

The effect of *Helicobacter pylori* on the gastric expression of LOX-1 and CD-36: the role of CRP and ox-LDL

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Abstract

Background: This study aimed to investigate the effect of serum C-reactive protein (CRP) and oxidized low-density lipoprotein (ox-LDL) concentrations on the expression of lectin-like oxidized low-density lipoprotein (*LOX-1*) and cluster of differentiation 36 (*CD-36*) genes in gastric biopsies of individuals with and without *Helicobacter pylori* (*H. pylori*) infection.

Methods and Results: In this cross-sectional study, we investigated 74 subjects based on gastritis and *H. pylori* infection in three groups. Enzyme-linked immunosorbent assay (ELISA) was used to measure serum levels of high-sensitivity CRP (hs-CRP) and ox-LDL. Quantitative real-time RT-PCR was run to compare *LOX-1* and *CD-36* gene expression.

Comparison of *LOX-1* gene expression in *H. pylori* and gastritis positive ($P = 0.025$) and *H. pylori*-negative and gastritis-positive ($P = 0.010$) to *H. pylori* and gastritis-negative groups showed a significant difference. *CD-36* expression levels were lower in the *H. pylori* and gastritis positive group than in the non-gastritis and *H. pylori* group ($p = 0.051$). Although there was a weak correlation between serum hs-CRP concentration and *LOX-1* expression ($r = 0.219$, $P = 0.058$), there was no correlation between serum levels of ox-LDL and *LOX-1* expression and *CD-36*.

Conclusion: Based on the investigation results, two factors, *H. pylori*, and gastritis increase *LOX-1* expression and decrease *CD-36* expression. Based on our results, an increase in plasma hs-CRP levels may be associated with an increase in *LOX-1* expression.

Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral, microaerophilic, and flagellate bacterium localized in the human stomach. Approximately half of the world's population is infected with this bacterium. *H. pylori* can colonize gastric tissue and attach it to epithelial cells with its flagella and adhesion molecules. By releasing toxins, it can cause tissue damage and inflammation [1]. Chronic gastritis is usually an asymptomatic disease that is highly important, since it causes stomach cancer in some patients. There are two types of gastritis. In most cases, gastritis is caused by *H. pylori* infection. The autoimmune type of gastritis is scarce [2].

Lectin-like oxidized low-density lipoprotein receptor-1 (*LOX-1*) is a type II membrane protein that structurally belongs to the type C lectin family [3]. In addition to being an oxidized low-density lipoprotein (ox-LDL) receptor, this protein can bind to C-reactive protein (CRP) in endothelial cells with a lower affinity than that of ox-LDL. Despite its lower CRP affinity for binding to this receptor, it induces *LOX-1* expression and can play a role in carcinogenesis [4–6, 3, 7–9]. *H. pylori*-induced acute and chronic gastritis can cause many changes in gene expression. It may lead to gastric cancer. Elevated serum levels before CRP treatment (> 10 mg / L) are significantly associated with poor prognosis in patients with gastric cancer, both in early and advanced stages [10, 11]. Activation of *LOX-1* causes the transformation and growth of several cancer cells, while decreased *LOX-1* expression can prevent such processes [12]. Some studies

have demonstrated that overexpression of *LOX-1* is involved in tumor progression in prostate, colorectal, gastric, pancreatic, and breast cancers [13, 6, 5, 4, 14].

Cluster of differentiation 36 (*CD-36*) is an 88 kDa membrane glycoprotein belonging to the scavenger receptor B family. *CD-36* is present on the surface of several cells, such as fat cells, monocytes, macrophages, platelets, endothelial, cardiac, skeletal, and smooth muscle cells, dendritic cells, retinal pigment epithelium, and red blood cell hematopoietic precursors. *CD-36* plays a minor role in the onset of primary tumors. *CD-36* is a glycoprotein that functions as a transporter of long-chain fatty acids and ox-LDL, and is involved in angiogenesis, immune responses, adhesion, and metastasis. This protein is expressed in stromal, immune, and cancer cells. Different patterns of expression have been observed from the onset to the spread of cancer in different malignancies. Today, this protein is considered one of the biomarkers and therapeutic targets of cancer. The expression is also generally reduced in tumor microvessels supporting tumor progression and invasion. In Tumor Stromal cells, *CD-36* expression is extremely low. The lower the *CD-36* level in Cancer-Associated Fibroblasts (CAFs) is, the more aggressive the tumor is [15–18].

In recent years, it has been indicated that fat metabolism has been involved in processes related to cell transformation and tumorigenesis [19, 20]. The results of various studies showed that serum levels of ox-LDL and hs-CRP increased the risk of cancers [21–24]. The relationship between *LOX-1* ligands and *CD-36* and *LOX-1* expression in patients with *H. pylori* infection is unclear. In this study, we investigated the relationship between serum CRP and ox-LDL levels and *CD-36* and *LOX-1* gene expression.

Materials And Methods

Subjects

In this cross-sectional study, we investigated 74 outpatients referred to the endoscopy department based on gastritis status in gastric biopsy and *H. pylori* infection in three groups: 1- *H. pylori*/gastritis positive 2- *H. pylori*-negative / gastritis positive 3 *H. pylori*-negative/gastritis negative. Gastritis was determined by a pathologist based on the Sydney criterion. Gastric tissue biopsy and serum specimens were used for molecular and biochemical experiments. People who, at the time of the study, had cancer, diabetes, infectious diseases, cardiovascular disease, high blood pressure and hyperlipidemia, pregnancy, anemia, kidney disease, autoimmune and inflammatory diseases, and gastrointestinal disorders, and thyroid problems, were omitted. Likewise, smokers and alcoholics and people taking anti-inflammatory, steroids, antacids, proton pump inhibitors, bismuth, and antibiotics drugs were excluded from the study.

Sampling

Blood samples were taken from the participants, and after centrifugation, its serum was isolated and kept at -70°C until we conducted experiments. Gastric antrum biopsy specimens were immediately stored in 10% formalin. After fixation, the samples were molded, cut, and stained by hematoxylin and eosin (H&E).

We used the rest of the tissue samples for RNA extraction and gene expression analysis. To detect *H. pylori* in the gastric mucosa, we used a urease test and direct observation of bacteria in stained tissue sections.

Rna Extraction And Real-time Rt-pcr

Total RNA was extracted from antrum biopsies according to the method of the kit manufacturer (Gene All). For cDNA synthesis, according to the instructions of the cDNA synthesis kit (YTA.Co), in the initial stage, 2µg of the total RNA with 2µl of primer (each of the oligo (dT) and random hexamer 1µl) and volume was raised to 13.4 µl by DEPC-H₂O. It was located at 70°C for 5 minutes. In the second step, 4µl of buffer (5X), 1µl of dNTPs, 0.5µl of RNase Inhibitor, and 1µl of M-MLV enzyme were added and incubated at 37°C for 60 min and then at 70 ° C for 5 min. AllelID 7.5 software was used to design the primers (Table 1). For the real-time RT-PCR, 10µl of 2x SYBR Green (YTA Cat No: YT2551) was mixed with 0.4µl of each forward and reverse primer, and 1.5µl of cDNA with 1µl of passive reference dye (50X) and DEPC H₂O. The volume was brought to 20µl and placed in a thermocycler. After an initial denaturation phase at 95°C for 3 minutes, the denaturation phase at 95°C for 5 seconds, and then the annealing/extension phase at 60 ° C for 20 seconds were performed in 40 cycles. BACT gene was an internal control, and after obtaining CT of each sample for genes, the mean was taken from CT. Afterward, the results were analyzed using the Δ CT method.

ELISA

Measurements of hs-CRP and ox-LDL were performed according to the manufacturer's kit instructions (Zell Bio).

Statistical analysis

SPSS 24 and GraphPad software programs were used for data analysis and graphs drawing, respectively. Shapiro-Wilk test was used to check the normality of the data. To compare data to normal distribution, a one-way ANOVA parametric test, and then the Tukey test was used to examine the differences between groups. Data with abnormal distributed nonparametric Kruskal-Wallis tests, and then groups were compared to the pairwise comparisons of the group test. Spearman (nonparametric) correlation was used to investigate the correlation between serum analyte concentration and gene expression. The value of $P \leq 0.05$ was considered a significant level in this study.

Results

Of the 74 participants in the study, 43 were female, and 31 were male. Pathological findings and the RUT test revealed gastritis and *H. pylori* infection in the groups (Table 2). The results indicated that 40 of these patients were *H. pylori*-negative, and 34 were *H. pylori*-positive. In addition, 11 patients had not gastritis, and 63 patients had gastritis. Comparison of BMI between the groups by the one-way ANOVA test

showed no significant difference in the participants' BMI ($P = 0.496$). Comparison of sex and age variables in the groups using the Chi-Square test showed no significant difference between age and sex traits ($P = 0.835$).

LOX-1 and CD-36 gene expression

According to the statistical analysis of *LOX-1* expression data using the Shapiro-Wilk test ($P \leq 0.05$), the data distribution was not normal. Comparison of the gene expression in the three groups using the Kruskal-Wallis test showed a significant difference ($p = 0.033$). Comparison of the results between the groups using the pairwise comparisons of the group test demonstrated a significant difference between *H. pylori*/gastritis positive and *H. pylori* /gastritis negative ($p = 0.025$) and between *H. pylori*-negative / gastritis positive and *H. pylori*/gastritis negative groups ($P = 0.010$). However, no significant difference was observed between *H. pylori*/gastritis positive and *H. pylori*-negative/gastritis positive ($p = 0.597$) groups (Fig. 1).

Comparison of *CD-36* expression using the Independent Samples Median Test showed a significant difference between the groups ($p = 0.013$). The comparison between the groups using the pairwise comparisons of the group test showed a significant difference between *H. pylori*/gastritis positive and *H. pylori*/gastritis negative ($p = 0.046$). There was no significant difference between *H. pylori*-negative / gastritis positive and *H. pylori* / gastritis negative ($p = 0.288$), and between *H. pylori* / gastritis positive and *H. pylori*-negative / gastritis positive ($p = 0.712$) (Fig. 2).

Hs-crp And Ox-ldl Results

Comparison of the results of the hs-CRP concentration measurement in the three groups performed using the Kruskal-Wallis test showed a significant difference in the hs-CRP variable ($p < 0.001$). The groups were compared by the pairwise comparisons of the group between *H. pylori*/gastritis positive and *H. pylori*/gastritis negative ($p = 0.013$), and between *H. pylori*-negative / gastritis positive and *H. pylori*/gastritis negative ($p < .001$). There was a significant difference between *H. pylori*/gastritis positive and *H. pylori*-negative / gastritis positive groups ($p = 0.016$).

Analysis of the ox-LDL concentration between the groups by the pairwise comparisons of the group test showed a significant difference between *H. pylori*-negative / gastritis positive and *H. pylori* and gastritis negative groups ($p = 0.032$). Furthermore, no significant difference was observed between *H. pylori*/gastritis positive and *H. pylori*/gastritis negative groups ($p = 0.440$), and between *H. pylori* / gastritis positive and *H. pylori*-negative / gastritis positive ($p = 0.051$).

Correlation between LOX-1, CD-36 expression level, and serum hs-CRP and ox-LDL concentration

Due to the abnormality of the data, the Spearman test was used to measure the relationship. There was a weak correlation between serum hs-CRP concentration and *LOX-1* expression ($r = 0.219$, $P = 0.058$).

Owing to the abnormality of the data, the Spearman test was used to measure the relationship between them. There was no correlation between serum ox-LDL concentration and *LOX-1* and *CD-36* expression.

Table 1
The primer sequences

Gene	Primers* (5'→3')	Product size (base pair)
LOX-1	TAGAAACCCTTGCTCGGAAGC TGCCAGATCCAGTCTTGCG	136
CD-36	CTTGGATATTGAACCTATAACTGGA TGTTCCTTCTCATCACC	176
ACTB	GCCTTTGCCGATCCGC GCCGTAGCCGTTGTCG	90
* Upper sequences are forward primers.		

Table 2
Demographic and clinical information of participants and groups.

Groups	Number (man)	BMI Mean ±SD	Age Mean ±SD	ox-LDL (ng/L) mean±SEM	hs-CRP (ng/ml) mean±SEM
H. pylori+ Gastritis +	34 (13)	25.83±4.6	39.88±11.6	503.9	2044
H. pylori- Gastritis +	29 (14)	26.33±3.8	48.21±11.4	698.7	3364
H. pylori- Gastritis -	11 (4)	24.83±2.6	39.82±11.5	482.1	676.4

Discussion

In this study, the expression levels of *LOX-1* and *CD-36* genes, and serum levels of hs-CRP and ox-LDL in our target groups were compared based on gastritis and *H. pylori*. The serum levels of hs-CRP and ox-LDL were higher in *H. pylori*-positive patients. Our results indicated that *H. pylori* increased *LOX-1* and decreased *CD-36* gene expression. Moreover, a weak correlation was observed between the serum level of CRP and the expression of *LOX-1*, while there was no correlation between the serum level of ox-LDL and the expression of genes. In summary, our results demonstrated that there were higher serum levels of CRP and ox-LDL and expression of the *LOX-1* gene in the group with negative *H. pylori*-gastritis positive than in the control group. Although in the *H. pylori* and gastritis-positive group, the serum level of CRP and *LOX-1* expression was higher, the expression of *CD-36* decreased despite the high level of ox-LDL (Fig. 5).

In this work, the effects of smoking, alcohol consumption, use of any drugs, use of antacids, use of anti-inflammatory medications, antibiotics, anti-*H. Pylori* drugs were excluded according to the inclusion and exclusion criteria. It furthermore balanced the body mass index in the three groups. In addition, none of

the people in their first-degree relatives had a history of gastric cancer. Therefore, the effects seen were due to infection with this bacterium and gastritis.

The role of *H. pylori*, inflammation and hyperlipidemia in the evolution of distal gastric adenocarcinoma has been demonstrated [25–27]; however, its molecular mechanism is unclear. According to the results of the study conducted by Huang *et al.*, plasma levels of hs-CRP and ox-LDL were higher in atherosclerotic CHD patients with Cag⁺*H. pylori* infection [28]. Studies by Jafarzadeh *et al.* showed that although serum hs-CRP levels increased in *H. pylori* infection, this increase in hs-CRP was not affected by the bacterial CagA status [10]. In our study, it appears in the *H. pylori*/ gastritis positive group, *H. pylori* were the leading cause of the increase in serum hs-CRP levels.

Studies show that in gastric cancer, ox-LDL interaction with the LOX-1 receptor causes NF- κ B pathway activation and increases vascular endothelial growth factor C (VEGF-c) expression [26]. Furthermore, the use of ox-LDL binding inhibitor inhibits VEGF-c expression. Pascual *et al.* in their study found that *CD-36*⁺ metastasis initiating cells in highly invasive melanoma, lung carcinoma, bladder, and breast cancer patients were associated with a poor prognosis. Moreover, Inhibition of *CD-36* in animal models of breast cancer and melanoma prevented metastasis [17].

In study conducted by the Kashihara *et al.* Investigating noncancerous gastric tissue obtained from 39 gastrectomy patients, the level of glycoprotein thrombospondin 1 (TSP-1), which is a *CD-36* ligand, was measured, and patients in both groups with high and low TSP-1 were compared. Noncancerous gastric tissue of patients with high TSP-1 levels had higher carcinogenesis and more active *CD-36* signaling. Although in these studies several patients had *H. pylori* infection, the effect of *H. pylori* on *CD-36* gene expression was not investigated [29].

Some studies have investigated the effect of palmitic acid fatty acids as *CD-36* ligand on signal transduction pathways in gastric cancer metastasis [30, 15]. Accordingly, *CD-36* levels show a significant upregulation in malignant tissue. In these studies, they introduced *CD-36* as an oncogenic factor involved in cancer progression. However, another study reported downregulation of *CD-36* in Cancer-Associated Fibroblasts (CAFs), in more aggressive tumors [18]. Although low levels of *CD-36* are associated with low TNM (tumor, node, metastasis) classification in pancreatic ductal adenocarcinoma (PDAC) cancer, they are associated with a larger tumor size and a weaker disease prognosis [31].

Analysis of the mRNA extracted from gastric tissue samples of 10 patients with *H. pylori* showed that out of 13817 transcripts, 98 transcripts increased after *H. pylori* treatment and bacterial eradication (P<0.02 fold change threshold) [32]. *CD-36* was one gene whose expression increased significantly (approximately 2.95 times). In agreement with the investigation conducted by Resnick *et al.*, the expression analysis in our study exhibited a decrease in *CD-36* expression in the *H. pylori* group.

According to the results, the primary reason for high LOX-1 expression in the *H. pylori* group is the activation of the inflammatory pathway. It appears that CRP acts as the dominant ligand for the LOX-1 receptor. There is evidence that CRP is suggested as a ligand for LOX-1 and induced genes involved in

tumorigenesis [33, 34]. In addition to the ligands for *LOX-1* and *CD-36*, direct bacterial interaction with these receptors may have caused the molecular changes observed in gastric cells. Kattoor *et al.* in their study revealed that infectious agents, such as *Chlamydia pneumoniae* and *H. pylori*, could increase their expression by direct interaction with the *LOX-1* receptor [35]. In this study, they showed that *Chlamydia pneumoniae* bound to *LOX-1* in human umbilical vein endothelial cells (HUVECs) and allowed ox-LDL to enter the cells. They also observed this mechanism in the lung and adductor tissues of mice. However, this study showed that *Chlamydia pneumoniae* was only useful on *LOX-1* and had no effect on the expression and signaling of the *CD-36* gene [36]. One limitation of this study was the small amount of biopsy and serum samples of patients; therefore, molecular studies at the protein level were impossible to conduct.

Conclusion

Based on the investigation results, two factors, *H. pylori*, and gastritis, increase *LOX-1* expression and decrease *CD-36* expression. The increase in plasma hs-CRP levels may be associated with an increase in *LOX-1* expression. In future studies, the effect of *H. pylori* and gastric cells coculture on the expression of *LOX-1* and *CD-36* genes and the impact of bacteria on the internalization of ox-LDL should be investigated.

Declarations

Acknowledgment

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The author contribution

AP: Concept generation, Study Design, Project supervision, Manuscript Preparation. GG: Data Collection, Experimentation. Literature Search. MH: Data Collection. RD: Data Collection. : MMK: Statistical Analysis, Data Interpretation.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests

Ethical approval All procedures performed in this study were approved in the Ethics Committee of Semnan University of Medical Sciences with the ethics code IR.SEMUMS.REC.1397.146.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Figures

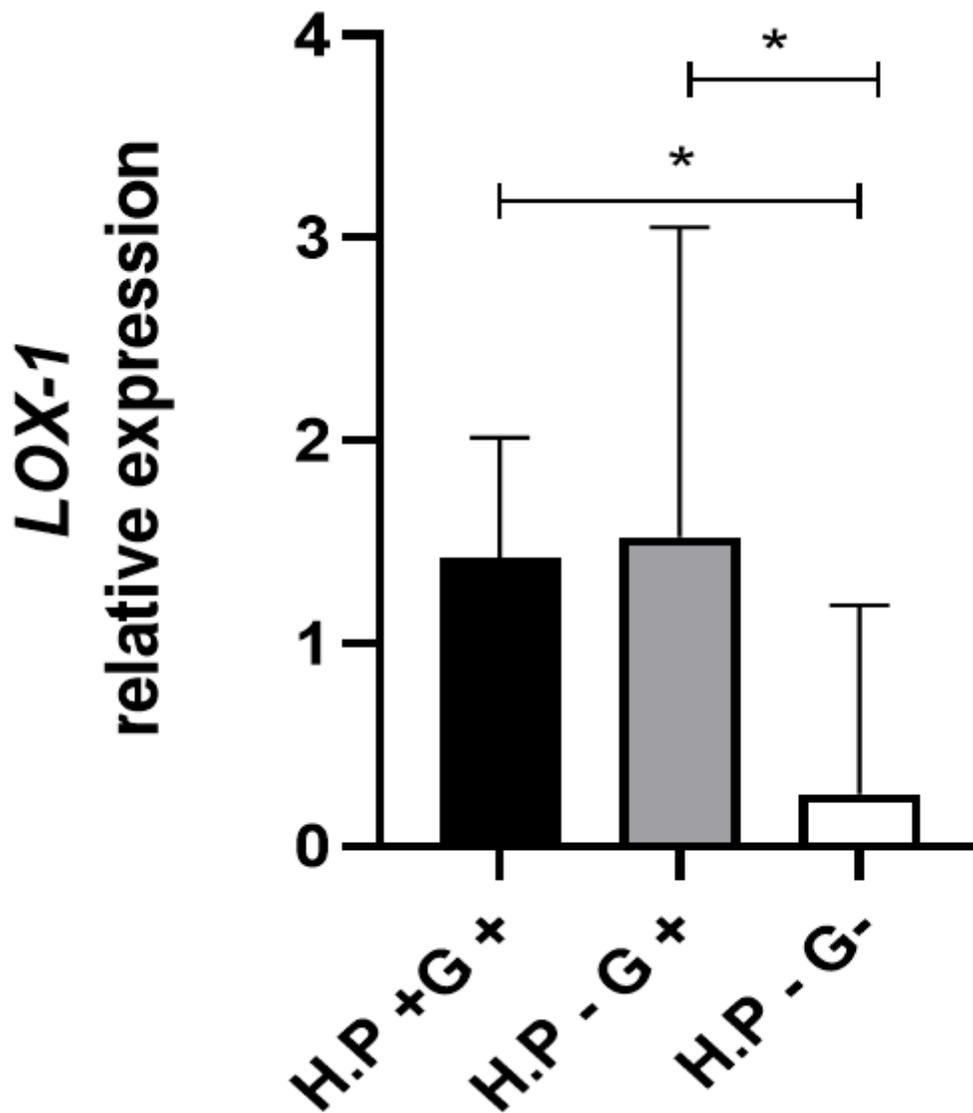


Figure 1

Comparison of *LOX-1* relative expression levels in the three groups. Data were expressed as median (Interquartile Range). * $P < 0.05$, Kruskal-Wallis test, H.P-G-, H.P-G+, H.P+G+ are *H. pylori*-negative without gastritis, *H. pylori*-negative with gastritis, and H+G+: *H. pylori*-positive with gastritis, respectively.

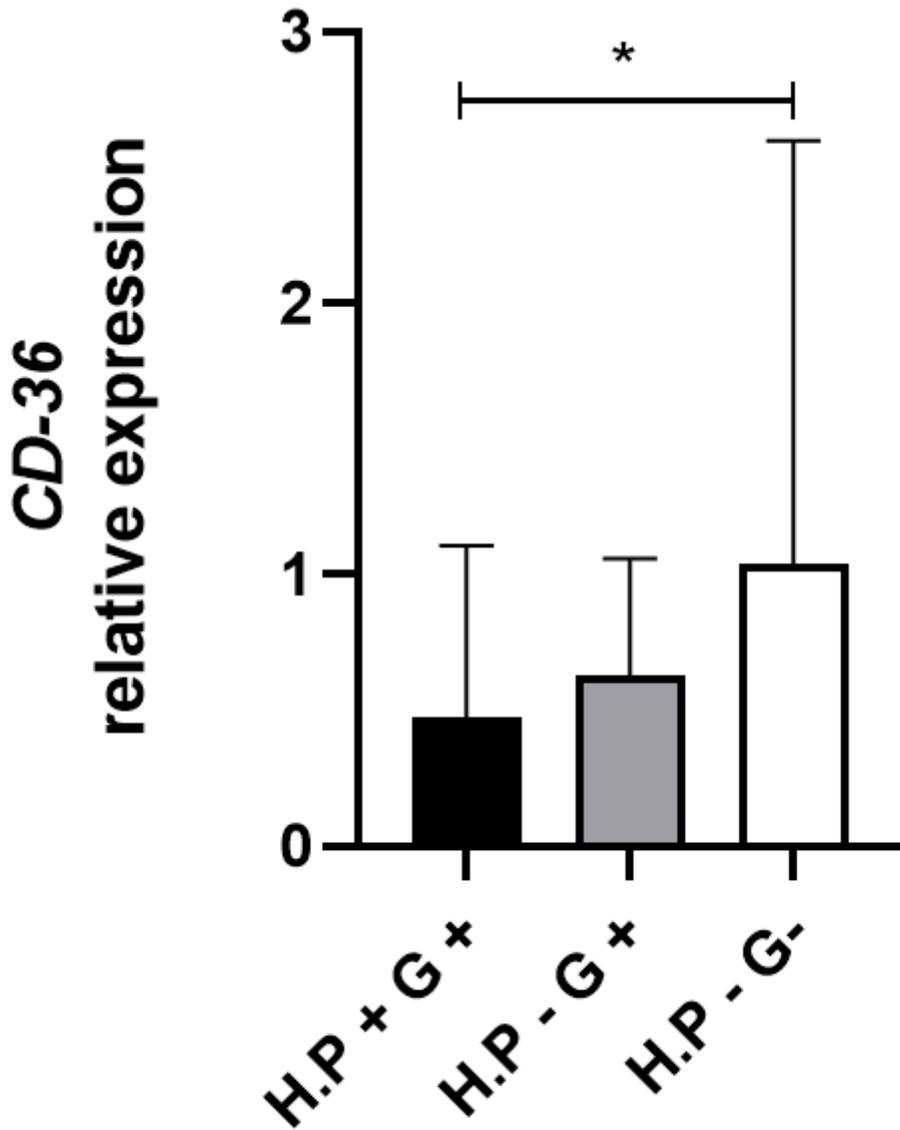


Figure 2

Comparison of *CD-36* relative expression levels in the three groups. Data were expressed as median (Interquartile Range). * $P < 0.05$, Kruskal-Wallis test, H.P-G-, H.P-G+, H.P+G+ are *H. pylori*-negative without gastritis, *H. pylori*-negative with gastritis, and H+G+: *H. pylori*-positive with gastritis, respectively.

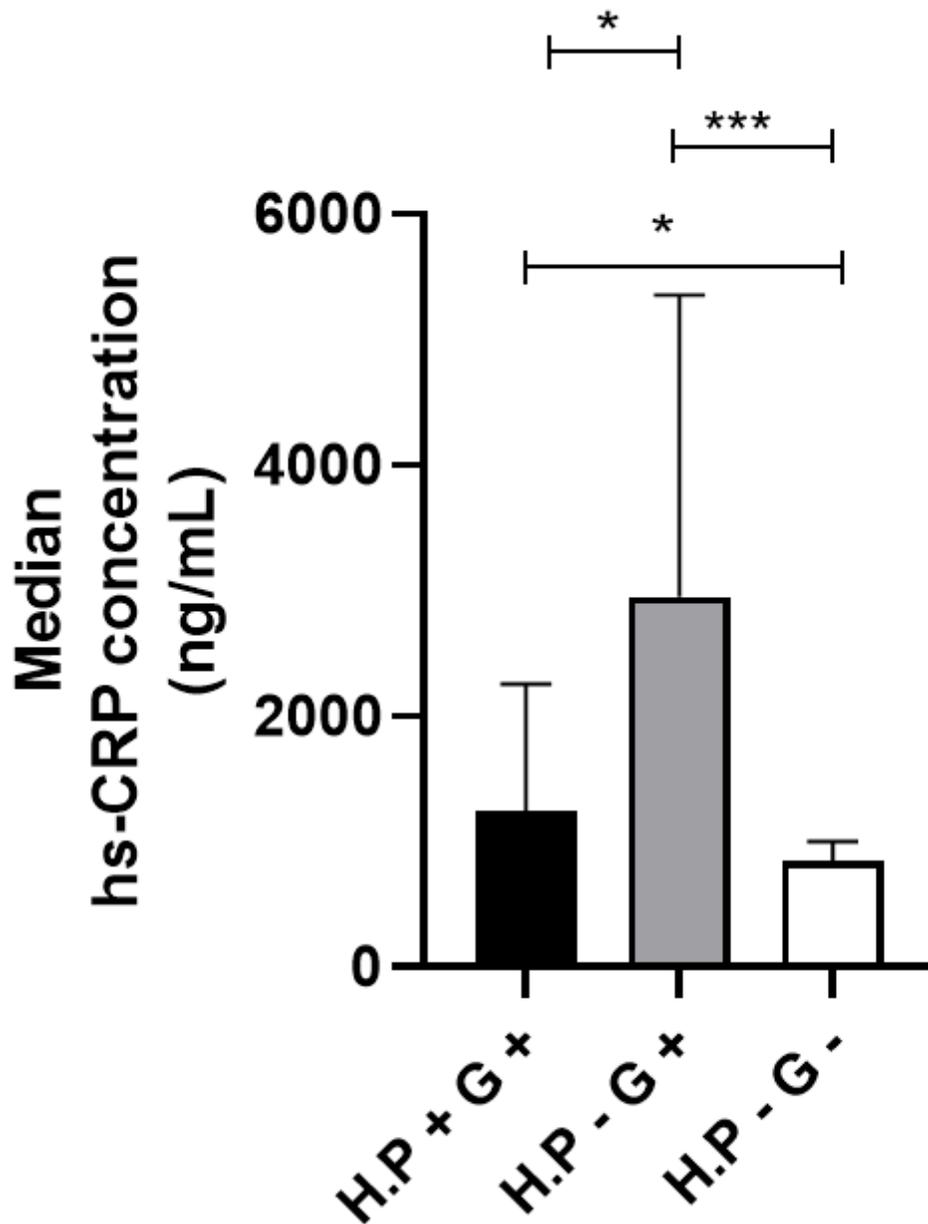


Figure 3

Comparison of hs-CRP levels in the three groups. Data were expressed as median (Interquartile Range). *P<0.05, *** P<0.001, Kruskal-Wallis test, H.P-G-, H.P-G+, H.P+G+ are *H. pylori*-negative without gastritis, *H. pylori*-negative with gastritis, and H+G+: *H. pylori*-positive with gastritis, respectively.

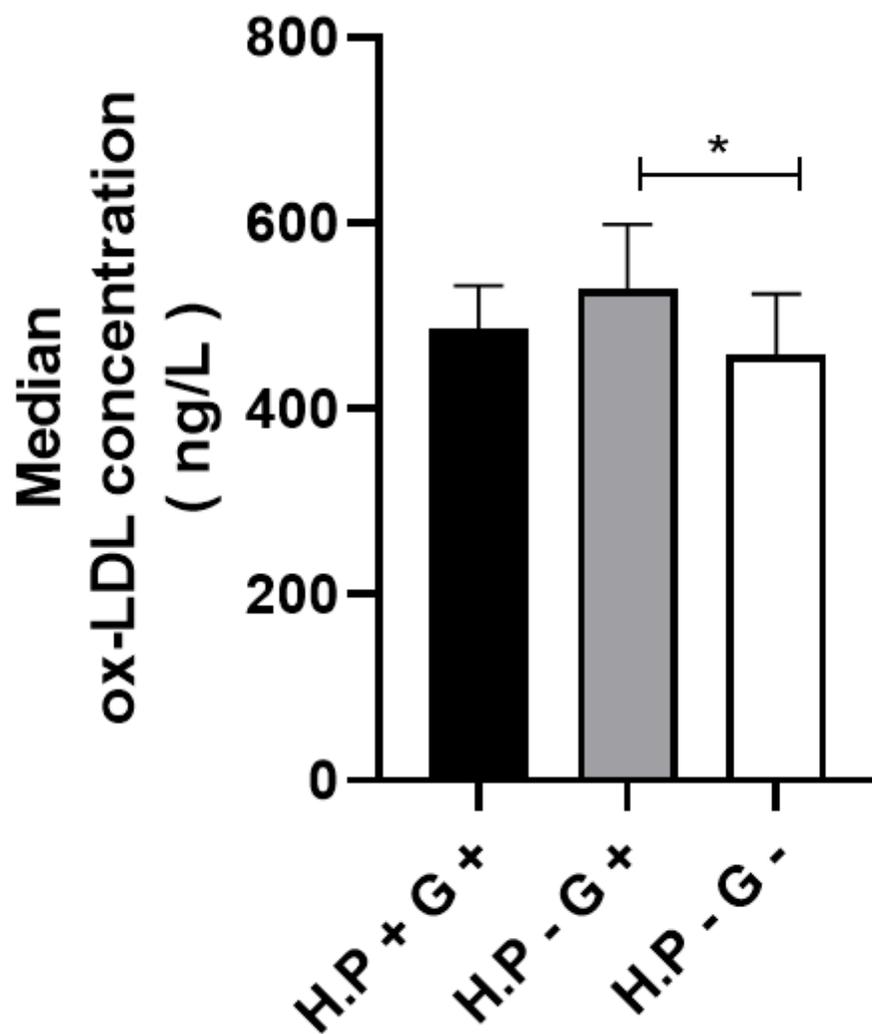


Figure 4

Comparison of ox-LDL levels in the three groups. Data were expressed as median (Interquartile Range). *P<0.05, *** P<0.001, Kruskal-Wallis test, H.P-G-, H.P-G+, H.P+G+ are *H. pylori*-negative without gastritis, *H. pylori*-negative with gastritis, and H+G+: *H. pylori*-positive with gastritis, respectively.

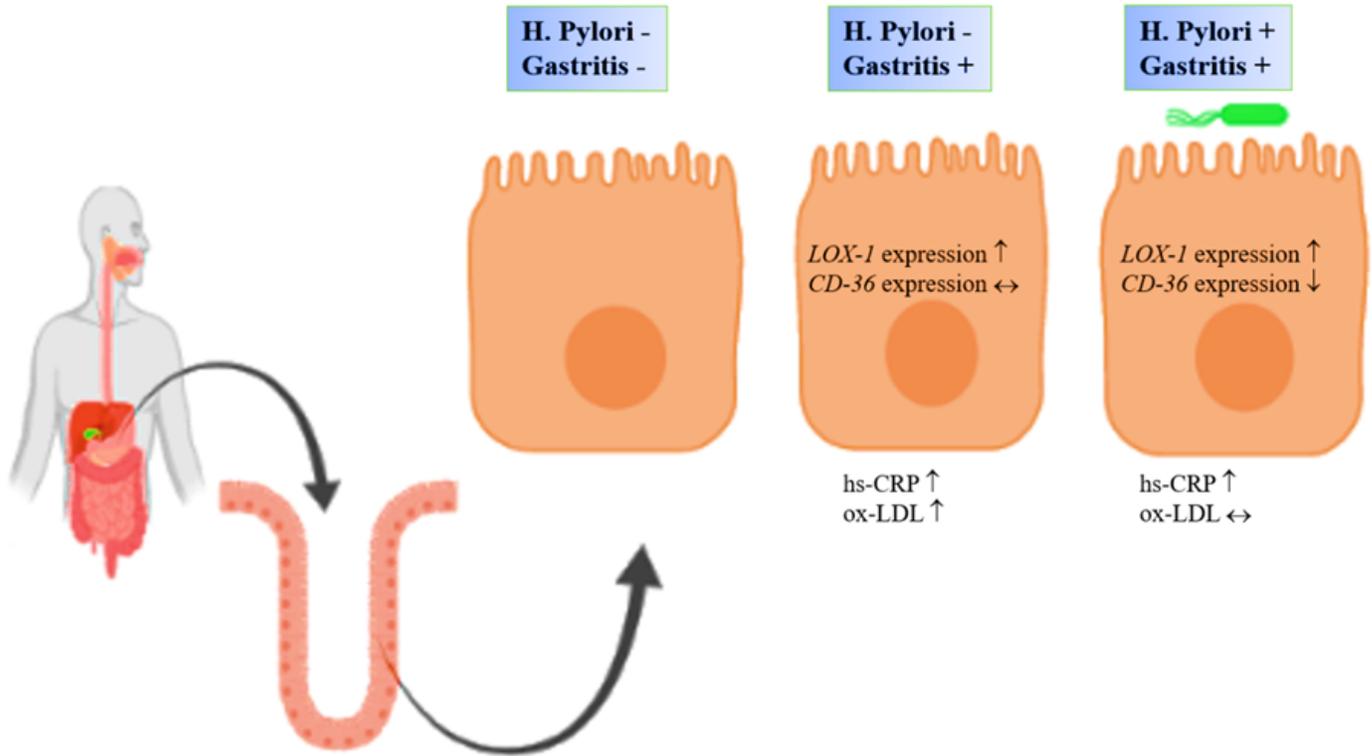


Figure 5

Gene expression status in the studied groups. Comparison of the groups was performed with *H. pylori* and gastritis negative. ↑: Increase. ↓: Decrease. ↔: Unchanged.