Observational Study

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Effects of active and latent *H. pylori* infection coupled with chronic alcohol ingestion on cytokine profiles and markers of oxidative balance in men seropositive for *H. pylori* CagA Ab

An observational study

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Abstract

This study aimed to explore the effects of active and latent *Helicobacter pylori* infection coupled with alcohol consumption on cytokine profiles and markers of oxidative balance in men seropositive for *H. pylori* CagA Ab.

The 100 male subjects were divided into groups with active *H. pylori* infection and *H. pylori* CagA Ab coupled with chronic alcohol ingestion (group A, n = 38), latent *H. pylori* infection with *H. pylori* CagA Ab coupled with chronic alcohol ingestion (group B, n = 30), and latent *H. pylori* infection with *H. pylori* CagA Ab without chronic alcohol ingestion (group C, n = 32).

No differences in serum levels of CRP, IL-10, ADP, E-selectin, MDA, or SOD were detected between the 3 groups or between any 2 groups (all $P > .05$). The serum IL-6 and TNF-α concentrations in groups A and B were significantly lower than those in group C ($P = .004$, $P = .005$, $P = .009$, and $P = .023$). However, there were no differences in serum IL-6 and TNF-α between group A and group B (all $P > .05$).

In conclusion, active or latent *H. pylori* infection coupled with chronic alcohol ingestion may decrease certain cytokines, that is, IL-6 and TNF-α, in men with *H. pylori* CagA Ab seropositivity. However, there was no difference in the detected cytokine profile between active and latent *H. pylori* infection coupled with chronic alcohol ingestion, and no changes were detected in markers of oxidative balance in men with *H. pylori* CagA Ab.

Abbreviations: ADP = adiponectin, CagA Ab− = CagA Ab negative, CagA Ab = cytotoxin-associated gene A antibody, CagA Ab + = CagA Ab positive, CHC = chronic hepatitis C, CRP = C-reactive protein, ELISA = enzyme-linked immunosorbent assay, *H. pylori* = *Helicobacter pylori*, IL-10 = interleukin-10, IL-6 = interleukin-6, MDA = malondialdehyde, pMMP-9 = pro matrix metalloproteinase-9, SOD = superoxide dismutase, TNF-α = tumor necrosis factor-α.

Keywords: chronic alcohol consumption, cytokine profiles, *H. pylori* CagA antibody positive, *H. pylori* infection, men, oxidative balance

1. Introduction

Helicobacter pylori (*H. pylori*) infection is one of the most common chronic bacterial infections affecting humans worldwide.[1] *H. pylori* has received much attention over the last 2 decades after its recognition as a pathogen that infects a significant proportion of the human population.[2] Low-to-moderate alcohol consumption is known to reduce the risk of cardiovascular disease; however, chronic high-dose alcohol consumption is associated with cardiovascular diseases, such as hypertension.[3] Previous studies have demonstrated that *H. pylori* and chronic ethanol intake are associated with increased incidences of a variety of illnesses, including atherosclerosis-related diseases such as cardiovascular and cerebrovascular diseases, metabolic diseases such as type 2 diabetes mellitus, fatty liver disease, gastrointestinal diseases, and cancers. The impact of chronic ethanol intake on *H. pylori* infection remains unknown. A previous study using a multiple logistic model demonstrated that alcohol consumption and related pathologies (i.e., active gastritis) are associated with *H. pylori* infection, establishing a link between alcohol consumption and this infection.[4] Chronic alcohol abuse appears to favor colonization by *H. pylori*, resulting in the production of ammonia that promotes the development of chronic gastritis.[5] Other studies have demonstrated an inverse relationship between ongoing moderate alcohol consumption and the presence of *H. pylori* infection, suggesting that alcohol consumption may facilitate the elimination of this chronic infection.[6] Daily alcohol consumption appears to have an additive effect on this eradication therapy,[7] and alcohol intake has also been suggested to promote

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elimination of *H. pylori* infection in adults.[6] For example, moderate consumption of wine and beer (approximately 7 units/wk) appears to protect against *H. pylori* infection, presumably by facilitating eradication of the organism.[8] The consumption of alcohol, particularly of wine, may reduce the risk of developing an active *H. pylori* infection.[9] Furthermore, heavy alcohol intake may be associated with reductions in the prevalence and severity of *H. pylori* infection.[10] However, contradictory results have demonstrated that the type of alcohol consumed does not affect the age-adjusted risk of *H. pylori* infection[11] and that smoking habits and alcohol consumption do not affect this infection in the stomach.[12] Our previous study[13] revealed that *H. pylori* CagA expression may lead to significantly higher levels of several inflammatory markers in both chronic alcohol users and nonconsumers. Chronic alcohol ingestion coupled with *H. pylori* CagA positivity does not result in significant changes in a subject's cytokine profile. However, it remains unclear whether male subjects presenting with *H. pylori* infection coupled with *H. pylori* CagA antibody positivity and chronic alcohol consumption exhibit cytokine profile changes or alterations in oxidative balance. We therefore sought to explore whether active and latent *H. pylori* infection with *H. pylori* CagA antibody positivity accompanied by chronic alcohol consumption might affect cytokine profiles and oxidative balance by measuring the levels of cytokines and oxidative markers.

2. Materials and methods

2.1. Ethics statement

Written informed consent was obtained from all the enrollees. The protocol was approved by the clinical research ethics committee of Taishan Hospital in Shandong Province.

2.2. Study population

A health examination-based cross-sectional study was conducted on 100 male subjects from January 2012 to May 2015. All of the subjects were evaluated for chronic alcohol consumption by completing a relevant questionnaire, and active *H. pylori* infection was assessed with the 13C-urea breath test.[14]*H. pylori* CagA positivity, in which a serum *H. pylori* CagA Ab concentration ≥80 pg/mL was considered positive (CagA Ab+), was analyzed in patients at Taishan Hospital, Shandong Province. Chronic alcohol ingestion for men was defined as a daily ethanol intake of greater than 40 g for a period of >5 years.[15] The subjects enrolled in this study were divided into the following 3 groups: active *H. pylori* infection with *H. pylori* CagA Ab positivity coupled with chronic alcohol ingestion (group A, n = 38), latent *H. pylori* infection with *H. pylori* CagA Ab and chronic alcohol ingestion (group B, n = 30), and latent *H. pylori* infection with *H. pylori* CagA Ab without chronic alcohol ingestion (group C, n = 32). This study was conducted to evaluate the correlations between alcohol consumption and cytokine profiles and oxidative balance in men with active and latent *H. pylori* infection coupled with *H. pylori* Ab positivity by measuring serum levels of *H. pylori* CagA Ab, C-reactive protein (CRP), interleukin (IL)-6, IL-10, adiponectin (ADP), E-selectin, tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), and superoxide dismutase (SOD) by enzyme-linked immunosorbent assay (ELISA). The clinical protocol conformed to the Declaration of Helsinki. Subjects were excluded based on the following criteria: a positive smoking status, the presence of a fever or infectious disease, the use of anti-inflammatory drugs, antibiotics or medication toxic to *H. pylori*, diagnosis of primary or secondary liver, kidney, heart, nerve, endocrine, autoimmune or hematological disease, the presence of an electrolyte or acid-base balance disorder, cancer, or mental disorders.

2.3. Experimental setup and reagents

The experimental equipment included an Enzyme Standard Instrument (Type ANTHOS 2010, Austria), and the reagents used in this study included ELISA kits for *H. pylori* CagA Ab, CRP, IL-6, IL-10, ADP, E-selectin, TNF-α, MDA, and SOD (Shanghai Enzyme-Linked Immune Co. Ltd., made by R&D Systems, USA).

2.4. Blood collection and handling

On the same day as the general health examinations were performed, peripheral venous blood samples were collected from the patients after fasting overnight for at least 10 hours. To measure serum levels of *H. pylori* CagA and CRP, IL-6, IL-10, ADP, E-selectin, TNF-α, MDA, and SOD, the samples were collected in ice-cold tubes containing EDTA (1 mg/mL) and centrifuged at 3000 rpm for 10 minutes. The plasma was then stored at −70°C until analysis. To ensure the reliability of the experimental results, all of the serum samples were carefully preserved, and repeated freeze-thaw cycles were avoided. Finally, all of the parameters were measured by ELISA according to the manufacturer's instructions.

2.5. Statistical analysis

The SPSS statistical package (version 17.0 for Windows; SPSS Inc., Chicago, IL) was used for all statistical analyses. All of the data for the 3 groups were expressed as the median and range; Kruskal–Wallis ANOVA was used for comparisons among the 3 groups, and the Mann–Whitney *U* test was used for comparisons between 2 groups. Differences with a *P* value of <.05 were considered statistically significant.

3. Results

Age, BMI, mean duration of alcohol use, and mean daily alcohol consumption are listed in Table 1. No differences in age were detected among the 3 groups or between any 2 groups, and no differences in the mean duration of alcohol use or mean daily alcohol consumption were detected between any 2 groups (all $P > .05$). No significant differences in BMI were detected among the 3 groups or between any 2 groups ($P > .05$).

Serum CRP, IL-6, and IL-10 concentrations from the subjects in each of the 3 groups are listed in Table 2. No differences in serum CRP and IL-10 levels were detected among the 3 groups or between any 2 groups (all $P > .05$). Significant differences in serum IL-6 concentrations were observed among the 3 groups ($P = .004$); the IL-6 concentrations in groups A and B were significantly lower than that in group C ($P = .004$, $P = .005$, respectively), and no difference in serum IL-6 was detected between group A and group B ($P > .05$). Serum ADP, E-selectin, and TNF-α concentrations in the 3 groups are listed in Table 3. No differences in serum ADP or E-selectin levels were detected among the 3 groups or between any 2 groups (all $P > .05$). Significant differences in serum TNF-α were observed among the 3 groups ($P = .017$); TNF-α levels were significantly lower in

Table 1

Comparison of age, BMI, mean duration of alcohol use, and mean daily alcohol consumption among 3 or 2 groups (medians with ranges).

Group	A	B	C	P
N	38	30	32	
BMI, kg/m^2	26.87 (20.10–35.60)	26.75 (21.10–30.20)	23.35 (19.50–29.50)	.089
Mean alcohol use duration, y	19.00 (5.00–40.00)	20.00 (5.00–30.00)		.648
Mean daily alcohol consumption, g	73.16 (29.25–146.26)	74.24 (43.88–146.26)		.548

BMI = body mass index.

Table 2

Comparison of serum CRP, IL-6, and IL-10 levels among the 3 groups (ng/L, medians with ranges).

Groups	N	CRP	IL-6	IL-10
A	38	3.06 (2.23–29.94)	29.35* (9.00–103.00)	621.00 (10.00–1998.00)
B	30	3.35 (2.53–6.14)	29.80† (19.00–72.00)	1080.80 (508.00–2921.00)
C	32	3.15 (2.18–20.58)	48.25 (21.00–109.00)	710.90 (350.00–1773.00)
P		.609	.004	.058

CRP = C-reactive protein, IL-10 = interleukin-10, IL-6 = interleukin-6.
* $P = .004$ (IL-6: group A vs group C).
† $P = .005$ (IL-6: group B vs group C).

Table 3

Comparison of serum ADP, E-selectin, and TNF-α levels among the 3 groups (ng/L, medians with ranges).

Groups	N	ADP	E-selectin	TNF-α
A	38	2481.50 (147.00–10412.00)	61.70 (6.00–240.00)	484.80* (258.00–1742.00)
B	30	2798.00 (860.00–6630.00)	95.50 (32.00–183.00)	650.20† (29.00–1774.00)
C	32	2506.30 (1582.00–7554.00)	84.60 (23.00–265.00)	894.95 (427.00–2978.00)
P		.761	.283	.017

ADP = adiponectin, TNF-α = tumor necrosis factor-α.
* $P = .009$ (TNF-α: group A vs group C).
† $P = .023$ (TNF-α: group B vs group C).

groups A and B than in group C ($P = .009$ and $P = .023$, respectively), and no difference in serum TNF-α was detected between group A and group B ($P > .05$).

Serum MDA and SOD concentrations in the 3 groups are listed in Table 4. No differences in serum MDA and SOD were detected among the 3 groups or between any 2 groups (all $P > .05$).

4. Discussion

Active *H. pylori* infection and alcohol consumption may induce changes in inflammatory markers levels. However, this viewpoint remains controversial. Previous studies have examined the association between *H. pylori* infection and *H. pylori* CagA positivity, but studies examining the relationship between active *H. pylori* infection and cytokine profile in patients with chronic alcohol consumption are lacking. Our present study demonstrated that active and latent *H. pylori* infection coupled with chronic alcohol ingestion may decrease the levels of certain cytokines, that is, IL-6 and TNF-α, in men with *H. pylori* CagA Ab seropositivity. However, there was no difference in the detected cytokine profile between active and latent *H. pylori* infection in patients with chronic alcohol ingestion, suggesting that chronic alcohol consumption may result in significantly lower levels of certain inflammatory mediators in men with active and latent *H. pylori* CagA Ab positivity, consistent with a previous study.[6]*H. pylori* infection has been reported to significantly and independently contribute to insulin resistance in a large asymptomatic population.[16]*H. pylori* is a highly pathogenic microorganism equipped with various strategies to evade human immune responses,[17] as supported by studies demonstrating that *H. pylori* infection is associated with increased serum TNF-α.[18] In contrast to previous findings, the presence of *H. pylori* infection was not found to affect the severity of portal hypertensive gastropathy or to augment IL-8 or TNF-α levels. A decrease in the abundance of virulent *H. pylori* strains has been associated with IL-10 levels in patients with advanced portal hypertensive gastropathy.[18] In addition, a study on serum cytokines revealed

Table 4

Comparison of serum MDA and SOD levels among the 3 groups (medians with ranges).

Group	n	MDA, ng/L	SOD, U/mL
A	38	10.85 (4.00–47.00)	107.40 (16.00–344.00)
B	30	14.00 (9.00–26.00	134.20 (76.00–243.00)
C	32	21.45 (4.00–43.00)	144.70 (60.00–380.00)
P		.360	.226

MDA = methane dicarboxylic aldehyde, SOD = superoxide dismutase.

that *H. pylori* infection in children does not affect systemic cytokine secretion, in contrast with adults.[19] The results of another study suggested that the TNF-857T/T genotype may confer protection against chronic *H. pylori* infection.[20]Therefore, the changes in systemic cytokine levels that have been observed in patients with various diseases occur differently in patients with *H. pylori* infection. Other previous studies have revealed that chronic infection with *H. pylori* expressing CagA is correlated with high circulating levels of IL-6,[13,21,22] TNF-α,[13] and ADP.[13] Similarly, alcohol consumption has been reported to alter the levels of certain cytokines, such as IL-6, IL-8, IL-10, IL-12, TNF-α,[23,24] and E-selectin.[25] Subjects who harbor CagA(+) strains of *H. pylori* exhibit more severe mucosal damage, increased bacterial colonization, an increased probability of developing duodenal ulcers, and increased serum TNF-α compared with subjects infected with CagA(−) strains.[26] In additionally, seropositivity for *H. pylori* was found to be strongly associated with CAG incidence, whereas advanced age and *H. pylori* infection are key risk factors for the development of CAG.[27] However, contradictory findings have suggested that *H. pylori* CagA is not associated with upregulation of IL-8 in gastric epithelial cells[19] and that host inflammatory responses in the gastric mucosa are not correlated with CagA expression.[28] Notably, different levels of alcohol ingestion can have distinct effects on the human body. Four weeks of moderate alcohol consumption can result in alterations in immune responses and lipid metabolism.[29] Chronic ethanol consumption is associated with increased incidences of a variety of illnesses, including cancer.[30] However, the subjects who slept well and consumed a moderate amount of alcohol exhibited the lowest IL-6 concentrations compared with the other 3 groups who consumed alcohol. Moderation and regularity in the practice of certain health behaviors, including sleep, have been associated with lower plasma levels of inflammatory markers in older adults.[31] Alcohol may modulate the inhibitory effect of TNF-α on ADP production and thus increase its plasma concentration.[32] Alcohol may specifically improve insulin sensitivity by increasing the expression of anti-inflammatory genes.[33] In agreement with previous studies, our study has demonstrated that active *H. pylori* infection, *H. pylori* CagA(+), and chronic alcohol consumption can affect the cytokine profile. In addition, *H. pylori* CagA positivity may be the main cause of changes in serum cytokines. However, additional studies are required to more deeply investigate the relationship between infection with CagA positive *H. pylori* and patient cytokine profile to determine the urgency in eradicating *H. pylori* infection and preventing the inflammatory reaction associated with *H. pylori* infection in patients displaying chronic alcohol consumption.

Substantial evidence indicates that *H. pylori* infection and chronic alcohol intake influence markers of oxidative stress. The results of the present study demonstrated that regardless of *H. pylori* infection or chronic alcohol ingestion, the subjects with *H. pylori* CagA Ab positivity presented with significant increases in the levels of MDA and SOD. *H. pylori* CagA Ab may therefore contribute to increased oxidative stress in men. Previous studies have demonstrated a close association between high MDA levels and *H. pylori* infection.[34,35] Oxidative stress has been shown to promote tissue damage in *H. pylori*-infected children.[36] In addition, moderate wine consumption may be advantageous for protection against this infection. For example, diabetic patients consuming a moderate amount of red wine and a polyphenol-enriched diet showed slower progression to diabetic nephropathy.[37] However, a contradictory study indicated that moderate alcohol consumption promotes oxidative stress in chronic hepatitis C (CHC) patients, suggesting a role of oxidative damage in CHC progression due to alcohol.[38] In addition, other studies have demonstrated that ethanol consumption may result in an oxidative stress imbalance[30,39,40] and that "adaptive cytoprotection" induced by chronic alcohol intake may increase the activities of gastric antioxidants to reduce mucosal damage.[41] Hence, alcohol may accelerate oxidative mechanisms directly by increasing the production of reactive oxygen species and indirectly by impairing protective mechanisms against these molecules.[42] In addition, increased levels of reactive oxygen species generated from acetaldehyde oxidation may contribute to oxidative stress damage.[43] Antioxidants and defense enzymes appear to confer protection as a consequence of chronic adaptation in alcoholics.[44] Research has shown that because antioxidant supplementation decreased the alcohol-induced pMMP-9 levels, oxidative stress could be one of the mediators of the generation of MMP-9.[45] Components in alcoholic and nonalcoholic wine, particularly polyphenols, may influence oxidative balance and endothelial function.[32] Furthermore, the roles of oxidative stress and *H. pylori* infection with CagA positivity in chronic alcohol ingestion and related diseases remain unknown. Previous studies have revealed that a low prevalence of *H. pylori* infection is associated with moderate alcohol consumption, suggesting a protective mechanism of adequate alcohol consumption mediated by "adaptive cytoprotection," which reduces the risk of *H. pylori* infection.[41] However, our previous study demonstrated no association between oxidative balance and *H. pylori* infection in patients with chronic alcohol consumption;[14] The present study detected no difference in markers of oxidative balance between active and latent *H. pylori* infection with *H. pylori* CagA Ab positivity and chronic alcohol ingestion. Hence, further studies are required to more rigorously evaluate these mechanisms.

Our study has several limitations. First, it is a prospective observational study rather than a randomized controlled study, and the number of subjects was low. Second, the roles of different types of alcohol in *H. pylori* infection with or without active *H. pylori* CagA Ab positivity were not examined in our study. In addition, the study samples were small and biased in that they only contained male subjects. This study was unable to control for the potential effects of other factors, such as other drugs.

In conclusion, active and latent *H. pylori* infection coupled with chronic alcohol ingestion may reduce levels of certain cytokines, that is, IL-6 and TNF-α, in men with *H. pylori* CagA Ab positivity. However, there was no difference in the cytokine profile between active and latent *H. pylori* infection in chronic alcohol users, and no changes were detected in markers of oxidative balance in men positive for *H. pylori* CagA Ab. These data suggest that chronic alcohol ingestion may help reduce the inflammatory response in men with active or latent *H. pylori* infection and CagA Ab positivity; we speculate that a curative treatment for *H. pylori* is not urgent in such populations. However, the number of subjects was low in this study, and more studies in the larger population are needed to confirm these findings.

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