric

Raynaud phenomenon and migraine) and with some autoimmune conditions such as Sjogren syndrome.

Until now, no attempt has been made to investigate the prevalence of *H pylori* in glaucoma patients. Only recently, Kountouras and associates reported a higher prevalence of *H pylori* in Greek patients with open-angle glaucoma (OAG) than in age-matched controls, suggesting for the first time an association between *H pylori* infection and glaucoma in this ethnic cohort. Demonstrating the association of *H pylori* and glaucoma and proving the benefit of eradicating *H pylori* in the clinical course of the disease may have a major impact on treatment. Nevertheless, before antibiotic therapy for *H pylori* infection becomes an established step in the management of chronic OAG, sufficient evidence must be provided that glaucoma
ring and 3 from the corpus. A biopsy specimen from each site was used for rapid urease slide testing for \textit{H. pylori} infection (CLOtest; Delta West, Draper, Utah), and the other 2 biopsy specimens were placed in 10% formalin and submitted for histologic examination. Before endoscopy, venous blood was drawn from each patient for serologic testing for \textit{H. pylori} IgG antibodies. Serum samples were stored at $-20^\circ C$ for analysis within 20 to 23 days for \textit{H. pylori} IgG antibodies by using an enzyme-linked immunosorbent assay technique (Elias, Osceola, Wis). Simultaneously, saliva samples were also collected in sterile tubes for rapid urease activity testing. To prevent contamination of specimens from different sites, biopsy specimens from each site were taken with a fresh pair of sterile forceps. The forceps were wiped with alcohol on withdrawal from the endoscope to remove any organism that might have been present in the biopsy channel. Endoscopes were sterilized between procedures according to standard guidelines.\textsuperscript{14}

\textbf{BIOPSY AND SALIVA UREASE TESTS}

Each biopsy specimen and saliva sample was placed in a tube containing 0.5 mL of 10% urea in deionized water to which had been added 2 drops of 1% phenol red as a pH indicator (CLOtest). The biopsy specimen test was read at 5 minutes, 1 hour, 3 hours, and 24 hours and was considered positive if the indicator changed from yellow to red at any time. The saliva sample test was read at 5 minutes, 1 hour, and 3 hours.\textsuperscript{12,13}

\textbf{HISTOPATHOLOGIC ANALYSIS}

All specimens were stained with hematoxylin-eosin and Cre-zyl fast violet and/or Giemsa stain (for detection of \textit{H. pylori} organisms). The presence of gastritis was classified in accordance with the Sydney System and included assessment of atrophy grade, chronicity, activity, and intestinal metaplasia on a scale of 0 (absent) to 3 (high), as previously reported.\textsuperscript{12} In particular, intestinal metaplasia was evaluated with Alcian blue stain in addition to hematoxylin-eosin. The same experienced pathologist, masked to the other determinants of \textit{H. pylori} status and to the patients’ group, assessed all specimens.

\textbf{\textit{H. pylori} SEROLOGIC TESTING}

\textit{Helicobacter pylori} serologic status was determined by using a commercial enzyme-linked immunosorbent assay kit (Elias). The manufacturer’s recommended cutoff value of 10 U/mL for \textit{H. pylori} IgG, validated in our laboratories, was used to define patient serologic findings as positive or negative. The diagnosis of \textit{H. pylori} infection was based on histologic findings. In particular, \textit{H. pylori} infection was assumed when active gastritis with bacteria of typical shape was found histologically. Other parameters used were positive CLOtest findings (biopsy specimens and saliva) and \textit{H. pylori} IgG serologic results.

\textbf{TREATMENT OF \textit{H. pylori} INFECTION}

To treat \textit{H. pylori} infection, a 1-week course of omeprazole (20 mg twice a day), clarithromycin (500 mg twice a day), and amoxicillin (1 g twice a day) was given followed by 20 mg of omeprazole daily for 1 month. The patients completed a questionnaire to record the adverse effects occurring during treatment and their compliance with the therapy. The adverse effects were recorded as absent, mild, moderate, or severe. Compliance was evaluated by counting tablets and capsules after therapy: good compliance was ensured when the patient had taken more than 90% of the tablets and capsules.

\textbf{FOLLOW-UP SCHEME}

Success of the \textit{H. pylori} eradication regimen was evaluated by control endoscopy at least 8 weeks after cessation of therapy, and we considered a patient to be \textit{H. pylori} negative if both histologic and the rapid urease test results were negative. Exclusion of \textit{H. pylori} reinfection was determined in patients with peptic ulcer who underwent repeated elective follow-up endoscopies with biopsies within 1 year. Gastricum parameters were prospectively recorded at baseline and after 1 and 2 years of follow-up with the same topical medication regimen. The ophthalmologists treating the patients in this study were masked to the \textit{H. pylori} status of these patients.

The follow-up study population was classified into 3 glaucoma groups: patients for whom \textit{H. pylori} treatment was successful (group A); those for whom eradication of \textit{H. pylori} had failed (group B); and those who were \textit{H. pylori} negative at baseline (group C).

\textbf{STATISTICAL ANALYSIS}

The prevalence of \textit{H. pylori} and respective 95% confidence intervals (CIs) were calculated at 3 months after eradication treatment. For the patients’ age (years), the Mann-Whitney U test was used, whereas for sex, the Fisher exact test was applied. The latter test was also used to assess the progress of the various upper GI endoscopic and histologic findings 3 months after treatment. An unpaired t test was applied to compare the glaucoma parameters of groups A and B with group C. For all glaucoma parameters (intraocular pressure and visual field data [CLV, MD, and SF]), comparisons were made between baseline and after 1 and 2 years of follow-up with the paired t test and 95% CIs of the difference. The paired t test was also applied to compare the \textit{H. pylori} serologic status at baseline with that at 3 months after treatment. Significance was set at $P<.05$.

The patients with glaucoma had a higher prevalence of \textit{H. pylori} infection than controls, as verified by the hist-

\begin{center}
\textbf{RESULTS}
\end{center}

Parameters are positively influenced by the eradication of \textit{H. pylori} infection.

The objective of the present study is to evaluate the effect of \textit{H. pylori} eradication on 2 well-established clinical parameters in glaucoma: intraocular pressure and visual field indices.\textsuperscript{13} We have therefore designed methods to confirm and quantify our hypothesis that \textit{H. pylori} eradication therapy has a beneficial effect on these 2 glaucoma parameters in \textit{H. pylori}–positive patients with glaucoma.
effects. Continued their therapy because of these mild adverse effects. None of the patients discontinued their therapy because of these mild adverse effects. When compared with baseline values (42.6±31.0 U/mL), the mean serum IgG anti–H pylori level was significantly reduced in group A patients at 3-month follow-up (19.6±14.3 U/mL) (P<.001). In group B patients, this parameter had increased at 3-month follow-up (28.5±21.6 U/mL at 3 months vs 25.4±19.4 U/mL baseline; P=.04). In group C patients, who did not receive H pylori eradication therapy, both mean serum IgG anti–H pylori values were below positive-limit levels (7.2±1.6 U/mL at 3 months vs 6.0±1.9 U/mL at baseline; P=.03).

All 5 group A patients with ulcers (2 duodenal and 3 gastric) were endoscopically confirmed to have healed at 3-month follow-up (P=.03; Table 2). In group B, endoscopic parameters and chronic gastritis activity did not show statistical differences between baseline readings and the values at 3 months, although ulcer healing did occur in 2 duodenal ulcers in this group. All 5 patients in group A with peptic ulcer disease who were reexamined 1 year after undergoing the eradication regimen remained free of the infection.

At baseline, comparisons for endoscopic evidence of esophagitis and duodenitis did not reveal significant differences between patients with glaucoma and controls. Patients with glaucoma more often than controls exhibited histologically confirmed antral gastritis (38/41 vs 17/30; P<.001) and peptic ulcer disease (7/41 vs 0/30; P=.01).

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OUTCOME OF GLAUCOMA PARAMETERS

Baseline visual field indices including MD and CLV were significantly lower in group C than in groups A and B (P = .04 for both), whereas no significant difference was observed in short-term fluctuation between these groups. Table 3 and Figures 1, 2, 3, and 4 detail and illustrate the glaucoma parameters in all glaucomatous eyes (n=74) of the 41 patients at baseline and 1 and 2 years after treatment. At the treatment end points selected in the present study (1 and 2 years), a significant improvement was found for all glaucoma parameters in group A compared with baseline readings except for MD at 1 year, the change for which did not reach statistical significance (P = .25). In contrast, glaucoma parameters did not differ or slightly deteriorated statistically from baseline to 1- and 2-year follow-up values in groups B and C.

Glaucomas comprise a group of age-related eye diseases that share common clinical and morphological features. These include an intraocular pressure too high for the health of the eye; progressive, insidious damage to the optic nerve; and visual field loss. It is estimated that more than 3 million Americans and more than 67 million people worldwide have glaucoma. Thus, glaucoma is currently the second leading cause of blindness in the Western world.1,4

Much remains to be learned about glaucoma, not only at the level of pathogenesis but also with regard to its systemic associations and influences. Among the key events in glaucoma are increased outflow resistance at the level of the trabecular meshwork, increased intraocular pressure, and a characteristic optic neuropathy.

### Table 3. Comparison of Mean Intraocular Pressure and Visual Field Parameters for All Glaucoma Cases at Baseline and After 1 and 2 Years of Follow-up*

<table>
<thead>
<tr>
<th>Patient Group†</th>
<th>Mean ± SD Measurement Value</th>
<th>Change From Baseline at 1 Year</th>
<th>Change From Baseline at 2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 1-Year 2-Year MDM (95% CI)</td>
<td>P Value</td>
<td>MDM (95% CI)</td>
</tr>
<tr>
<td>Intraocular Pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (n = 56)</td>
<td>18.91 ± 3.6</td>
<td>17.84 ± 2.3</td>
<td>17.70 ± 2.0</td>
</tr>
<tr>
<td>B (n = 9)</td>
<td>19.00 ± 4.3</td>
<td>18.67 ± 2.6</td>
<td>18.22 ± 1.8</td>
</tr>
<tr>
<td>C (n = 9)</td>
<td>18.56 ± 2.9</td>
<td>18.33 ± 3.0</td>
<td>18.89 ± 2.9</td>
</tr>
<tr>
<td>Short-term Fluctuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>2.44 ± 0.8</td>
<td>2.16 ± 0.9</td>
<td>1.99 ± 0.6</td>
</tr>
<tr>
<td>B</td>
<td>1.94 ± 0.4</td>
<td>2.43 ± 0.6</td>
<td>3.13 ± 1.0</td>
</tr>
<tr>
<td>C</td>
<td>2.01 ± 1.0</td>
<td>2.22 ± 0.8</td>
<td>2.09 ± 1.1</td>
</tr>
<tr>
<td>Corrected Loss Variance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>12.23 ± 15.8</td>
<td>9.93 ± 14.4</td>
<td>8.63 ± 12.3</td>
</tr>
<tr>
<td>B</td>
<td>16.53 ± 25.4</td>
<td>16.91 ± 24.9</td>
<td>22.70 ± 24.3</td>
</tr>
<tr>
<td>C</td>
<td>2.77 ± 3.3</td>
<td>3.03 ± 3.0</td>
<td>1.89 ± 1.0</td>
</tr>
<tr>
<td>Mean Defect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>3.43 ± 5.2</td>
<td>3.08 ± 4.6</td>
<td>2.63 ± 4.6</td>
</tr>
<tr>
<td>B</td>
<td>5.74 ± 5.8</td>
<td>4.82 ± 4.9</td>
<td>4.62 ± 4.8</td>
</tr>
<tr>
<td>C</td>
<td>0.56 ± 1.4</td>
<td>0.38 ± 1.1</td>
<td>0.8 ± 1.1</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, all data are decibels (dB). MDM indicates mean difference of the means; CI, confidence interval.
†Group A includes only patients in whom Helicobacter pylori was successfully eradicated; group B, patients in whom the H pylori eradication regimen was unsuccessful; and group C, H pylori-negative patients at baseline; n indicates the number of eyes treated.

Figure 1. Mean intraocular pressure at baseline and 1 and 2 years after treatment in patients for whom Helicobacter pylori treatment was successful (group A); those for whom eradication of H pylori had failed (group B); and those who were H pylori negative at baseline (group C). Error bars indicate SD.

Figure 2. Mean short-term fluctuation at baseline and 1 and 2 years after treatment in patients for whom Helicobacter pylori treatment was successful (group A); those for whom eradication of H pylori had failed (group B); and those who were H pylori negative at baseline (group C). Error bars indicate SD.
The only way to prevent visual loss with glaucoma is early diagnosis and treatment. At the present time, glaucoma therapy entails decreasing aqueous humor production, increasing fluid drainage, or a combination of these 2 using medical, laser, or surgical means. This approach, however, treats only a risk factor (elevated intraocular pressure) and not the disease per se and thus fails to address the events that lead to the elevated intraocular pressure. A far more rational management of glaucoma in the future may be to direct our therapeutic interventions to the risk factors leading to glaucomatous neuropathy. However, appropriate management of glaucoma requires a better understanding of the pathogenetic mechanisms involved.

As knowledge of glaucoma has accumulated, ophthalmologists have increasingly focused on prevention of the initial events that lead to optic nerve damage. Important in determining who will contract glaucoma are a number of risk factors, of which raised intraocular pressure is the best known. Several of these risk factors, such as advancing age and family history, are not modifiable. However, other risk factors may be modifiable, and their elimination may help to decrease incidence of blindness from glaucoma. Significantly, the populations of patients with glaucoma have a higher prevalence of systemic conditions such as arterial hypertension, obesity, and diabetes. To date, the increased prevalence of glaucoma in patients with these conditions has not been elucidated. Consequently, when the ophthalmologist treats glaucoma, he or she is treating a patient more likely to have, or be at greater risk for developing, vascular disorders. In addition, the most widely prescribed medicine to treat glaucoma (timolol, a topical β-blocker) may adversely affect serum lipid levels. Thus, understanding how systemic disorders adversely affect glaucoma risk, as well as the effect of treatment of systemic conditions on glaucoma course and prognosis, may lead to better overall care of the patient with glaucoma.

In the first part of this study, by documenting a higher prevalence of \textit{Helicobacter pylori} in an OAG cohort than in an age- and sex-matched control group, we established for the first time a significant relationship between \textit{Helicobacter pylori} infection and glaucoma in a Greek ethnic cohort. The \textit{Helicobacter pylori} infection was determined by histologic detection of organisms in mucosal biopsy specimens, which is considered the gold standard for the diagnosis of this infection. The \textit{Helicobacter pylori} prevalence of our control group is similar to that reported by other investigators who used serodiagnostic assay to evaluate Greek cohorts and other ethnic populations.

It is worthwhile to consider whether the rate of \textit{Helicobacter pylori} infection in the control group has been negatively influenced by the coexistence of anemia. There is no evidence to suggest that anemia protects against development of \textit{Helicobacter pylori} infection. Anemic controls have been used before, and the frequency of \textit{Helicobacter pylori} infection in the anemic control group matches that of the general population in Greece and that reported in other ethnic groups. Furthermore, it is unlikely that individuals with iron-deficiency anemia are protected against \textit{Helicobacter pylori} infection because it is thought that the infection is actually associated with iron- and/or vitamin B\textsubscript{12} deficiency anemia. In addition, eradication of \textit{Helicobacter pylori} infection may be associated with reversal of iron and/or vitamin B\textsubscript{12} deficiency and improvement of anemia.

In part 2 of the present study, we obtained an acceptable eradication rate of 83\% by using a triple eradication regimen of omeprazole, clarithromycin, and amoxicillin for 1 week, which is standard practice in Europe. Similar eradication rates have been achieved by others. Moreover, recurrence of duodenal and gastric ulcers was prevented after a successful \textit{Helicobacter pylori} eradication regimen for up to 1 year, findings that have also been reported for long-term follow-up periods.

The present study established that patients in whom \textit{Helicobacter pylori} was successfully eradicated (group A) showed a statistically significant reduction in intraocular pressure at both clinical end points (1 and 2 years after treatment). This was not the case in groups B and C, despite the fact that all groups were maintained on the same antiglaucoma therapy they received at baseline. Thus, it seems that \textit{Helicobacter pylori} eradication was beneficial for the intraocular pressure control in these patients. Although a reduction of 1.2 mm Hg may not seem clinically significant (as opposed to statistically significant), we should...
bear in mind the progressive nature of glaucoma and the fact that all patients were maintained on the same regimen for 2 years. Longer-term follow-up is required to validate the beneficial effect of *H pylori* eradication therapy.

Results of the present study suggest that eradication therapy may somehow improve the outflow facility of the eye. It should be noted, however, that the numbers of patients in groups B and C were small, and it may not, therefore, be possible to draw definitive conclusions. Future studies are needed to focus on the influence of *H pylori* in the outflow system of the eye. It is conceivable that *H pylori* induces the synthesis of various mediators (eg, cytokines), which may be detrimental to the outflow system of the glaucomatous eye. A fruitful line of future investigation would be comparison of the aqueous humor of patients with glaucoma who test positive for *H pylori* with those who test negative for the infection.

A similar improvement occurred in visual field data (mean SF and CLV at 1 and 2 years’ follow-up). These results in group A are of interest because it is unusual for these parameters to improve over time. It should be noted that these changes occurred while patients were maintained on the same glaucoma regimen. Group B patients, on the other hand, showed a slight deterioration in SF and CLV mean values after 2 years of follow-up. These findings clearly suggest that patients in group A did better than those in group B over a period of 2 years. It is reasonable to hypothesize that it was the *H pylori* eradication that improved the parameters of these patients. These results are encouraging and suggest that possibly *H pylori* eradication should be attempted in patients with glaucoma. However, before this strategy becomes established practice, further evidence from large-scale prospective trials in various ethnic groups is needed to confirm our findings.

With regard to group C patients (*H pylori* negative at baseline), it is interesting to note that all baseline visual field indices were approximately within upper normal limit values and, in particular, 2 baseline visual field indices (MD and CLV) were significantly lower than in groups A and B. In addition, all glaucoma parameters showed a slight worsening over time, although these changes were not statistically significant. We do not know whether these observations will persist or progress over a longer period of follow-up. Because of the small number of glaucoma cases included in this group, future studies are needed to elucidate the natural course of *H pylori*–negative patients.

It should be noted that local administration of antiglaucoma drops results in systemic absorption through the nasal mucosa. It is known, for example, that within the upper GI tract, prostaglandins seem to heal ulcers by secretory inhibition rather than “cytoprotective” actions. Therefore it is conceivable that latanoprost treatment (a prostaglandin analogue) may have influenced slightly the alimentary tract by inducing minor ulcer healing activity via inhibition of acid secretion. Timolol, a nonselective β-adrenoreceptor antagonist, is known to have failed to protect against ethanol-induced gastric lesions and is not believed to meaningfully affect the GI tract. Pilocarpine has been known to affect GI motility, and potential effects on the GI tract include prolonged salivary secretion, diarrhea, and acid secretion. Swallowed saliva secretion induced by pilocarpine might neutralize, at least in part, acid output. However, only 1 patient received pilocarpine in our group. We think that it is the administration of omeprazole (strong proton pump inhibitor under all known stimuli) that was the major contributor to ulcer healing in *H pylori*–positive and *H pylori*–negative patients.

The question arises exactly how *H pylori* infection influences the pathophysiology of glaucoma. The following possible mechanisms are suggested. *Helicobacter pylori* may promote the formation of L- and P-selectin–dependent platelet-leukocyte aggregates in murine gastric microvessels, and *H pylori* may also induce platelet activation and aggregation and atherosclerosis. This phenomenon may play a part in the proposed relationship between *H pylori* and glaucoma, in which platelet activation and aggregation play a relevant pathophysiological role.

Alternatively, release of large amounts of variable proinflammatory and vasoactive substances such as cytokines (interleukin [IL] 1, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor α, and interferon γ), eicosanoids (leukotrienes and prostaglandins), and acute-phase proteins (fibrinogen and C-reactive protein) following gastric colonization by *H pylori* may be involved in a number of vascular disorders thought to be associated with the bacterium. These disorders include Raynaud phenomenon, idiopathic migraine, coronary heart disease, and now possibly glaucoma (a similar cytokine profile seems to be involved in the pathogenesis of glaucoma disease). Increased endothelin-1 (a potent constrictor of arterioles and venules), nitric oxide, and inducible nitric oxide synthase levels in peptic ulcer disease associated with *H pylori* infection suggest that the resulting microcirculatory disturbance may be a major factor in the pathogenesis of local gastric mucosal ulceration and systemic damage, including glaucoma. Indeed, endothelin–1–induced vasoconstriction of the anterior optic nerve vessel and modulation of vascular tone in the ophthalmic artery by nitric oxide may be involved in the pathogenesis of glaucomatous damage. *Helicobacter pylori* can coagulate blood by stimulating mononuclear cells. Under bacterial stimulation, mononuclear leukocytes produce a tissue factor–like procoagulant activity that, through the extrinsic pathway of blood coagulation, converts fibrinogen into fibrin. Thus, apart from its effect on fibrinogen level, *H pylori* has another activity (blood clotting), which might contribute to the pathogenesis of cardiovascular disorders or glaucoma. Other factors such as the development of cross mimicry between endothelial and *H pylori* antigens and excessive production of reactive oxygen metabolites and circulating lipid peroxides, which are associated with cardiovascular risk in patients with *H pylori* infection, may also be involved indirectly in glaucoma pathophysiology. However, further studies are needed to elucidate these points.

Accepted for publication October 2, 2001.

Corresponding author and reprints: Jannis Kountoutras, MD, PhD, 8 Fanariou St, Byzantio, Thessaloniki 55133, Thessaloniki, Macedonia, Greece (e-mail: jannis@med.auth.gr).
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