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【 ORIGINAL ARTICLE 】

Influence of the Degree of Gastric Mucosal Atrophy on the Serum Lipid Levels Before and After the Eradication of *Helicobacter pylori* Infection

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Abstract:

Objective To clarify the influence of the degree of gastric mucosal atrophy on the serum lipid levels before and after the eradication of *Helicobacter pylori* infection.

Methods The subjects were individuals who underwent an annual detailed medical checkup. Serum anti-*H. pylori* IgG antibody detection and upper endoscopic examinations were performed in all subjects. Gastric mucosal atrophy was evaluated by the classification of Kimura and Takemoto. The serum levels of total cholesterol, high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), LDLC/HDLC ratio, and triglycerides were compared among the different degrees of gastric mucosal atrophy in *H. pylori*-positive subjects. In addition, changes in those serum lipid levels during a two-year period were compared among *H. pylori* post-eradication cases that showed different degrees of gastric mucosal atrophy prior to eradication.

Results In subjects with higher degrees of gastric mucosal atrophy, the serum levels of total cholesterol, LDLC, and triglycerides were elevated. Furthermore, the LDLC/HDLC ratio in subjects with moderate and severe grades of gastric mucosal atrophy was significantly higher than in subjects with mild atrophy. In subjects with higher degrees of gastric mucosal atrophy, the serum level of LDLC and the LDLC/HDLC ratio were decreased following eradication of *H. pylori*.

Conclusion Lipid metabolism is influenced by the degree of gastric mucosal atrophy present before the eradication of *H. pylori*, and the favorable effects of such eradication are significant in patients with higher degrees of atrophy.

Key words: lipid metabolism, *Helicobacter pylori*, eradication, gastric mucosal atrophy

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Introduction

Lipid metabolism and arteriosclerosis progression have been repeatedly demonstrated to be affected by several different types of bacterial and viral infections, such as Chlamydia and cytomegalovirus (1-3). *Helicobacter pylori* infection has also been reported to worsen lipid metabolism (4-9), and its eradication is known to have a favorable effect on lipid metabolism (10-15).

Infection with *H. pylori* typically occurs during childhood, and a long-term persistent *H. pylori* infection can cause chronic gastritis, which is closely associated with the development of atrophic gastritis (16-18). Therefore, *H. pylori*-induced changes in lipid metabolism may be influenced by the degree of gastric mucosal atrophy, since the duration of continuous *H. pylori* infection and grade of gastric mucosal inflammation have effects on the degree of gastric mucosal atrophy. Gastric mucosal inflammation has also been demonstrated to affect the production of pro-inflammatory cytokines, which is also correlated with lipid metabolism (19). However, the relationship between the de-

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gree of gastric mucosal atrophy and lipid metabolism has not been clarified. In addition, no known investigations have been conducted to determine whether or not the degree of gastric mucosal atrophy prior to *H. pylori* eradication influences the changes in lipid metabolism following successful eradication.

The present study was performed to clarify the influence of the degree of gastric mucosal atrophy on the serum lipid levels before and after the eradication of *H. pylori*.

Materials and Methods

Study 1

The subjects in Study 1 were individuals who visited the Health Center of Shimane Environment and Health Public Corporation for an annual detailed medical checkup between April 2014 and March 2015. The majority were socially active and productive and considered to be socioeconomically middle class. A precise medical history was obtained by a trained public health nurse from each subject. Those taking medication for hyperlipidemia were excluded in order to eliminate the influence of medication on serum lipid parameters, as were subjects with a history of *H. pylori* eradication. Each subject underwent an upper endoscopic examination performed by a licensed experienced endoscopist. Gastric mucosal atrophy was evaluated based on the endoscopic findings using the classification of Kimura and Takemoto, in which gastric mucosal atrophy is classified into six groups (C1, C2, C3, O1, O2, O3) (20). This classification has been proven to correlate well with the histological features of atrophy. For the study, C1-C2 was defined as mild, C3-O1 as moderate, and O2-O3 as severe gastric mucosal atrophy.

Serum anti-*H. pylori* IgG antibody detection was performed using a SphereLight *H. pylori* antibody J® kit (Wako Pure Chemical Industries, Osaka, Japan) (21). The antibody titer was automatically measured using a chemiluminescent enzyme immunoassay, and a value of ≥4.0 U/mL was defined as positive, according to the manufacturer's instructions. Subjects with endoscopic gastric mucosal atrophy of C2-O3 and negative in anti-*H. pylori* IgG antibody test findings were excluded from the study, as they might have had a post-eradication status even though they had not previously undergone eradication therapy or been positive for *H. pylori* infection (21).

All subjects underwent a physical examination, and hematological and biochemical blood tests of samples obtained after an overnight fast were performed at the laboratory of Shimane Environment and Health Public Corporation. Factors investigated in this study included the gender, age, body mass index (BMI), smoking habit, and drinking habit (>50 mL alcohol/day), as well as the serum levels of total cholesterol, high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), and triglycerides. The serum total cholesterol, HDLC, LDLC, and triglyceride levels, as well as the LDLC/HDLC ratio (22-25) were compared between the *H. pylori*-positive and -negative subjects before and after adjusting for covariate factors (gender, age, BMI, smoking, drinking) using an analysis of covariance method. In addition, factors were compared among *H. pylori*-positive subjects with different degrees of gastric mucosal atrophy.

Study 2

Study 2 investigated the changes in the serum lipid levels in subjects from Study 1 who revisited the same medical center between April 2016 and March 2017 for another annual examination. Therefore, all Study 2 subjects underwent biochemical blood tests for serum lipids twice with a two-year interval. Those who received medical care for hyperlipidemia during those two years were excluded.

The history of eradication therapy for *H. pylori* and successful eradication prior to the second visit were determined based on a precise medical history of each subject obtained by a trained public health nurse. Nearly all of the *H. pylori*-positive subjects still had not undergone eradication therapy for *H. pylori*, even though we advised all who were found to be positive for *H. pylori* infection at the first examination to undergo eradication therapy. Successful eradication of *H. pylori* was determined based on the results of a urea breath or stool antigen test. Those without successful eradication were included in the group positive for *H. pylori* infection, even if they had received eradication therapy. When eradication therapy was determined to be not successful, we recommended that the subject undergo an *H. pylori* stool antigen test at our institution. Successful eradication was also confirmed by changes in the gastric mucosal findings obtained in an upper GI endoscopic examination, which was performed for all subjects.

The gastric mucosal findings used to determine successful eradication included the presence of map-like redness or depressed patchy redness, as well as absence of diffuse redness, mucosal swelling, sticky mucous, and enlarged folds (26-29). When the gastric mucosal findings were not changed in comparison with those prior to eradication therapy, we diagnosed the subject as positive for *H. pylori* infection, regardless of the history of eradication therapy. All endoscopic images for each subject were simultaneously reviewed by three licensed endoscopists who performed the diagnosis of each endoscopic finding. When there were inconsistencies in judgment of the endoscopic images among the endoscopists, the final diagnosis was decided by the lead endoscopist (K.A.).

Changes in the serum levels of total cholesterol, HDLC, and LDLC, as well as the LDLC/HDLC ratio and triglycerides during the two-year period were analyzed and compared among the *H. pylori*-positive, *H. pylori*-negative, and *H. pylori*-eradicated groups. Those parameters were also analyzed in post-eradicated cases with different degrees of gastric mucosal atrophy shown prior to undergoing eradication.

Table 1. ***Helicobacter pylori*** **Infection Status and Serum Lipid Parameters at First Visit (2014).**

H. pylori status	Negative	Positive			
		Total	Mild atrophy	Moderate atrophy	Severe atrophy
Gender (male/female)	184/112	283/150	100/48	113/74	70/28
Age in years	48.4±0.5	53.0±0.5*	50.1±0.8	52.4±0.6#	58.7±0.9#,##
BMI	22.6±0.2	22.8±0.2	22.9±0.3	22.8±0.2	22.7±0.3
Habitual smoking	48 (16.2%)	99 (22.9%)*	35 (23.6%)	36 (19.3%)	28 (28.6%)
Habitual drinking	165 (55.7%)	243 (56.1%)	83 (56.1%)	101 (54.0%)	59 (60.2%)
T cho. (mg/dL)	207.9±1.8	208.0±1.6	201.4±2.6	210.4±2.4#	213.7±3.6#
	(209.0±1.9)	(207.0±1.6)	(202.1±2.6)	(209.6±2.3#)	(210.1±3.4)
HDLC (mg/dL)	68.1±1.1	63.9±0.8*	65.0±1.3	63.2±1.2	63.6±1.9
	(67.7±0.9)	(64.2±0.7*)	(65.7±1.3)	(63.1±1.1)	(64.1±1.6)
LDLC (mg/dL)	128.0±1.7	130.0±1.5	123.1±2.2	134.0±2.2#	132.7±3.4#
	(129.4±1.7)	(129.0±1.4)	(123.3±2.4)	(133.3±2.2#)	(129.8±3.1)
LDLC/HDLC ratio	2.04±0.05	2.19±0.04*	2.02±0.06	2.27±0.06#	2.29±0.10#
	(2.08±0.04)	(2.16±0.04)	(2.00±0.06)	(2.26±0.05#)	(2.23±0.08#)
TG (mg/dL)	100.7±3.7	115.4±4.6*	109.3±5.6	109.2±4.9	136.6±15.8##
	(103.7±4.8)	(113.8±4.0)	(107.3±6.7)	(110.2±6.0)	(132.1±8.6#,##)

Data was expressed by mean±SE. Gastric mucosal atrophy was evaluated using the classification of Kimura and Takemoto (C1-C2: mild, C3-O1: moderate, O2-O3: severe gastric mucosal atrophy). Numbers in parenthesis indicate adjusted value for covariant factors (gender, age, BMI, smoking, drinking). *p<0.05 in comparison with *H. pylori*-negative subjects. #p<0.05 in comparison with the subjects with mild gastric mucosal atrophy. ##p<0.05 in comparison with the subjects with moderate gastric mucosal atrophy. BMI: body mass index, T cho.: total cholesterol, HDLC: HDL-cholesterol. LDLC: LDL-cholesterol, TG: triglycerides

Statistical analyses were performed using a chi-squared test, unpaired and paired t tests, and an analysis of covariance. Stat View 5.0 (Abacus Concepts, Berkeley, USA) for Macintosh and the SPSS statistical package (Version 19J for Windows; SPSS, Chicago, USA) were used to perform statistical analyses. Differences of $p<0.05$ were considered to be statistically significant.

This study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee of the Shimane Environment and Health Public Corporation. Written informed consent indicating that the clinical data would be used for a clinical study without the release of individual information was obtained from all subjects before performing the medical checkups.

Results

Study 1

There were 729 subjects (467 men, 262 women; mean age 51.1 years) in Study 1. None had a history of eradication for *H. pylori* or medical care for hyperlipidemia. The number of subjects with and without *H. pylori* infection was 433 and 296, respectively. Those with infection were older than those without (Table 1). The serum level of HDLC in the *H. pylori*-positive group was significantly lower than in the *H. pylori*-negative group, even after adjusting for covariate factors. In addition, the serum levels of total cholesterol and triglycerides in the *H. pylori*-positive subjects tended to be higher than in the *H. pylori*-negative group. The LDLC/HDLC ratio was also higher in the *H. pylori*-positive group than in the *H. pylori*-negative group. The analysis after dividing the study subjects by gender also showed that the serum level of HDLC was lower and the LDLC/HDLC ratio higher in the *H. pylori*-positive group than in the *H. pylori*-negative group (data was not shown).

When the serum lipid levels were compared among the different degrees of gastric mucosal atrophy in *H. pylori*-positive cases, they were found to be significantly influenced by the degree of atrophy. In subjects with a higher degree of gastric mucosal atrophy, the levels of total cholesterol, LDLC, and triglycerides were high, while the level of HDLC was low. In addition, the LDLC/HDLC ratios in subjects with moderate and severe grades of gastric mucosal atrophy were significantly higher than in those with a mild grade, even after adjusting for covariate factors.

Study 2

Of the 729 subjects who participated in Study 1, there were 437 who made a repeat visit for an annual checkup between April 2016 and March 2017. Among them, the numbers of *H. pylori*-positive, *H. pylori*-negative, and *H. pylori*-eradicated subjects were 174, 64, and 199, respectively. Both *H. pylori*-positive and post-eradication subjects were positive for *H. pylori* infection at the first visit, which occurred between April 2014 and March 2015, and nearly all who were positive for *H. pylori* at the second visit did not undergo eradication therapy for the bacterium. The BMI was significantly increased at the second visit compared to the first visit only in the *H. pylori*-negative subjects, with no marked change noted in the post-eradication subjects. The serum levels of total cholesterol and HDLC were increased

Table 2. ***Helicobacter pylori*** **Infection Status and Time-course Changes of Serum Lipid Parameters.**

H. pylori status at 2016	Negative group	Positive group	Eradicated group
Gender (male/female)	113/61	49/15	134/65
Age in years at 2014	49.4±0.6	50.8±1.2	53.2±0.6
Habitual smoking	27 (15.5%)*	22 (34.4%)	35 (17.6%)*
Habitual drinking	103 (59.2%)	37 (57.8%)	129 (64.8%)
BMI (2014/2016)	22.5±0.2/22.6±0.2#	23.0±0.4/23.1±0.4	22.6±0.2/22.6±0.2
T cho. (mg/dL) (2014/2016)	212.2±2.4/214.1±2.4	206.2±4.0/211.2±3.5	208.7±2.2/211.7±2.2
HDLC (mg/dL) (2014/2016)	68.5±1.4/69.0±1.1	61.4±1.8/62.2±1.9	64.8±1.2/66.1±1.3*
LDLC (mg/dL) (2014/2016)	131.8±2.3/131.8±2.3	129.2±3.6/132.1±3.4	131.1±2.1/130.2±2.0
LDLC/HDLC ratio (2014/2016)	2.095±0.062/2.083±0.064	2.240±0.098/2.292±0.108	2.178±0.058/2.132±0.057
TG (mg/dL) (2014/2016)	100.5±4.5/102.5±5.7	122.3±10.5/118.7±8.8	110.1±7.8/111.3±8.3

Data was expressed by mean±SE. *p<0.05 in comparison with *H. pylori*-positive subjects. #p<0.05 in comparison with the data of 2014. BMI: body mass index, T cho.: total cholesterol, HDLC: HDL-cholesterol, LDLC: LDL-cholesterol, TG: triglycerides

Table 3. **Degree of Gastric Mucosal Atrophy and Time-course Changes of Serum Lipid Parameters in Eradicated Cases.**

Gastric mucosal atrophy	Mild	Moderate	Severe
Gender (male/female)	42/19	55/39	37/7
Age in years at 2014	50.8±1.1	52.5±0.8	58.3±1.2
Habitual smoking	6 (9.8%)	18 (19.1%)	11 (25.0%)
Habitual drinking	43 (70.5%)	57 (60.6%)	29 (65.9%)
BMI(2014/2016)	22.5±0.3/22.6±0.4	22.6±0.3/22.7±0.3#	22.7±0.4/22.5±0.4
T cho. (mg/dL) (2014/2016)	201.0±3.7/209.6±3.8#	212.0±3.1/214.6±3.0	212.4±5.4/208.6±5.3
HDLC (mg/dL) (2014/2016)	67.4±2.1/68.6±2.0	64.2±1.8/65.5±2.0	62.0±2.3/63.7±2.7
LDLC (mg/dL) (2014/2016)	122.3±3.2/127.1±3.3	136.3±3.0/135.3±2.8	132.2±5.2/123.7±4.9#
LDLC/HDLC ratio (2014/2016)	1.919±0.078/1.961±0.083	2.285±0.082/2.236±0.078	2.309±0.152/2.146±0.160#
TG (mg/dL) (2014/2016)	97.6±6.5/107.0±14.6	102.3±5.1/97.2±4.1	144.0±32.0/147.7±29.9

Data was expressed by mean±SE. Gastric mucosal atrophy was evaluated using the classification of Kimura and Takemoto at 2014 (before eradication) (C1-C2: mild, C3-O1: moderate, O2-O3: severe gastric mucosal atrophy). #p<0.05 in comparison with the data of 2014. BMI: body mass index, T cho.: total cholesterol, HDLC: HDL-cholesterol, LDLC: LDL-cholesterol, TG: triglycerides

in the *H. pylori*-negative and -positive, and post-eradication subjects at the second visit as compared to those at the first visit, though a significant increase was only observed with regard to the HDLC level in subjects who underwent eradication. The level of LDLC in the serum and the LDLC/HDLC ratio each showed a tendency to increase in subjects continuously positive for *H. pylori*, while these values were decreased in the post-eradication subjects (Table 2).

When changes in the serum lipid levels were analyzed in post-eradication subjects divided based on the degree of gastric mucosal atrophy, there were significant differences among the groups. The serum level of HDLC showed a mild increase in all groups. The values of LDLC and the LDLC/HDLC ratio were increased after *H. pylori* eradication in subjects with mild gastric mucosal atrophy but were decreased in subjects with greater degrees of gastric mucosal atrophy. In contrast, there was no obvious trend regarding the changes in the serum triglyceride levels in the subjects regardless of the degree of gastric mucosal atrophy (Table 3). The same differences in the changes in serum lipid parameters after eradication for *H. pylori* between the different degrees of gastric mucosal atrophy were observed after analyzing by dividing the study subjects by gender (Table 4).

Discussion

Bacterial and viral infections have been repeatedly demonstrated to be associated with increased serum levels of fibrinogen and lipids, well-known risk factors for cardiovascular disease (1-3). *H. pylori* infection is known to be related to the onset of several gastroduodenal diseases, including gastritis, peptic ulcer disease, gastric cancer, and low-grade B cell lymphoma in gastric mucosa-associated-lymphoid tissue (17, 18, 30-32). Furthermore, persistent low-grade inflammation induced by *H. pylori* infection was reported to produce pro-inflammatory cytokines, such as C reactive protein, and interleukin (IL)-6 and IL-8, which have major effects on lipid metabolism and arteriosclerosis progression (19). Indeed, serum lipid metabolism has been demonstrated to be influenced by *H. pylori* infection (4-9). In addition, the successful eradication of *H. pylori* infection has been shown to have a favorable effect on lipid metabolism (10-15). The degree of gastric mucosal atrophy is influ-

Table 4. Degree of Gastric Mucosal Atrophy and Time-course Changes of Serum Lipid Parameters in Eradicated Male and Female Cases.

Gastric mucosal atrophy		Mild	Moderate	Severe
BMI (2014/2016)	male	23.0±0.4/23.0±0.4	23.5±0.4/23.7±0.4	23.2±0.4/23.1±0.5
	female	21.4±0.6/21.5±0.7	21.2±0.5/21.4±0.5	19.9±0.8/19.7±0.8
T cho. (mg/dL) (2014/2016)	male	198.5±4.2/209.8±4.7#	208.1±4.2/210.3±3.9	211.6±6.3/207.2±5.9
	female	206.5±7.2/209.2±6.7	217.5±4.5/220.6±4.8	216.6±8.4/215.9±11.4
HDLC (mg/dL) (2014/2016)	male	64.6±2.5/66.4±2.5	58.7±2.0/59.9±2.0	57.9±2.1/59.6±2.6
	female	73.7±3.1/73.7±3.2	72.0±2.9/73.4±3.5	83.3±3.4/85.4±3.6
LDLC (mg/dL) (2014/2016)	male	120.5±3.7/127.3±4.1#	136.4±3.8/135.6±3.4	133.5±6.0/123.9±5.6#
	female	126.1±6.1/126.7±5.6	136.1±4.8/134.9±4.8	125.1±6.1/122.9±9.8
LDLC/HDLC ratio (2014/2016)	male	1.990±0.100/2.044±0.109	2.459±0.103/2.395±0.095	2.462±0.170/2.281±0.182
	female	1.762±0.112/1.776±0.107	2.040±0.125/2.012±0.124	1.500±0.038/1.434±0.088
TG (mg/dL) (2014/2016)	male	110.8±8.4/122.6±20.5	117.6±6.9/105.4±5.5	161.1±37.5/165.2±34.9
	female	68.3±5.1/72.5±8.1	80.8±6.0/85.6±5.9	54.1±5.4/55.3±4.3

Data was expressed by mean±SE. Gastric mucosal atrophy was evaluated using the classification of Kimura and Takemoto at 2014 (before eradication) (C1-C2: mild, C3-O1: moderate, O2-O3: severe gastric mucosal atrophy). #p<0.05 in comparison with the data of 2014. BMI: body mass index, T cho.: total cholesterol, HDLC: HDL-cholesterol, LDLC: LDL-cholesterol, TG: triglycerides

enced by the duration of *H. pylori* infection as well as the grade of gastric mucosal inflammation (20). Therefore, gastric mucosal atrophy degree may be related to lipid metabolism and those serum parameters.

In the present study, the level of HDLC in serum in the *H. pylori*-positive group was significantly lower than in the *H. pylori*-negative group, which has also been shown in previous studies. Furthermore, the serum level of HDLC in our *H. pylori*-positive subjects with a higher degree of gastric mucosal atrophy was decreased compared with those with a mild degree of atrophy. As a result, LDLC/HDLC ratio was high in the *H. pylori*-positive subjects, especially those with a higher degree of gastric mucosal atrophy. In addition, other serum lipid levels were worse in subjects with a higher degree of gastric mucosal atrophy. Since the initial *H. pylori* infection typically occurs during childhood (16, 18), the period of infection in individuals with a higher degree of gastric mucosal atrophy is considered to be longer than in those with a milder degree, indicating that a long-term *H. pylori* infection is associated with severely worse serum lipid metabolism. In the present study, the influence of a higher degree of gastric mucosal atrophy on serum lipid metabolism was significant, even after adjusting for covariate factors. Therefore, the degree of gastric mucosal atrophy is considered to be an important factor that influences the lipid metabolism.

Several investigators have reported that successful eradication of *H. pylori* favorably affects lipid metabolism (10-15). Our analysis of the changes in the serum lipid level after eradication also showed that the level of LDLC in serum as well as the LDLC/HDLC ratio tended to increase in subjects continuously positive for *H. pylori*, whereas those values were decreased following eradication. The most interesting observation in our study was that the degree of gastric mucosal atrophy prior to eradication had effects on the change in the serum lipid level following successful eradication. The level of LDLC in the serum and the LDLC/HDLC ratio were both increased after eradication of *H. pylori* in subjects with a mild degree of gastric mucosal atrophy, whereas those values were decreased after eradication in subjects with either a moderate or severe degree of gastric mucosal atrophy. Therefore, the favorable effect on lipid metabolism following eradication in subjects with *H. pylori* infection is considered to be high in cases with a higher degree of gastric mucosal atrophy. The present findings fail to explain why the degree of gastric mucosal atrophy prior to eradication of *H. pylori* is related to the change in the serum lipid level after eradication. Since the level of serum lipids prior to eradication was worse in cases with a higher degree of gastric mucosal atrophy than in those with a milder degree of atrophy, the effect of *H. pylori* infection on lipid metabolism may be greater in individuals with a higher degree of gastric mucosal atrophy than in those with a milder degree. The changes in the serum levels of pro-inflammatory cytokine and ghrelin after eradication for *H. pylori* might have influenced the difference in the lipid metabolism among the subjects with different degrees of gastric mucosal atrophy, since those have been shown to be related to not only the degree of gastric mucosal inflammation and atrophy but also the lipid metabolism and dietary habits (19, 33, 34). Further studies are needed to clarify why the degree of gastric mucosal atrophy influenced lipid metabolism before and after the eradication of *H. pylori* infection.

Several limitations associated with the present study warrant mention. First, the subjects were not representative of the general population, as they were individuals who voluntarily visited our medical center for annual checkups, with the numbers of young and elderly subjects relatively few. Furthermore, we did not investigate the changes in the upper gastrointestinal symptoms and dietary habits during the two-year interval, although the successful eradication of *H. pylori* is well-known to induce changes in several upper gastrointestinal symptoms. Changes in the dietary and lipid intake might have affected the time-course of changes in the

serum lipid parameters in the subjects. In addition, the two-year follow-up period was too short to investigate the progression of arteriosclerosis or occurrence of cardiovascular events. Therefore, additional large-scale long-term prospective studies are needed in order to confirm the influence of the degree of gastric mucosal atrophy on lipid metabolism before and after the eradication of *H. pylori*.

In conclusion, lipid metabolism before and after *H. pylori* eradication are influenced by the degree of gastric mucosal atrophy present prior to performing eradication. In addition, the favorable effect of eradication of *H. pylori* on the lipid metabolism was particularly significant in subjects with a higher degree of atrophy.

The authors state that they have no Conflict of Interest (COI).

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