The evaluation of the effect of Helicobacter pylori *infection on choroidal thickness*

Cemile Üçgül Atılgan[1], Ahmet Yozgat[2], Pınar Kösekahya[1], Mehtap Çağlayan[3], Selam Yekta Şendul[4], Nilüfer Berker[1], Zeynep Altıparmak[1], Emin Altıparmak[2], Pelin Yılmazbaş[1]

[1]Department of Ophthalmology, Ulucanlar Eye Education and Research Hospital, Ankara, Turkey
[2]Department of Gastroenterology, Ankara Numune Training and Research Hospital, Ankara, Turkey
[3]Department of Ophthalmology, Mardin State Hospital, Mardin, Turkey
[4]Department of Ophthalmology, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, Turkey

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ABSTRACT

Background/Aims: *To evaluate the effects of* Helicobacter pylori *infection on choroidal thickness (CT) using enhanced depth imaging spectral domain-optical coherence tomography (SD-OCT).*

Materials and Methods: *A total of 63 right eyes of 63 patients who tested positive for* H. pylori *(Group 1) and 46 right eyes of 46 patients who tested negative for* H. pylori *(Group 2) were evaluated. The CTs at the subfoveal area and at 1 mm ranging up to 3 mm from the fovea at the nasal and temporal quadrants were measured and compared. After the eradication of* H. pylori*, the CT values were also compared with the pre-eradication values in 38 patients.*

Results: *The mean age of patients was 43.6±9.5 years in Group 1 and 46.6±11.5 years in Group 2 (p=0.13). Differences in CT values between Groups 1 and 2 before and after* H. pylori *eradication were not statistically significant (p>0.05 for all values).*

Conclusion: *The CT values of* H. pylori *positive and* H. pylori *negative patients were similar. Eradication of* H. pylori *infection appears to have produced no change in short-term CT.*

Keywords: *Choroidal thickness, enhanced depth imaging spectral domain-optical coherence tomography, gastric infection,* Helicobacter pylori

INTRODUCTION

Helicobacter pylori is a spiral-shaped, Gram-negative bacterium that adheres to the gastric epithelium and lives within or beneath the gastric mucous layer. It is one of the most frequently occurring bacteria worldwide and is associated with several digestive pathologies (1). Recent interest in the extradigestive pathologies of *H. pylori*, such as vascular, hematopoietic, central and peripheral nervous systems, autoimmune, dermatological, rheumatologic, and eye diseases, has been steadily increasing (2,3). There are also studies linking *H. pylori* to some eye diseases, such as blepharitis, glaucoma, and idiopathic central serous chorioretinopathy (ICSCR) (4-6). ICSCR is a posterior segment disease that is characterized by neurosensorial retinal detachment. It is a self-limiting disease with a good prognosis. However, it may cause visual problems when it affects the macular region of the retina. It occurs more frequently in individuals with Type A personality (7). In recent years, *H. pylori* has been frequently incriminated in the etiology of ICSCR (6,8,9). Some studies have also demonstrated improvement in ICSCR via the eradication of *H. pylori* infection (10,11). Long-term *H. pylori* infection causes occlusive arterial pathologies, such as coronary artery disease (CAD) and atherosclerosis, by secreting various vasoactive and proinflammatory cytokines (12-14). The relationship between *H. pylori* and ICSCR is also evoked by the atherosclerotic effects of *H. pylori* on choroidal vessels.

The choroid layer of the eye, which primarily consists of vascular structures, is one of the most vascularized organs in the body (15). Choroidal thickness (CT) can increase or decrease in response to vasodilatation and vasoconstriction in its vascular structures. It can be manually measured with the enhanced depth imaging (EDI) mode of spectral domain-optical coherence to-

ORCID IDs of the authors: *C.Ü.A. 0000-0002-8875-1567; A.Y. 0000-0002-4414-9929; P.K. 0000-0002-7493-5779; M.Ç. 0000-0003-4878-824X; S.Y.S. 0000-0002-0934-1026; N.B. 0000-0002-9706-5139; Z.A. 0000-0002-0379-7938; E.A. 0000-0001-8900-9498; P.Y. 0000-0002-3995-2530.*

Corresponding Author: ***Cemile Üçgül Atılgan; cemileucgul@ymail.com***
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mography (SD-OCT) and obtained through an increase in the wavelength of light used in SD-OCT (16). We hypothesized that *H. pylori* infection could change CT as a consequence of possible atherosclerotic effects on choroidal vessels. The aim of the present study was to evaluate the effects of *H. pylori* infection on CT using the EDI mode of SD-OCT.

MATERIALS AND METHODS

This prospective observational study comprised 109 eyes of 109 patients. Written informed consent was obtained from patients after approval from the Non-Drug Clinical Research Ethics Advisory Committee.

Patients were divided into the following two groups: Group 1 consisted of 63 patients who tested positive for *H. pylori* (63 eyes) and Group 2 consisted of 46 controls who tested negative for *H. pylori* (46 eyes) and who were similar to Group 1 participants in terms of age and gender. The exclusion criteria of patients included a history of intraocular surgery; media opacities, such as cataract and band keratopathy; inflammation (e.g., uveitis and vasculitis); glaucoma; age <18 or >60 years; refraction error more than −1/+1 diopters; active or previous history of ICSCR; sildenafil citrate and/or corticosteroid usage; cigarette and/or alcohol addiction; and any systemic disorders. The examination for *H. pylori* infection was on the basis of the gastroscopy and histological examinations of the obtained tissue specimens. Gastroscopy was performed after induction of sedation with midazolam (Dormicum; Roche) via intravenous administration at a dosage of 3-5 mg according to the weight of the patient. Next, a spray of xylocaine was applied to the nasopharynx. A minimum of four biopsy specimens were then retrieved from the antrum and the body of the stomach (17).

Hematoxylin and eosin (H&E) staining was used for the histological detection of *H. pylori* bacteria. However, in some cases in which *H. pylori* could not be entirely detected with H&E, immunohistochemical tests were also used as an ancillary test.

All patients underwent routine ophthalmic examinations, including best-corrected visual acuity (BCVA) to dismiss patients with impaired vision, corrected intraocular pressure (IOP) to exclude patients with glaucoma, and anterior and posterior segment examination with slit-lamp biomicroscopy to exclude any eye disorders. Central corneal thickness was measured with an ultrasound pachymetry device for calculating corrected IOP. The EDI mode of SD-OCT (Heidelberg Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) was used for obtaining the choroidal measurements. In each case, after recording the spherical and cylindrical refraction values in the OCT device, a single individual measured CT at the subfoveal area and at 1 mm ranging up to 3 mm from the fovea at the nasal and temporal quadrants by keeping the signal strength index greater than 50 after converting the color table of OCT images into black-and-white mode and modifying the brightness on the Heidelberg Eye Explorer Program to more clearly distinguish choroidal vascular layers (Figure 1). An average was calculated after all measurements were repeated three times. All measurements were obtained during the morning period (from 8:30 a.m. to 11 a.m.) to avoid diurnal variation. The CT values were manually measured from the bottom of the hyper-reflective line of the retinal pigment epithelium to the choroidal-scleral border (Figure 1).

Patients in Group 1 were treated using a 14-day conventional antimicrobial quadruple treatment regimen (tetracycline 500 mg four times a day, metronidazole 500 mg three times a day, pantoprazole 40 mg twice a day, and two tablets of colloidal bismuth subcitrate 300 mg twice a day) for *H. pylori* eradication (18). One month after the end of treatment, *H. pylori* antigen analyses were performed on the stool specimens of the patient (Alcon Laboratories, Inc.). All routine ophthalmic examinations were repeated on 38 eyes of 38 patients who tested negative for *H. pylori*. The remaining 25 patients did not come to the gastroenterology clinic for control examinations after eradication therapy.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 17.0 for Windows (SPSS Inc.; Chicago, IL, USA). The Shapiro-Wilk test was used for determining normal distribution. The Mann-Whitney U test was used for comparing the parameters of the *H. pylori* positive and negative groups. The paired sample t-test and Wilcoxon test were used for comparing the before and after eradication parameters of each patient. A p-value of <0.05 was considered statistically significant for all tests.

RESULTS

There were no statistically significant differences between the groups in terms of age, gender, BCVA, IOP, or pachymetry (p=0.13, p=0.78, p=0.31, p=0.49, and p=0.95, respectively). Table 1 shows the demographic and clinical characteristics of all patients.

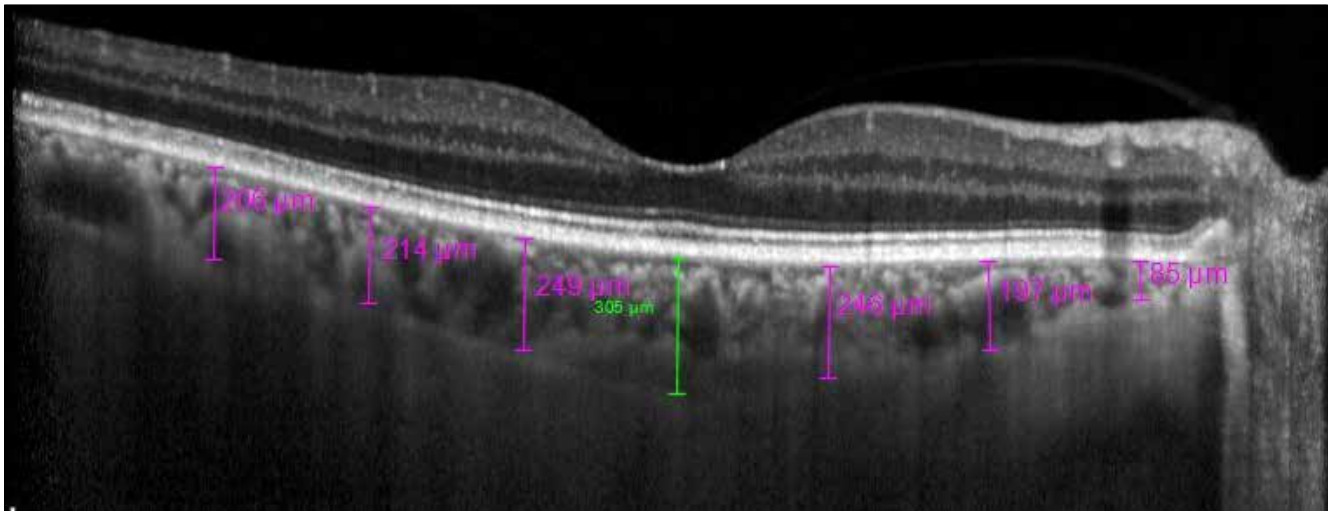

Figure 1. Choroidal thickness measurements of a patient. Green caliper shows the choroidal thickness at the subfoveal area; purple caliper shows the choroidal thicknesses at 1 mm ranging up to 3 mm from the fovea at the nasal and temporal quadrants from the basal edge of the retinal pigment epithelium to the inner scleral border

Table 1. Demographic and clinical characteristics of *Helicobacter pylori* positive (Group 1) and negative patients (Group 2)

Characteristics	HP positive (Group 1)	HP negative (Group 2)	p
Number of patients (eyes)	63 (63 eyes)	46 (46 eyes)	
Age, mean±SD (range)	43.6±9.5 (23-60)	46.6±11.5 (27-60)	0.13*
Gender: Female/Male	39/24	28/18	0.78†
BCVA, mean (range)	0.94 (0.8-1.0)	0.96 (0.8-1.0)	0.31††
IOP, mean±SD (mmHg)	14.45±3.1	14±3.6	0.49††
Pachymeter, mean± SD (µm) 535.3±32	535.6±24.7	0.95*	

HP: *Helicobacter pylori*; SD: standart deviation; BCVA: best corrected visual acuity; IOP: intraocular pressure
Values are expressed as mean±SD (µm)
*Independent samples t test
†Chi-square test
††Mann-Whitney U test

Table 2. Comparison of choroidal thicknesses of *Helicobacter pylori* positive (Group 1) and negative patients (Group 2)

Choroidal Thickness	HP positive (group 1)	HP negative (group 2)	p
	Mean thickness±SD (µm)	Mean thickness±SD (µm)	
Subfoveal	331.57±74.91	358.36±111.07	0.13*
Nasal (1mm)	285.55±73.52	304.0±96.95	0.26*
Nasal (2mm)	228.77±77.2	251.60±98.92	0.17*
Nasal (3mm)	142.28±53.96	169.10±89.13	0.17*
Temporal (1mm)	311.49±73.43	327.89±97.69	0.31*
Temporal (2mm)	282.42±70.34	298.36±93.75	0.31*
Temporal (3mm)	245.90±68.07	270.36±83.45	0.09*

HP: *Helicobacter pylori*; SD: standart deviation
Values are expressed as mean±SD (µm)
Nasal 1, 2, 3 mm: Choroidal thickness at nasal 1, 2 and 3mm away from the fovea
Temporal 1, 2, 3 mm: Choroidal thickness at temporal 1, 2 and 3mm away from the fovea
* Independent t test

Table 3. Comparison of choroidal thickness values before and after *Helicobacter pylori* eradication therapy in *Helicobacter pylori* positive patients (Group 1)

ChoroidalThickness	Before HP Eradication	After HP Eradication	p
	Mean thickness±SD (µm)	Mean thickness±SD (µm)	
Subfoveal	322.97±73.37	329.97±73.82	0.38*
Nasal (1mm)	287.71±76.45	290.84±87.02	0.31*
Nasal (2mm)	236.84±77.92	249.50±92.87	0.15*
Nasal (3mm)	151.86±53.72	154.42±57.6	0.66*
Temporal (1mm)	299.47±65.63	300.05±72.41	0.95*
Temporal (2mm)	267.84±61.00	268.57±68.02	0.93*
Temporal (3mm)	231.89±61.19	236.18±58.50	0.66*

HP: *Helicobacter pylori*; SD: Standart Deviation
Values are expressed as mean±SD (µm)
Nasal 1, 2, 3 mm: choroidal thickness at nasal 1, 2 and 3 mm away from the fovea
Temporal 1, 2, 3 mm: choroidal thickness at temporal 1, 2 and 3 mm away from the fovea
*Wilcoxon test

The nasal and temporal CT values at 1, 2, and 3 mm distances from the fovea and the mean subfoveal CT showed no significant differences between Groups 1 and 2 (Table 2).

Choroidal thickness measurements were repeated in 38 patients who tested negative for *H. pylori* after eradication treatment. No systemic adverse effects of treatment were observed. The nasal and temporal CT values at 1, 2, and 3 mm distances from the fovea and the mean subfoveal CT did not demonstrate significant differences before and after *H. pylori* eradication (Table 3). In addition, the BCVA, IOP, and pachymetry values did not significantly differ before and after eradication treatments (p=0.24, p=0.49, and p=0.41, respectively).

DISCUSSION

Even though more than half of the population is infected with *H. pylori*, only a small number of individuals develop symptomatic diseases, especially those involving the gastrointestinal tract, such as chronic gastritis, peptic ulcer, and gastric cancer. In recent years, the extragastrointestinal effects of *H. pylori* infection have been the subject of several studies. Although *H. pylori* prefers to live in the stomach mucosa, if not treated, it causes strong immunological and inflammatory reactions within the host, causing extragastrointestinal effects, especially atherosclerosis. The relationship between atherosclerosis caused by *H. pylori* and CAD and cerebrovascular and peripheral vascular diseases is well established (19). Several hypotheses have been proposed regarding the link between *H. pylori* infection and atherosclerosis. First, there is a mild inflammatory stimulus caused by *H. pylori* infection. The concentrations of proinflammatory, vasoactive substances, and autoantibodies are increased in the sera of patients with *H. pylori* infection, resulting in atherosclerosis (20). Second, IgG antibodies that emerge in response to *H. pylori* infection are significant factors that lead to endothelial dysfunction (21). Third, *H. pylori* infection increases anti-heat shock protein antibodies and upregulates endothelial adhesion molecules, ultimately inducing ischemia (22).

Since occlusive arterial disease shares some features with ICSCR (e.g., ischemia and Type A personality), *H. pylori* infection is believed to be a potential etiologic factor in ICSCR. ICSCR was defined by Von Graefe in 1866 as an accumulation of subretinal fluid accompanied by serous macular detachment (23). Even though the pathophysiology of ICSCR is not entirely known, the major cause of ICSCR is considered to be choroidal vascular abnormalities. The primary cause of ICSCR is focal occlusion at the choriocapillaris level according to the study by Kitaya et al. (24). Venous congestion originates from this focal occlusion and increases choroidal hyperpermeability (25). Hyperfluorescent areas connected to choroidal hyperpermeability, which is a considerable marker of increased CT, can be seen only during the intermediate stages of ICSCR using indocyanine green angiography (ICGA) (25,26). Therefore, CT is expected to increase only during the intermediate stages of the disease.

Choroidal thickness is known to be thicker in the eyes of patients with ICSCR than in those with healthy eyes because of the widespread presence of large choroidal vessels (27). Chung et al. (27) used EDI SD-OCT for investigat-

ing subfoveal CT together with Haller's and Sattler's layers in ICSCR-affected eyes, in uninvolved fellow eyes, and in the eyes of healthy controls. The researchers found that, rather than Sattler's layer, Haller's layer leads to increased CT in patients with ICSCR, a finding that supports the view that focal occlusion at the level of the choriocapillaris, which is considered to be the primary cause of ICSCR, may not lead to increased CT (27). A recent study reported that the choriocapillaris and CT values of patients with ICSCR are significantly thicker than those of healthy controls in response to increased perfusion pressure in patients with ICSCR connected to transitioning from an upright to a supine position (28). The researchers suggested that the autoregulatory response is presumably better in the choriocapillaris layer than in the Haller's and Sattler's layers that consist of larger blood vessels (28).

Regardless of its etiology, patients with ICSCR tend to spontaneously recover; it is thus difficult to understand whether recovery from ICSCR is a spontaneous, functional recovery or whether it is because of the eradication of *H. pylori* in patients with both ICSCR and *H. pylori*. For determining the true impact of *H. pylori* on CT, we aimed to carry out the present study on healthy eyes. A tendency toward reduction in CT in *H. pylori*-positive patients who have not yet developed ICSCR can be regarded as a predictable result. *H. pylori* may cause the focal occlusion of choriocapillaris and may initially lead to choroidal ischemia. However, if the choroidal hyperpermeability resulting from vessel congestion continues to increase, ICSCR may develop, and increased CT may be noted in the later stages of the disease

One of the limitations of the present study is the short follow-up duration after *H. pylori* eradication. This short duration for the assessment of CT measurements may have caused non-significant differences after *H. pylori* eradication. The second limitation is the stool antigen test, which is used for detecting *H. pylori* eradication. Although the specificity of the stool antigen test is high, antigen excretion may vary over time, and antigens may degrade while passing through the intestines, which can decrease the sensitivity of the test. Third, we could not perform ICGA. ICGA can assess the vascular anatomy of the choroid in detail in addition to EDI SD-OCT. The fourth limitation of the present study is the manual CT measurement, since CT cannot yet be automatically measured.

In conclusion, *H. pylori* infection does not appear to affect CT in the eyes of healthy individuals. However, when *H. pylori* and other concurrent risk factors, such as genetic diversity and host factors (e.g., polymorphisms of cytokines), are combined, it may still be a potential risk factor for ICSCR. Further research with larger numbers of *H. pylori* positive participants should be conducted for evaluating all vascular layers of the choroid using ICGA and OCT angiography in addition to EDI SD-OCT.

Ethics Committee Approval: Ethics Committee Approval has received for this study from the Non-Drug Clinical Research Ethics Advisory Committee.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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