

No Significant Effect of Helicobacter Pylori Eradication on Serum Lipoproteins: CagA Negative Patients May Be an Exception

Helicobacter Pylori Eradikasyonun Serum Lipid Düzeylerine Etkisi Yoktur: CagA Negatif Hastalar İstisna Oluşturabilir

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ABSTRACT

Objective: *Helicobacter pylori* infection is associated with a modified lipid profile, especially lower HDL cholesterol levels. Cytotoxin Associated Gene A (CagA) positive strains with increased inflammation may further deteriorate lipids levels. Therefore, we investigated the effect of *Helicobacter pylori* eradication on serum lipid levels, apolipoproteins, and high sensitive C reactive protein (hsCRP) and its relation with CagA status.

Methods: Fifty-one patients with positive rapid urease test (33 female, 18 male) were enrolled in the study. Seventeen (33%) patients were CagA positive. Serum lipids, apolipoproteins, and hsCRP levels were measured at baseline and 3 months after eradication therapy. According to the urea breath test, patients with successful eradication formed Group 1, and those in whom eradication treatment failed constituted Group 2.

Results: Lipid, apolipoprotein, and hsCRP levels did not change after treatment in Group 2. Serum lipids, Apo-B, and Lp(a), and hsCRP levels were also similar in Group 1 after eradication, whereas Apo-AI levels increased significantly in this group ($p=0.002$). In subgroup analysis, CagA negative, but not CagA positive, patients in Group 1 had increased Apo-AI levels after successful eradication.

Conclusion: With the exception of an isolated increase in Apo-AI levels in CagA negative subjects, eradication of *Helicobacter pylori* does not seem to have a significant effect on the lipid profile. (*Gazi Med J* 2012; 23: 122-5)

Key Words: *H. pylori*, eradication, CagA, serum lipids, hsCRP

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ÖZET

Amaç: *Helicobacter pylori* enfeksiyonu özellikle HDL'de düşme olmak üzere lipid profil değişiklikleri yapabilmektedir. Sitotoksin aracılı gen A (CagA) pozitif şuşlarda, inflamasyon artacağından lipid düzeyi üzerine etki daha belirgin olabilir. Bu nedenle, *Helicobacter pylori* eradikasyonun serum lipid, apolipoprotein ve yüksek duyarlı CRP (ydCRP) üzerine etkisini ve bu durumun CagA ile ilişkisini araştırmayı planladık.

Yöntemler: Hızlı üreaz testi pozitif olan 51 hasta (33 kadın, 18 erkek) çalışmaya alındı. Hastaların 17'sinde (%33) CagA pozitifliği. Serum lipid, apolipoprotein ve ydCRP düzeyleri başlangıçta ve eradikasyon sonrası 3. ayda ölçüldü. Üre nefes testi sonuçlarına göre eradikasyonu başarılı olanlar Grup 1, olmayanlar ise Grup 2 olarak sınıflandırıldı.

Bulgular: Grup 2'de tedavi sonrasında lipid, apolipoprotein ve ydCRP konsantrasyonlarında değişiklik izlenmedi. Grup 1'de lipid, Apo-B, Lp(a) ve ydCRP düzeyleri farklılık göstermezken, Apo-AI seviyesi tedavi sonrasında önceye göre anlamlı olarak yüksek bulundu ($p=0.002$). Alt grup analizlerinde eradikasyon sonrası Apo-AI yükselmesinin CagA pozitif değil, negatif hastalarda izlendiği saptandı.

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Sonuç: Sadece CagA negatif hastalarda izlenen izole Apo-AI artışı haricinde, *Helicobacter pylori* eradikasyonun lipid düzeyi üzerine etkisi yok gibi görünmektedir. (*Gazi Med J* 2012; 23: 122-5)

Anahtar Sözcükler: *H. pylori*, eradikasyon, CagA, serum lipidleri, yüksek duyarlı CRP

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INTRODUCTION

Helicobacter pylori (*H. pylori*), is one of the most common bacterial infections, affecting more than half of the world population. *H. pylori* infection starts in childhood, has a long subclinical period during which it causes gastric inflammation and mucosal damage. *H. pylori* has several virulence factors that trigger a diversity of diseases, varying between gastritis and gastric carcinoma. Cytotoxin Associated Gene A (CagA), a well-known virulence factor, is related to increased inflammation, peptic ulcers and gastric carcinomas (1).

Atherosclerosis is widely accepted to be an inflammatory process. Low grade inflammation, accompanied by increased high sensitive C-reactive protein (hsCRP) levels, predicts cardiac events (2). Trials investigating the association of *H. pylori* with atherosclerosis have led to conflicting results. CagA positive, but not negative, strains seem to be associated with vascular diseases (3). Preliminary studies studying metabolic effects of *H. pylori* infection, documented decreased HDL levels (4). A recent retrospective study that investigated the effect of *H. pylori* eradication on lipid profile showed significantly increased apolipoprotein A and HDL levels (5). We hypothesized that infection with strains positive for CagA, a virulence marker, may additionally impair the lipid profile due to increased inflammation. Therefore, we conducted a prospective study in order to evaluate the effect of eradication of *H. pylori* on serum lipids, apolipoproteins, and hsCRP levels and its relation with CagA status. To the best of our knowledge, this is the first study investigating the metabolic effects of *H. pylori* eradication with regard to CagA status.

METHODS

Fifty-one adult subjects (33 female, 18 male) with dyspeptic complaints and positive rapid urease tests on upper gastrointestinal endoscopies were enrolled in the study. Patients were excluded if they were on a diet, receiving bismuth, antacids, H2 receptor antagonists, proton pump inhibitors, or anti-hyperlipidemic drugs. Patients with familial hyperlipidemia, pregnancy, liver or renal failure, nephrotic syndrome, hypothyroidism, diabetes mellitus, connective tissue disorders, pernicious anemia and history of gastric surgery were also excluded. The study protocol was approved by the local ethics committee of our institution. Written informed consent was obtained from every subject.

For detection of *Helicobacter pylori*, endoscopic biopsy specimens from the gastric antrum and corpus were taken for the rapid urease test (HPfast, GI Supply, U.S.A.). Fasting blood samples for lipid profile, apolipoproteins, and hsCRP were taken before and after eradication therapy. The medical history of patients including hypertension, smoking, and alcohol consumption were recorded. The patients were given Lansoprazol 30 mg, Amoxicillin 1g, clarithromycin 500 mg p.o. bid for 14 days. Subsequently, the patients remained on Lansoprazol 30 mg/day for two more weeks. The success of eradica-

tion was verified by the 14C urea breath test (Helicap, Noster System, Sweden) on follow-up visit, 3 months after treatment.

Total cholesterol, HDL-cholesterol (HDL), and triglycerides were measured using Aeroset autoanalyzers (Abbott, U.S.A.). VLDL and LDL levels were calculated according to Friedewald's equation. Apolipoprotein AI (Apo-AI), Apolipoprotein B (Apo-B), Lipoprotein(a) [Lp(a)] and hsCRP levels were measured by using BN ProSpec (Dade-Behring, Germany) nephelometry. Serum CagA immunoglobulin A levels were detected with antisera from Dia-Pro (Italy) by an immunoassay method. Results were given as arbitrary units per mL (arb/mL), CagA levels greater than 5 arb/mL were considered as positive.

Statistical analysis was performed using SPSS software version 11.5. Continuous variables were expressed as mean±standard deviation (SD), and categorical variables were summarized as counts and percentages. Data was tested for normal distribution. Paired t-test and Mann-Whitney U test were used for the univariate analysis of the continuous variables, where appropriate, and the χ^2 test for the categorical variables. P values <0.05 were considered as statistically significant.

RESULTS

Fifty-one patients (18 male, 33 female) were enrolled in the study. Follow-up examinations were made 16.4±6 weeks after eradication therapy. According to the urea breath test results, the patients with successful eradication were assigned to Group 1 and those in whom eradication was not successful formed Group 2. Demographic characteristics, endoscopic diagnosis and CagA seropositivity did not differ between the two groups (Table 1). None of the patients had a history of alcohol consumption.

Serum lipid and hsCRP levels in Group 2 did not differ at baseline and post-treatment. Serum lipids, Apo-B, Lp(a) and hsCRP levels

Table 1. Demographic characteristics of study participants

	Group 1	Group 2	p Value
Gender (Female/Male)	21/13	12/5	0.53
Age (years, mean±SD)	39.5±9.8	37.2±7.2	0.41
Hypertension, n (%)	2 (5.9%)	2 (5.9%)	1.00
Smoking, n (%)	12 (35.3%)	5 (29.4%)	0.67
Cytotoxin Associated Gene A Seropositivity, n (%)	11 (32.4%)	5 (29.4%)	0.83
Endoscopic Diagnosis			
Antral Gastritis, n (%)	15 (44.1%)	8 (47.1%)	0.84
Pangastritis, n (%)	16 (47.1%)	8 (47.1%)	1.00
Duodenal ulcer, n (%)	3 (8.8%)	1 (5.9%)	1.00
Group 1: patients with successful eradication, Group 2: patients with failed eradication			

also remained similar after eradication in Group 1, whereas Apo-AI levels increased significantly in response to eradication treatment ($p=0.002$, Table 2).

When the effect of CagA seropositivity on serum lipid and hsCRP levels was taken into account in Group 1, only the CagA seronegative subgroup had increased Apo AI levels after successful eradication ($p=0.01$), whereas, in the CagA seropositive subgroup baseline and post treatment, Apo-AI levels were similar.

DISCUSSION

The association of *H. pylori* with atherosclerosis has been sought for several years. The largest population based study, involving approximately 60.000 subjects, evaluated the association of *H. pylori* seropositivity with atherosclerosis risk factors. This study revealed increased total cholesterol, LDL and Apo-B levels and decreased HDL and Apo-A levels in patients seropositive for *H. pylori*. No significant correlation between *H. pylori* antibodies and hsCRP was found. Interestingly, the differences in lipid profile and hsCRP was not related to the presence of peptic ulcer in this study, except for HDL levels (6). Thus, lipid profile changes in *H. pylori* infection may take place without overt inflammation.

CagA has been shown to increase gastric inflammation and local complications (7). Recently, several studies have focused on the effect of CagA on the inflammatory atherosclerotic process. Mayr et al. (8) evaluated the effect of *H. pylori* and CagA seropositivity on carotid intima media thickness in a prospective, population-based study. Carotid intima media thickness absolute values or changes over time were significantly increased only in CagA seropositive subjects after a five-year follow-up period. Kowalski revealed *H. pylori* DNA in atherosclerotic coronary plaques of CagA seropositive patients (9). Cross-reaction between antiCagA and blood vessel antigens has also been documented (10). Thus CagA may be a vascular risk factor during *H. pylori* infection.

Two studies have investigated the association of CagA seropositivity with lipid profile changes so far. Parente et al. (11) reported no differences in lipid profile, whereas Chimenti et al. (12) demonstrated increased total cholesterol, LDL and Lp(a) levels in CagA seronegative subjects.

Current medical literature contains little data regarding the effect of *H. pylori* eradication on lipid and hsCRP levels. De Luis et al.

(13) demonstrated increased HDL, decreased Lp(a) and CRP after eradication in type I diabetic patients. A retrospective study, including 87 patients with duodenal ulcer revealed increased ApoA and HDL (5). Similarly, Kanbay et al. (14) showed decreased CRP and increased HDL concentrations following eradication.

In our study, with the exception of Apo-AI as described below, serum lipid and apolipoprotein levels remained unchanged after successful eradication treatment.

Interestingly, we demonstrated increased Apo-AI levels in response to successful *H. pylori* eradication only in the CagA seronegative group. We may speculate that CagA, a virulence factor, may interfere with the response of Apo-AI levels to eradication treatment. Alternatively, we may hypothesize that the lipid profile is somewhat more impaired in CagA seronegative subjects, so their response to *H. pylori* eradication is more prominent (12). However, as the sample size is relatively small, the raised Apo-AI levels in CagA negative subjects may also be due to chance.

Inflammatory response elicits cytokine secretion. Tumor necrosis factor (TNF- α) can inhibit lipoprotein lipase (LPL) activity by decreasing synthesis (15). Increased TNF- α concentrations accompanied with insulin resistance have been observed in cancer, trauma and infections (16). Thus, infections can decrease HDL by increasing TG levels.

The subjects in our study were young adults with a low cardiovascular risk profile. In accord with preceding studies, significantly increased Apo AI was observed after successful *H. pylori* eradication. This effect was observed only in the CagA seronegative subgroup. In contrast to previous studies, a significant rise in hsCRP and HDL levels after successful eradication was not observed. Contrary to a preceding study that showed increased Apo A and HDL levels after successful *H. pylori* eradication in patients with duodenal ulcers, only four patients had duodenal ulcers in our group (5). This difference in duodenal ulcer incidence and relatively small study population size might be the reasons why a significant rise in HDL levels after successful eradication was not observed in our study.

Salgado et al. (17) tested the ability of extracted *H. pylori* lipopolysaccharides (LPS) to stimulate TNF- α synthesis, induce mitogenic activity and spleen growth. Based on these characteristics, two different LPS types were isolated; one with low and the other with high biological activity. High activity LPS was associated with increased epithelial

Table 2. Serum lipid, apolipoprotein and hsCRP levels at baseline and after *H. pylori* eradication therapy in patients with successful eradication (Group 1) and unsuccessful eradication (Group 2)

	Group 1			Group 2		
	Baseline	Post-treatment	p Value	Baseline	Post-treatment	p Value
TC (mg/dL)	177.0 \pm 32.0	174.4 \pm 32.0	0.441	189.0 \pm 31.2	194.2 \pm 39.3	0.345
HDL (mg/dL)	46.1 \pm 8.2	47.0 \pm 7.4	0.448	48.8 \pm 12.7	48.8 \pm 10.0	0.977
LDL (mg/dL)	120.1 \pm 56.0	108.5 \pm 28.1	0.209	118.3 \pm 26.0	118.5 \pm 26.2	0.966
TG (mg/dL)	96.8 \pm 49.0	100.1 \pm 61.0	0.214	109.7 \pm 48.8	133.8 \pm 101.6	0.116
Apo-AI (mg/dL)	126.9 \pm 21.3	134.6 \pm 18.8	0.002	127.2 \pm 24.2	129.8 \pm 22.0	0.512
Apo-B (mg/dL)	84.4 \pm 26.2	87.4 \pm 23.1	0.421	98.0 \pm 27.4	96.5 \pm 21.5	0.592
Lp(a) (mg/dL)	27.0 \pm 26.6	28.2 \pm 29.3	0.103	27.7 \pm 20.4	26.8 \pm 20.5	0.581
hsCRP (mg/dL)	0.67 \pm 2.01	0.25 \pm 0.32	0.234	0.33 \pm 0.59	0.15 \pm 0.18	0.188

Apo-AI: Apolipoprotein AI, Apo-B: Apolipoprotein B, HDL: High density lipoprotein, hsCRP: High sensitive C reactive protein, Lp(a): Lipoprotein(a), LDL: Low density lipoprotein, TC: Total cholesterol, TG: Triglycerides

inflammation and damage. Interestingly, they were isolated from low virulence CagA negative strains. Therefore, CagA does not seem to be the single virulence factor of *H. pylori* infection and may not be the mediator of lipid profile changes during *H. pylori* infection.

Apo-AI has antioxidant and anti-inflammatory properties and plays a central role in reverse cholesterol transport. These properties have provided the rationale to measure Apo-AI levels for assessment of cardiovascular risk (18). Apo-AI has been shown to be a stronger predictor of coronary heart disease than HDL in a cohort study and to be an independent risk factor in patients at low risk (19, 20).

To the best of our knowledge this is the first study in current medical literature studying the impact of *H. pylori* eradication on lipid profile, apolipoproteins, and hsCRP with regard to CagA status.

Study Limitations

The main limitation of this study is the relatively small sample size. The lack of a control group which consists of *H. pylori* negative subjects may also be considered as a limitation.

CONCLUSION

With the exception of an isolated yet significant increase in Apo-AI levels in CagA negative subjects, successful eradication of *Helicobacter pylori* does not seem to have a significant effect on lipid profile and hsCRP. While it may be speculated that Apo-AI is an independent risk marker and its response to eradication treatment may vary from that of HDL, this finding should be interpreted with caution due to the relatively small sample size.

Further large scale prospective studies are needed in order to clarify the effect of CagA status on the cardiovascular outcomes of *H. pylori* eradication therapy.

Conflict of Interest

The authors have no conflict of interest to declare.

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