Original Article

Association between the Treatment of Rosacea and Eradication of *Helicobacter Pylori* Infection

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Abstract

Background: Rosacea is a multifactorial skin inflammatory disorder with an unknown cure. Genetics and environmental factors such as microorganisms are involved in the rosacea etiology, for example, *Helicobacter pylori* have been suggested in rosacea progression. The present study investigated the relationship between *H. pylori* eradication and rosacea patient's improvement.

Materials and Methods: *H. pylori* infection was investigated in 60 rosacea patients and 65 sex- and age-matched healthy control through enzyme-linked immunosorbent assay (ELISA) and HpSag tests. After infection confirmation, randomly half of the rosacea patients were treated for *H. pylori* eradication (test), and others received standard treatment (control). HpSag and ELISA tests were repeated after infection eradication and disease flow was surveyed for 60 days. The groups were compared using the ANOVA (Analysis Of Variance) test at the significant level of $P < 0.05$.

Results: At the baseline, the mean of immunoglobulin G (IgG) (59.27 ± 41.4 RU/mL) and immunoglobulin M (IgM) (11.55 ± 6.1 RU/mL) in rosacea patients was higher than the level of IgG (41.38 ± 54.33 RU/mL) and IgM (8.11 ± 8.91 RU/mL) in healthy control ($P < 0.04$) and ($P < 0.01$), respectively. Also, the values for *H. pylori* infection were positive in all patients and 10 healthy controls. The mean titer of IgM and IgG in the test and control patients groups were different at baseline and after treatment. Furthermore, in the test patients group, the mean of IgG was reduced in active rosacea after treatment, and 63.9% of active patients showed rosacea remission after *H. pylori* eradication.

Conclusion: Data suggest the exacerbating role of *H. pylori* in rosacea, and its eradication along with other therapeutic methods causes rosacea improvement.

Keywords: Enzyme-linked immunosorbent assay (ELISA), immunoglobulin G (IgG), immunoglobulin M (IgM), rosacea, seropositivity

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Introduction

Rosacea is an inflammatory disease that affects the central convexities (central forehead, chin, cheeks, and nose) of the face skin[1] and is characterized by four subgroups of erythema, papules, papulopustular, and telangiectasia.[2] This disease can affect any sex, age, or skin type. However, it generally affects middle-aged, fair-skinned females, and when affecting men, the disease may be more severe.[3] The demographic profile of rosacea prevalence is similar among countries; however, it is most prevalent in Germany (12.3%) and Russia (5.0%).[4]

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The prevalence of rosacea in Iran is unknown but seems to be on the rise. There is no permanent therapy for rosacea. Although the pathophysiology of the disease is unknown yet, genetic predisposition, climatic factors, and microorganisms such as *Demodex folliculorum* and *Helicobacter pylori* have been mentioned as pathogenic factors in a variety of studies.[1]

H. pylori is a gram-negative and spiral-shaped bacillus that comprises a high number of different strains and infects half of the world's population.[5,6] *H. pylori* has been addressed in the pathogenesis of several gastrointestinal disorders such as chronic gastritis, gastric cancer, gastrointestinal ulcers, and various extra-gastric diseases.[7]

Because the risk of contact with bacteria is related to socioeconomic status and poor living conditions, infection is more common in developing countries, particularly in children under 10 years.[8] As a possible path of intestinal diseases, *H. pylori* induces cytokine production that induces the inflammation in gastric mucosa and host response, which results in the infiltration of inflammatory cells such as neutrophils and monocytes to the intestinal mucosa and mucosal inflammation.[9] It also produces enzymes such as urease, catalase, protease, lipase, and phospholipase that may be involved in the pathogenesis of intestinal inflammation.[10]

Besides its known role in intestinal diseases, some studies have proposed a potential role of *H. pylori* infection in other extra-intestinal diseases including distinct immune and non-immune disorders with skin manifestations such as Behçet's disease, psoriasis, chronic itching and burning, and rosacea.[11] In recent years, concerning manifestations of improvement after eradicating *H. pylori* infection, some studies have indicated that *H. pylori* infection is associated with the occurrence of acne rosacea.[12-14]

As it has been suggested that *H. pylori* induces rosacea through cytotoxin-mediated chronic inflammation and gastrin-induced flushing.[15,16] The role of chronic inflammation is highlighted with host pro-inflammatory cytokines (tumor necrosis factor-alpha [TNF-α], interleukin-1 beta [IL-1β]), nitric oxide (NO), matrix metalloproteinases (MMP-1, MMP-3, and MMP-9), vascular endothelial growth factor (VEGF), and reactive oxygen species (ROS), which have been linked to rosacea in recent studies.[17] The cytokines associated with rosacea are adapted to the known pathogenicity of the gram-negative bacteria.[18] Also, endotoxins (such as lipopolysaccharides), as parts of the external membrane of the gram-negative bacteria, stimulate a variety of inflammatory responses (mild to severe).[19]

Hence, according to this evidence, it has been accepted that the absence or presence of *H. pylori* infection may trigger or develop rosacea. Therefore, this study assayed whether *H. pylori* infection plays a pathogenic role in rosacea. Thus, the prevalence of *H. pylori* infection in rosacea patients, in comparison with control individuals, and the effect of *H. pylori* infection eradication on disease improvement were investigated.

Materials and Methods

Study area

The study was conducted in 2021 in Isfahan city, located in the central part of Iran, with moderate and dry weather ranging between 10 and 40°C and a population belonging to the Persian/Caucasian ethnicity. So far, the prevalence of rosacea in this city has not been reported.

Study description

This study was a without blinding, randomized, and case-controlled trial. After receiving the code number (IR.MUI.MED.REC.1399.628) of the Ethics Committee of Isfahan University of Medical Sciences, 60 patients with definite rosacea (42 active and18 inactive) being treated by dermatologists of skin diseases clinics, with or without considerable improvement, were chosen randomly according to a preexisting list produced by a computer program of the subjects attending to skin centers. Also, 65 healthy controls who matched in age and gender were subjected. Written informed consent was obtained from all participants, and researcher-made questionnaires were filled out at the time of enrollment. The course of the disease was defined as "active" if there was an alternation of worsening and improvement phases in the last 1 year and "inactive" otherwise.

Age under 17 years, presence of any intestinal or stomach symptoms such as bloating, nausea, intake of antibiotics [Proton pump inhibitors (PPIs) and bismuth subsalicylate] and (Prilosec and Nexium) during a month before the study onset, pregnancy, recent childbirth, patients with depression and anxiety, presence of antibiotic complications, and reluctance to continue contribution were considered as exclusion criteria for the study.[20]

The dermatology team examined rosacea based on assaying primary and secondary signs and symptoms of rosacea and classified them based on the Duluth scoring system, as absent, mild, moderate, or severe (0–3). Primary manifestations of rosacea included papules and pustules, flushing (transient erythema), non-transient erythema, and telangiectasia. Secondary manifestations include plaques, burning or stinging, edema, dry appearance, peripheral location (present or absent), ocular manifestations, and phymatous changes. Outcome measurements were made at the start of the trial (day 0) and the end of the trial (day 60).[14]

Then, fresh feces were collected from all participants in sterile sampling containers and the samples were stored in 10% formalin. Also, 5 mL of blood sample was taken from each individual and was centrifuged, and the separated sera were stored at –20°C. Screening for *H. pylori* was done using *H. pylori* serum immunoglobulin G (IgG)/immunoglobulin M (IgM) and feces antigen tests, and all tests were read by the same researcher.

H. pylori surface antigen (HpSag) test

To detect *H. pylori* antigens qualitatively, feces samples were analyzed using the Premier Platinum HpSAg kit (DRG International Inc.). According to the manufacturer's instructions, HpSAg values ≤0.9 U/mL and >0.9 U/mL were considered negative and positive, respectively.[21]

ELISA

The serum level of *H. pylori* IgM and IgG was determined by the ELISA test using *H. pylori* IgG and IgM kits (Euroimmun olfactory, Germany). Tests were conducted based on the manufacturer's instructions and *H.pylori* IgM titer >12 RU/mL and *H. pylori* IgG titer >20 RU/mL were regarded as seropositive.

Intervention in the treatment

In this study, the intervention was an antibiotic treatment. As, after infection confirmation, randomly half of 60 rosacea patients ($n = 30$) (test group) in addition to standard treatment of rosacea (local gels of metrogel + metronidazole 75% [250 mg] two times daily),[22] were treated for *H. pylori* eradication with standard 2-week triple therapy including clarithromycin 500 mg p.o. b.i.d., metronidazole 500 mg p.o. b.i.d., and pantoprazole 40 mg p.o. q.d.[14] The other half of the 60 rosacea patients ($n = 30$) (control group) received the standard treatment of rosacea.[22]

At the end of the treatment course, again blood and feces samples were taken from patients to investigate the eradication of *H. pylori.* Then, all rosacea patients (test and control groups) were regularly followed up and the severity of rosacea was investigated based on the Duluth rosacea grading score at the end of the trial (day 60) by the same dermatology team.[14]

Statistical analysis

Quantitative data are shown as mean ± standard deviation (SD), and qualitative data are presented as percent and frequency (%). The demographic data were compared with the Chi-squared test and *H. pylori* antibody levels (including IgM and IgG) compared in the two groups of rosacea patients and healthy control/patient control by Student's *t*-test. Also, the level of IgG and IgM before and after treatment was compared by Wilcoxon signed-rank and ANOVA tests. Furthermore, in each group, the levels of IgM and IgG were compared with other factors using the Chi-Square test. A *P*-value <0.05 was considered significant. Probable confounding factors such as anxiety and depression were included as inclusion and exclusion criteria and other factors such as age and sex, which could have been confounding factors were assayed using multivariate analysis. Also, instrumental variables (IVs) analysis to adjust for the probable bias created by contamination was used.

Results

Comparisons of data of rosacea patients with healthy control

A total of 60 patients with rosacea (48 females and 12 males F/M = 4/1, median age 48 years [SD 12.48]) and 65 healthy control (35 females and 30 males F/M = 1.05/1, median age 39 years [SD 15.08]) were included in the study. Among patients with rosacea, 18 patients (30%) had an inactive course and 42 patients (70%) had an active course of rosacea. The most common clinical manifestations of rosacea were red bumps and sensory symptoms such as facial itching and burning. The percentage of patients' characteristics is mentioned in Table 1.

HpSag test was positive in all 60 patients with rosacea (100%) and 10 healthy controls (6.5%).

Moreover, a statistically significant correlation was found between *H. pylori* positivity in patients with rosacea compared to the seropositivity of healthy control. The mean level of *H. pylori* IgG and IgM in the rosacea group was higher than the healthy control group [Table 2].

Furthermore, the analysis of data based on gender showed that the mean titer of either *H. pylori* IgG/IgM in the females of rosacea was statistically higher than in healthy control females [Table 2]; however, the mean either IgG/IgM in the men of the rosacea group was not statistically different in comparison with the healthy control men [Table 2].

Comparisons of data of test and control groups

Statistically, we did not observe any correlation between either *H. pylori* IgG or IgM at baseline with age, disease symptoms, smoking, taking supplements, menopause, history of autoimmune, sexual, and breathing diseases as well as the progression of rosacea in both groups; however, there was only a correlation between IgM at baseline and onset age. In contrast, in both groups, there was a significant relationship between the mean of IgG and IgM levels at baseline with the disease duration i ($P = 0.000$) and ($P = 0.05$), respectively. The levels of IgG and IgM increased with the duration of the disease in the test group compared with the control.

Table 1: Percentage of patients' characteristics

Characterization	Patients ($n=60$)
Nationality (Iranian)	100%
Race (Persian/Caucasian)	95%
Family history of Rosacea	13.3%
Skin color	
White	35%
White to light brown	48.3%
Dark brown	16.7%
History of travel to the sea	36.7%
History of self-autoimmune diseases (vitiligo, lupus, alopecia, type 1 diabetes, hypothyroidism)	31.7%
Family history of autoimmune diseases	45%
History of menopause	33.3% (Female)
History of Pap smear test	61.7%(Female)
History of respiratory diseases	23.3%
History of sexual diseases	16.7%
Taking supplements	63.3%
Smoking history	0 (Male)
Drinking history	1.7% (Male)

Table 2: Baseline data and IgG and IgM serum levels of patients and healthy control groups

	Patients ($n=60$)		Healthy control ($n=65$)		P	
H. pylori IgG (RU/mL)	59.2776±41.4	F (58.2990±40.9)	41.3846±54.3	F (30.7714±47.6)	0.04	F (0.006)
		M (63.1918±44.9)		M (53.7667±59.6)		M (0.625)
H. pylori IgM (RU/mL)	11.5550±6.1	F (11.2146±6.41)	8.1123±8.1	F (6.6843±8.8)	0.01	F (0.008)
		M (12.9167±4.6)		M (9.7783±8.8)		M (0.143)

Regarding the progression of the disease, there was no significant difference between the progression of the disease and time exposed to sunlight, skin color, and autoimmune diseases in both groups.

Moreover, the *post hoc* analysis of data based on gender demonstrated that at baseline, the titer of IgG/IgM in the females of the test group was higher than that in the control group females; however, the mean titer of either *H. pylori* IgG or IgM was not statistically different between control men and test men [Table 3].

Also, there was a significant difference between the two groups regarding the level of IgG and IgM after treatment. Furthermore, the mean of IgG and IgM titer was significantly different before and after treatment in each group and control [Table 4].

Rosacea severity scores of test and control groups were statistically indifferent before the intervention; however, rosacea symptoms in the test group subsided (63.9%) after 60 days in most of the criteria, except for telangiectasia ($P = 0.512$) compared with control. In addition, there was a significant relationship between lesion size and the levels of IgG and IgM before treatment ($P < 0.05$) and ($P < 0.04$) and after treatment ($P < 0.05$) and ($P < 0.04$) in both test and control groups, respectively. Baseline data and serum levels of *H. pylori* IgG and IgM of 60 subjects (test and control groups) are compared in Table 4.

Moreover, the mean titer of *H. pylori* IgG at the baseline was not significantly different between inactive and active rosacea of both groups; however, the mean level of IgM at baseline was higher in the active rosacea patients of control (8.4350 ± 4.57 RU/mL) than in inactive patients (4.5900 ± 4.05 RU/mL) ($P < 0.033$). After treatment, the disease progression was lower than the baseline in the test group. In contrast to the control group, the mean level of IgG in active patients of the test group was lower than that in inactive patients [Figure 1]. Also, in contrast to the control group, the mean level of IgM was not different between the active rosacea and inactive rosacea of the test group [Figure 2].

Furthermore, IgG or IgM levels were significantly different in comparison with digestive problems after treatment in the test group ($P = 0.026$) and ($P = 0.001$), respectively. Also, there was a significant relationship between the progression of the disease and the digestive problems before ($P < 0.000$) and after treatment ($P < 0.049$) in both the test and control groups. After treatment, the level of digestive problems was reduced in active patients of the test group compared to inactive patients [Figure 3].

Table 3: Baseline IgG and IgM serum levels of F/M in test and control patient groups

		Test group ($n=30$)	Control group ($n=30$)	P
*H. pylori*IgG titer (RU/mL)	Gender	F (77.98±34.9)	F (42.98±39.14)	0.002
		M (59.42±42.13)	M (74.50±61.47)	0.638
H. pylori IgM titer (RU/mL)	Gender	F (16.93±3.67)	F (6.76±4.12)	0.000
		M (13.67±2.65)	M (10.63±8.96)	0.618

Table 4: Baseline data and IgG and IgM serum levels of test and control groups

	Test ($n=30$)	Control ($n=30$)	P
Age (yr)	51.8000 (±12.6)	45.2667 (±11.6)	0.04
Onset age (yr)	42.5667 (±14.3)	38.8667 (±12.9)	0.29
Mean duration of rosacea (yr)	9.2333 (±9.5)	6.4000 (±6.8)	0.19
H. pylori IgG titer (RU/mL) before treatment	72.4152 (±37.5)	46.1399 (±41.5)	0.013
H. pylori IgG titer (RU/mL) after treatment	27.8633 (±15.8)	13.0287 (±13.4)	0.000
H. pylori IgM titer (RU/mL) before treatment	15.9567 (±3.67)	7.1533 (±4.7)	0.000
H. pylori IgM titer (RU/mL) after treatment	4.8469 (±3.61)	1.3762 (±1.95)	0.000
Duluth score before treatment	9.32 (±4.46)	9.2 (±3.49)	0.09
Duluth score after treatment	2.39 (±2.49)	5.35 (±3.02)	0.001

Discussion

Numerous studies have obtained different results about the relationship between *H. pylori* infection and rosacea.In agreement with several studies that pointed to a probable pathogenic role of *H. pylori* in rosacea,[23-25] the results of our study revealed a significant mean level of anti-*H. pylori* antibodies (IgG and IgM) in a sample of 60 rosacea patients compared to 65 healthy controls. Other researchers did not obtain any significant difference in the prevalence of *H. pylori* infection between rosacea patients and controls,[26-28] which might be because of the different methods of *H. pylori* infection evaluation between these studies and ours (i.e., serology versus 13C urea breath test [UBT], respectively).

We also investigated whether the eradication of *H. pylori* infection affected symptoms of rosacea. Our study showed

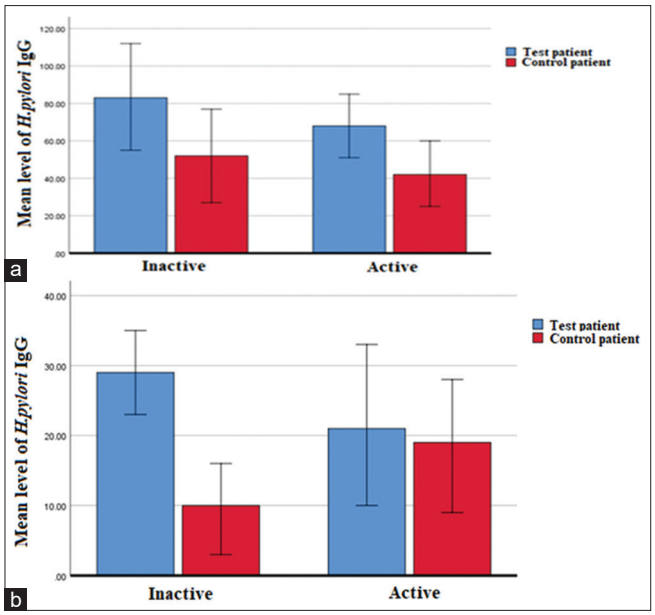

Figure 1: Comparison of the level of *H.pylori* IgG and the progression of rosacea disease at baseline (a) and after treatment (b) in test and control groups. The mean level of IgG at baseline in inactive patients of both groups was higher than in active patients. Also, in contrast to the control, the mean level of IgG in active patients of the test group was lower than in inactive rosacea after treatment

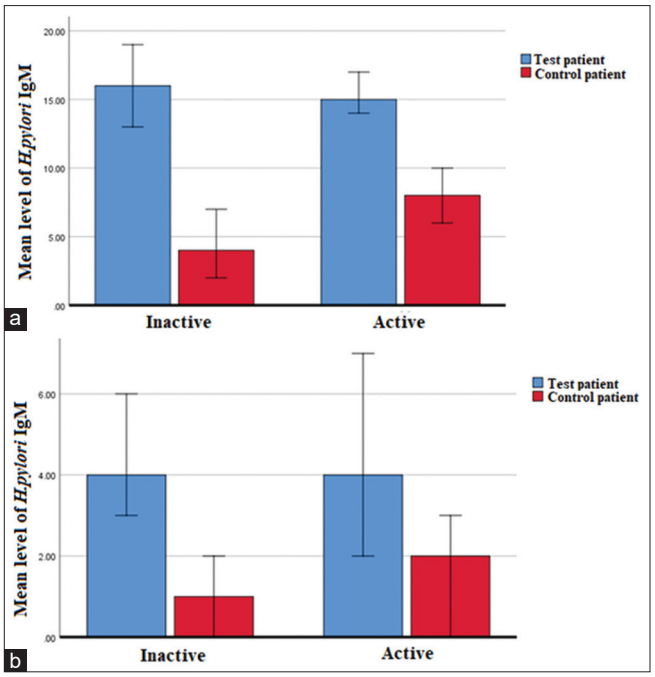

Figure 2: (a) Comparison of the level of *H. pylori* IgM and the progression of rosacea disease at baseline (a) and after treatment (b) in test and control groups. In contrast to the control group, the mean level of IgM was not different between active rosacea and inactive rosacea of the test group

that *H. pylori* eradication can be effective in decreasing the symptoms of rosacea. There was a significant difference between the levels of anti-*H. pylori* antibodies (IgG and IgM) before and after infection eradication and disease remission was found in 63.9% of the test group after infection eradication. The scores for erythema intensity revealed a significant difference between baseline and follow-up in the test group, and a significant reduction was shown for the number of pustules in the test group. We expected that clearing *H. pylori* infection would permanently clear or markedly decrease the rosacea; however, this did not happen, which may depend on the remained bacteria in the extragastric mucosa of rosacea patients. Similar to our study, numerous researchers reported a total or partial improvement in rosacea signs after the eradication of bacteria with antibiotics. For example, Bothaina *et al*.[29] found earlier and more marked improvement in rosacea in negative (75%) patients than still positive patients for *H. pylori*. Furthermore, in the study by Tampouratzi *et al*.[30] the *H. pylori*-positive group on eradication therapy showed significant improvement in the rosacea severity. In contrast, Gravina *et al*.[31] showed that only the prosperous eradication of *H. pylori* resulted in the total or partial regression of the skin lesions. The skin lesions of rosacea disappeared or decreased markedly in 97.2% of patients after eradication of *H. pylori,* within 10 weeks from the end of antibiotic therapy. In contrast, the results of other studies opposed substantially our results on the relation of the eradication of *H. pylori* with the clinical improvement in skin lesions.[32,33]

It is well known that Caucasians are more commonly affected by rosacea. Moreover, females between the ages of 30 and 60 years present rosacea symptoms three times more than men, which may be related to the greater medical request of females and the hormone's role in the pathogenesis of rosacea.[25] In the present study, there was no age-related increased frequency of *H. pylori* infection in patients and females who were more frequently affected. The mean level of IgG/IgM in females of the rosacea group was higher than in females in the healthy control group; however, there was no difference between men of both groups. In agreement with our results, previous reports by Berg and Liden[34] and Sharma *et al*.[26] also found rosacea is more common in females (76.5 and 89%, respectively). In contrast, other studies revealed that gender had no contribution to the etiology of the disease. Researches also show that the progression of rosacea is different among persons, depending on factors such as genetics, infections, skin sensitivity, menopause, exercise, consumption of alcohol, and smoking. These risk factors may potentially exacerbate the conditions although rosacea generally can be well controlled through suitable treatment and avoidance of triggers.[35] Our study showed that against the control patient group, the disease progression after treatment in the test patient group reduced in comparison to baseline; however, we did not find any evidence of an association between risk factors and the progression of rosacea. Recently, studies also have shown rosacea patients have higher genetic risks for a variety of autoimmune disorders such as type 1 diabetes and celiac disease.[36] Our study also included rosacea patients with a history of autoimmune diseases such as vitiligo, lupus, alopecia, type 1 diabetes, and hypothyroidism.

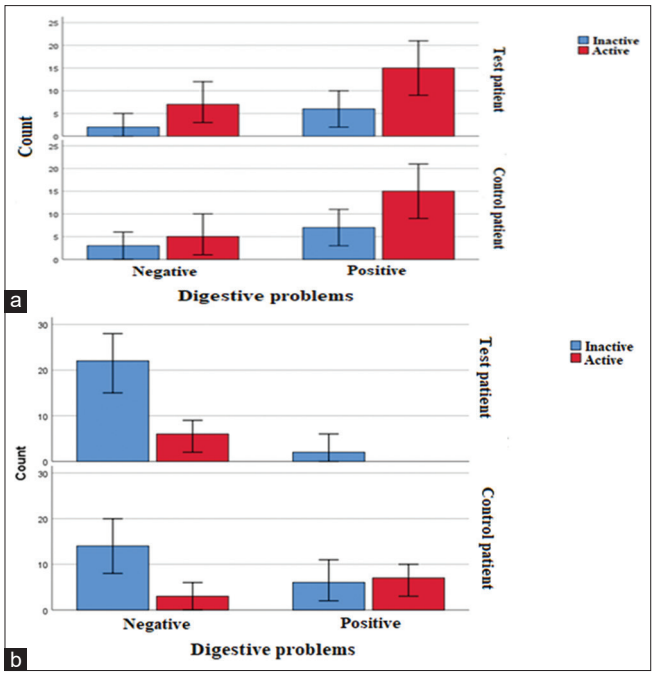

Figure 3: (a) Comparison of the progression of rosacea and digestive problems at baseline (a) and after treatment (b) in test and control groups. In contrast to the control group, the mean level of digestive problems was reduced in inactive patients compared with inactive patients in the test group

Furthermore, late research has shown that infections may have a significant role in severe forms of rosacea.[37] Likewise, in this study, the mean level of *H. pylori* IgG/IgM in patients with inactive rosacea was significantly lower than in patients with active rosacea. Indeed, *H. pylori* chronic infection results in the production of higher levels of pro-inflammatory cytokines and can cause uncontrolled proliferation of CD5 cells, which produce self-activating IgM and IgG3 antibodies. In our study also, the progressive reduction in rosacea and disease symptoms improvement was obtained only when second-line therapy for *H. pylori* was given, which seems antibiotics improve rosacea possibly by changing intestinal flora. After treatment, IgG or IgM levels were significantly different in comparison with disease symptoms and disease progression.

Because the present study was a randomized clinical trial, we expected comparable patients in both the test and control groups. This expectation was fulfilled by adjusting the effect of sex and age as confounding variables. Also, according to our results, there were no differences between the two groups of test and control regarding their gender and age; therefore, these two variables were not confounders in this study. Moreover, because none of the drugs showed any side effects, the total adherence for both groups was >90% throughout the study and the 60 participants completing the study took all prescribed drugs. Because of the limitations of our study (including the type of our study [case–control study]), its inability to blind study because of the interventional nature of the study, its weakness in completely controlling confounding variables, low sample size, and other feasible factors that may be responsible for positive results and the loss of various laboratory tests for better detecting *H. pylori* infection), other studies should be performed in larger multivariable cohorts and controlled trials to express more precise evidence in the future and generalize this idea to a larger population.

Conclusion

Concerning the higher prevalence of *H. pylori* infection in rosacea patients than control and significant improvement in skin symptoms in patients after eradication of *H. pylori* infection, these results propose the need to consider diagnostic tests for assessing and eradicating this bacterium in the list of therapeutic approaches for rosacea patients, especially in areas with a high prevalence of *H. pylori* infection. Also, researchers on the precise molecular mechanism of *H. pylori* infection on rosacea progression could be useful. Thus, further studies in different populations with more precise diagnostic tests and methods are needed to evaluate the importance of this finding.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her/his consent for her/his images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Ethical approval

The experimental protocols of this study were approved by the Institutional Research and Ethics Committee of Medical Sciences from the Isfahan University of Medical Sciences with the code number IR.MUI.MED.REC.1399.628.

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Conflicts of interest

There are no conflicts of interest.

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