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ABSTRACT

Background. Helicobacter pylori has been suggested to have extra gastroduodenal complications other than the gastroduodenal conditions. Serological surveillance is the most discussed H. Pylori role in the incidence of cardiovascular disease. We have designed this research to evaluate the effect of H. Pylori infection on endothelial dysfunction in children.

Methods. This quasi-experimental research recruited 50 children Between 4-18 years old with H. Pylori infection. Endoscopic results, histopathologic reports, and the presence of Helicobacter pylori in biopsy samples were recorded after esophagogastroduodenoscopy. Echocardiography was done and carotid intima-media thickness (IMT) and flow-mediated diameter percent change (FMD) were assessed in three main stages: at the time of admission, 1.5 months, and 3 months after antibiotic eradication started.

Results. The vascular diameter at rest and in the hyperemic state, and also FMD had significant statistical differences between the admission time and 1.5 months later. All four vascular

variables have been improved significantly after 3 months of treatment. The analyses revealed a significant difference in FMD and vascular diameter in a hyperemic state between the second and third visits. Significant positive correlations were found between age and diameter at rest and also between age and diameter in hyperemic state, at the time of admission, after 1.5 months and 3 months of medication.

Conclusion. Based on our results, treatment of H. Pylori was significantly correlated with FMD and vascular diameters at rest and hyperemic state; therefore, it seems that eradication of H. Pylori infection would improve cardiovascular parameters.

Keywords: Helicobacter, FMD, IMT, gastritis, Endothelial disorders

INTRODUCTION

Cardiovascular abnormalities comprise a wide range of diseases, such as myocardial infarction, coronary artery atherosclerosis, etc [1]. Coronary artery diseases are a group of life-threatening illnesses following endothelial dysfunction, intima media alterations, local inflammation, platelets aggregation, blood clot formation, and finally myocardial blood supply dysfunction [2,3].

Several infectious and non-infectious risk factors have been introduced for cardiovascular diseases [4]. Chlamydia pneumonia, CMV, EBV, HIV, and HSV are considered infectious risk factors for heart diseases [1,5].

Helicobacter pylori (H. Pylori) has been recently introduced as a contributing factor to the development of heart diseases [6]. Infection of H. Pylori in children is mostly asymptomatic; however, it has a wide spectrum of signs and symptoms such as nausea, vomiting, dyspepsia, epigastric pain, chronic abdominal pain, heartburn, halitosis, and regurgitation [7]. Extra gastroduodenal manifestations have been also reported as unjustifiable iron deficiency anemia, Henoch-Schoenlein purpura, autoimmune thrombocytopenic purpura, inflammatory bowel disease, asthma, etc [8-10].

Various immunological and inflammatory processes leading to cardiovascular disorders have been revealed to be provoked by H. Pylori which induces multiple direct and indirect impacts on vessels' endothelium [1,11]. Endothelial injury, circulating endotoxins inducing dysfunctional circulation, and smooth muscle proliferation are instances of direct influences of H. Pylori. While, hypercoagulability, atherogenesis, cross-reactive antibody production, and LDL oxidation are probable indirect effects [12]. Additionally, there are some studies supporting some other indirect influences such as nutrient malabsorption, ammonia over-production, and oxidative modification [13].

Due to diverse epidemiological research, a higher prevalence of H. Pylori infection has been reported during recent decades [6]. The frequency of h. Pylori among 9–15-month-old children has been reported almost 57-82% [14,15].

Regarding the fact that coronary artery diseases appear from childhood and the likelihood effect of h. Pylori infection on the cardiovascular system [16,17], and also the increasing rate of chronic H. Pylori infection in children [6,18], we have designed this research to evaluate the impact of H. Pylori infection on endothelial dysfunction in children.

METHODS AND MATERIALS

This quasi-experimental study enrolled 50 children aged 4 to 18 years with confirmed H. pylori infection, identified through Urea Breath Test (UBT) or stool antigen tests, at Mofid Children's Hospital, Tehran, Iran, from 2020 to 2022.

Inclusion and exclusion criteria: Inclusion criteria encompassed children presenting with symptoms such as halitosis, abdominal pain, nausea, vomiting, gastroesophageal reflux, and dyspepsia alongside positive H. pylori tests. Exclusion criteria included pre-existing cardiac conditions or any history of heart-related medications. Due to the COVID-19 pandemic, participant retention was affected: 50 children were initially enrolled, but only 43 completed the 1.5-month follow-up, and 25 attended the 3-month follow-up.

Sample Size: The study aimed to recruit 50 children aged 4 to 18 years with confirmed H. pylori infection. This sample size was selected to ensure adequate statistical power to detect significant differences in vascular parameters post-treatment. Due to challenges posed by the COVID-19 pandemic, 43 participants completed the 1.5-month follow-up, and 25 completed the 3-month follow-up, allowing for a robust analysis of treatment effects on endothelial dysfunction.

Study Procedures

1. Esophagogastroduodenoscopy (EGD): Conducted by a pediatric gastroenterologist, this included a Rapid Urease Test. All endoscopic findings and histopathological reports were documented using a standardized questionnaire.

2. Echocardiography: Performed by a pediatric cardiologist to assess carotid intima-media thickness (IMT) and flow-mediated dilation (FMD).

3. FMD Measurement: The brachial artery FMD measurement involved a two-dimensional ultra-sonographic measurement of the brachial artery diameter before and after a 10-minute occlusion of the cubital blood flow by inflating (50mmHg over systolic blood pressure) and deflating a proximal upper arm cuff under cardiac monitoring. The process was performed after 6 hours of fasting at the supine position on a bed in a quiet and dark environment with a

temperature of 24-26°C, based on the Guidelines of the International Brachial Artery Reactivity Task Force (DMAX-DMIN) /DMIN * 100=FMD%) [19,20].

4. IMT Measurement: It involved a B-MODE ultra-sonographic estimation of the thickness of the inner most two layers of the arterial wall which provided us with the span of the lumen-intima and media-adventitia interfaces [21]. We calculated the IMT by estimating an average of three digits measured from the right common carotid artery exactly before the bifurcation site. IMT≥1 mm was considered an abnormal range for carotid artery [22].

5. Treatment Protocol: All participants received a quadruple therapy regimen for H. pylori eradication—amoxicillin, metronidazole, bismuth for 14 days, and omeprazole as a proton pump inhibitor for 30 days.

Follow-Up Assessments

All evaluations (UBT, stool antigen tests, echocardiography for FMD and IMT) were repeated at three time points: at admission, after 1.5 months of treatment, and after 3 months of treatment.

Data Collection

Data were meticulously recorded in a pre-prepared questionnaire divided into five sections:

1. Clinical manifestations

2. Stool H. pylori antigen results at three stages

3. UBT results at three stages

4. Endoscopic findings and histopathological reports

5. Echocardiographic results (IMT, FMD, vascular diameters at rest and during hyperemia) at three stages.

Ethical Considerations and consent to participation: The study was approved by the local ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1400.602). Informed consent was obtained from each participant or their guardian prior to inclusion in the study, ensuring that all individuals were fully aware of the research purpose, procedures, potential risks, and benefits. Participants were informed of their right to withdraw at any time without penalty, in accordance with the principles outlined in the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were executed using SPSS Statistics version 26.0 (Illinois, USA). Quantitative variables were expressed as mean ± standard deviation (SD), while qualitative variables were reported as rates and percentages. The Chi-square test, T-test, and ANOVA

were employed for statistical comparisons with significance set at $P < 0.05$. A repeated measures analysis was utilized for FMD data assessment.

RESULTS

A total of 50 children (4-18 years old) positive for H. Pylori infection with a mean age of 10.6±3.1 entered our study. 29 (58%) were female and 21 (42%) were male. The frequency of H. Pylori among males was more than among females and was statistically significant(p-value≤0.05).

The most common symptoms were abdominal pain (86%) and polydipsia (78%). Other clinical manifestations are listed in Table 1.

Table 1 Clinical signs and symptoms of children with H. Pylori infection

Clinical symptoms and signs	Total (n=50)
Abdominal pain	43 (86.0%)
Polydipsia	39 (78.0%)
Halitosis	34 (68.0%)
Prone Sleeping	30 (60.0%)
Early satiety	28 (56.0%)
Anorexia	26 (52.0%)
Rolling in sleep	26 (52.0%)
Heartburn	24 (48.0%)
Nausea	23 (46.0%)
Drooling	21 (42.0%)
Regurgitation	17 (34.0%)
Vomiting	15 (30.0%)
Globus sensation	15 (30.0%)
Pyrosis	13 (26.0%)
Dysphagia	11 (22.0%)
Constipation	10 (20.0%)
Polyphagia	10 (20.0%)
GI bleeding	4 (8.0%)

Each test (UBT test, stool HP-Ag) was performed in three stages (at the time of admission, 1.5 months, and 3 months after admission). Positive UBT and positive Stool HP-Ag were obtained in 47 and 48 children, respectively. Stool HP-Ag was negative in 48 cases after 3 months. Almost 96% of cases had positive stool HP-Ag test which changed into 2% after 3 months of medication (Four-drug regimen: Amoxicillin, Metronidazole, Bismuth, and Omeprazole). Additionally, positive UBT results decreased from 96% at the first visit to 2% at the third visit.

The 2% positive UBT residue at the third visit was due to H. Pylori infection in one of the parents or family members.

Rapid test was also evaluated in the first step at the time of endoscopy. All cases had positive results at the first visit. On the second visit, it turned into 2% positive. The results of laboratory findings in all three stages are summarized in Table 2.

Table2- Results of laboratory findings in three steps of patients

Positive Laboratory findings	Total (n=50)
UBT (First Result)	48(96.0%)
UBT (Second Result)	6(12.0%)
UBT (Third Result)	1(2.0%)
Stool HP-Ag (First Result)	47(94.0%)
Stool HP-Ag (Second Result)	6(12.0%)
Stool HP-Ag (Third Result)	1(2.0%)
Rapid Test (First Result)	50(100.0%)
Rapid Test (Second Result)	1(2.0%)
Rapid Test (Third Result)	-

The most common endoscopic findings of the esophagus were 68% normal view and 28% esophagitis. None of the cases had gastric prolapse; however, 72% had pan-gastritis with no evidence of gastric ulcer, antral ulcer, or gastric outlet obstruction. In addition, a normal view of duodenum was found in 62% of patients; 18% had erythematous duodenitis. The endoscopic findings are shown in Table 3.

Table 3 - Endoscopic findings in patients with H. pylori infection

Variable	Total (n=50)
Esophagus	
Normal	34 (68.0%)
Esophagitis	14 (28.0%)
Esophageal ulcer	4 (8.0%)
Gastric Prolapse	-
Hiatal Hernia	2 (4.0%)
Stomach	
Normal	-
Nodularity (nodular gastritis)	35 (70.0%)
Antral Gastritis	11 (22.0%)
Pan gastritis	36 (72.0%)
Erosive Gastritis	14 (28.0%)
Gastric Ulcer	-
Antral Ulcer	-
Gastric Outlet Obstruction	-

Hypertrophic Gastropathy	1 (2.0%)
Duodenum	
Normal	31 (62.0%)
Duodenal Ulcer	5 (10.0%)
Erythematous Duodenitis	9 (18.0%)
Atrophic Duodenitis	2 (4.0%)
Nodularity	2 (4.0%)
Erosive Duodenitis	3(6.0%)

Histopathologic study of esophagus showed 43% normal, 43.9% mild esophagitis, 7.3% moderate esophagitis, and 4.9% severe esophagitis. Barret esophagus and esophageal ulcer had not been reported.

The most common finding of the gastric pathology was 56.1% moderate chronic gastritis with moderate activity. Other gastric histopathologic findings are listed in Table 4.

Table4- gastric pathology results

Gastric pathology	**Total(n=50)**
Normal	0
Mild chronic gastritis with mild activity	19.5%
Mild chronic gastritis without activity	9.8%
Moderate chronic gastritis with moderate activity	56.1%
Moderate chronic gastritis without activity	7.3%
Severe chronic gastritis with moderate activity	4.9%
Severe chronic gastritis without activity	2.4%

Pathological study of duodenum revealed 19.5% normal, 53.7% mild duodenitis, 24.4% moderate duodenitis, and 2.5% erosive duodenitis. 5 cases had gastric metaplasia.

An echocardiographic study was performed in all three stages to evaluate IMT and FMD and to compare the diameters at rest and hyperemic state. The statistical comparison was done due to the paired T-test to compare the measures at the time of admission, 1.5 months, and 3 months after medication.

The analyses among 43 cases revealed that the vascular diameter at rest and vascular diameter in the hyperemic state had significant statistical differences between the first time and 1.5 months later(p-value<0.05). Additionally, FMD had a significant statistical difference between the first time and 1.5 months later(p-value<0.05). Moreover, the same comparisons in terms of the vascular evaluations between the time of admission and 3 months later showed that all four variables have improved significantly after 3 months (p-value<0.05).

Table 5 shows a general schema of the above-mentioned details. The comparison of four variables between the second visit (after 1.5 months) and the third visit (after 3 months) showed a significant difference in FMD and the vascular diameter in hyperemic state (P-value<0.05).

Table5. Comparison of four variables of cardiac findings in patients with H. pylori infection

Variable	Before (n=43)	1.5 Months After (n=43)	*P*-value	1.5 Months After (n=25)	3 Months After (n=25)	*P*-value
FMD (%)	8.22 ± 0.77	9.14 ± 1.06	<0.001	9.15 ± 1.12	9.53 ± 1.15	0.03
IMT (mm)	0.52 ± 0.06	0.51 ± 0.05	0.17	0.51 ± 0.05	0.51 ± 0.05	0.53
Vascular diameter at rest (mm)	2.32 ± 0.32	2.33 ± 0.31	<0.001	2.36 ± 0.33	2.36 ± 0.33	0.08
vascular diameter in hyperemic state (mm)	2.51 ± 0.34	2.53 ± 0.35	<0.001	2.57 ± 0.36	2.58 ± 0.35	0.03

FMD: flow-mediated dilation; IMT: Intima media thickness, Analysis with Paired t-test

The pathological study of endoscopic samples showed 80.5% positive for H.Pylori. No difference was found between H.pylori pathology of groups in terms of vascular variables.

Regarding to Repeated Measures Test, we compared the vascular factors(diameter at rest, diameter in hyperemic state, FMD, and IMT) in terms of gender in three stages of the study(at the admission time, 1.5 months later, and 3 months later).

The comparison of FMD evaluations between the two genders in all three stages revealed significant statistical differences (P-value<0.05) (Figure 1). Vascular Diameter at rest, vascular diameter in hyperemic state, and also IMT showed no difference in each stage in terms of gender(P-value>0.05) (figure 2, figure 3, and Figure 4).

The increase in FMD between the second and third visit in females was more than in males and the difference was statically meaningful(p-value<0.05).

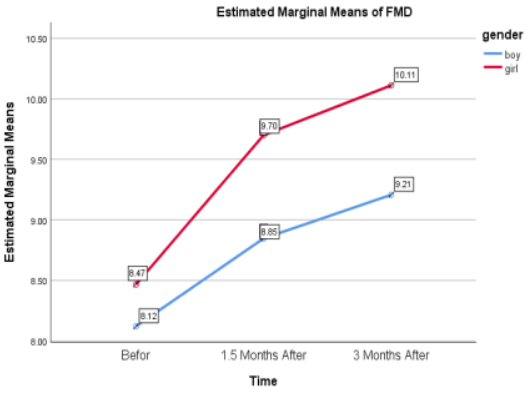

Figure 1- FMD at each stage in terms of gender.

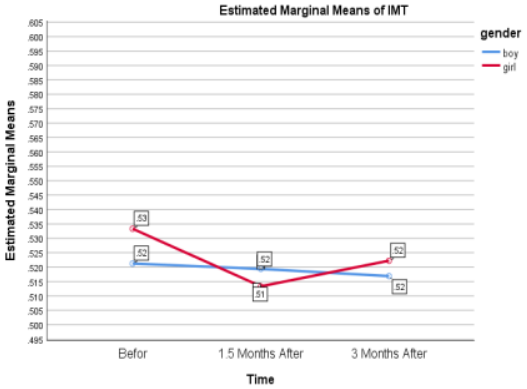

Figure 2- IMT at each stage in terms of gender

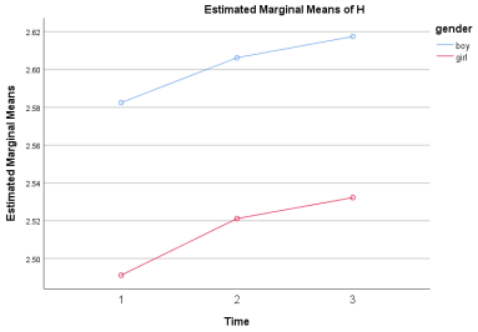

Figure 3- vessels diameter at hyperemic state in terms of gender

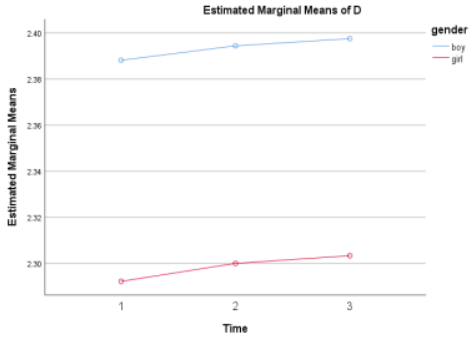

Figure 4- vessels diameter at rest in terms of gender

Based on the Pearson correlation Test, no meaningful statistical relationship was found between FMD and age in any of the stages of the study. However, the same test revealed a

significant positive correlation between age and vascular diameter at rest at all three stages(at the time of admission, 1.5 months, and 3 months after medication) (P-value<0.001) (r: 0.70, 0.73, and 0.72, respectively). Pearson correlation Test also showed a significant positive correlation between age and vascular diameter at hyperemic state at all three stages (P-value<0.001) (r: 0.70, 0.73, and 0.72, respectively). Furthermore, A positive relationship was found between age and IMT at all three stages(P-value<0.001) (r: 0.68, 0.75 and 0.76, respectively).

In other words, a positive statistical correlation was found between age and vessel diameter and also between age and IMT at all three stages: the vessel diameter and IMT were higher in older cases (p-value≤0.05).

The vessel diameter at rest and also in hyperemic state at the second visit in comparison with the first visit was higher (p-value≤0.05).

The vessel diameter at rest and in a hyperemic state at the third visit in comparison with the first and second visits were higher (p-value≤0.05).

The increase in FMD at the second visit in comparison with the first visit was statistically meaningful (p-value≤0.05).

The increase in FMD at the third visit in comparison with the first and second visits was statistically meaningful (p-value≤0.05).

The IMT of the third visit was lower than the first visit and was statistically significant(p-value≤0.05). The IMT of the second visit was reported to be lower than the first visit; however, it was not statistically meaningful.

To summarize the results, the frequency of h. Pylori among males was more than females. The most common symptoms were abdominal pain and polydipsia. 96% of cases had positive stool HP-Ag test which changed into 2% after 3 months. Positive UBT results altered from 96% at the first visit to 2% at the third visit. All cases had positive rapid test at the first visit which turned into 2% at the second visit. FMD had a significant statistical difference between the first visit and the second visit. FMD, IMT, vascular diameter at rest, and vascular diameter in hyperemic state all improved significantly after 3 months (p-value<0.05). Two variables-FMD and the vascular diameter in the hyperemic state showed a significant difference from the second visit to the third visit. The increase in FMD between the second and third visit in females was more than in males. Significant positive correlations were revealed between age and vascular diameter at rest, between age and vascular diameter in the hyperemic state, and also between age and IMT at all three stages: the vessel diameter and IMT were higher in older cases. The vessel diameter at rest and also in hyperemic state at the second visit was higher in comparison with the first visit. The vessel diameter at rest and in a hyperemic state at the third visit was higher in comparison with the first and second visits. The increase in FMD at the second visit was statistically meaningful in comparison with the first visit. The increase in FMD at the third visit in comparison with the first and second visits was statistically meaningful. The IMT of the third visit was lower than the first visit and was statistically significant.

DISCUSSION

Based on our analyses, the frequency of positive results for UBT, stool HP Ag, rapid test, and biopsy was 97.6%, 93.7%, 100%, and 80.5%, respectively. The lower frequency of positive pathology in comparison with UBT, stool HP Ag, and also rapid test is because the H.pylori microorganisms are less-detectable in the histopathological view of children than adults which is regarding the lower microbial load in children and also the history of antibiotics ingestion in most of them [23]. Therefore, despite the negative pathology, the four-drug regimen was prescribed for the symptomatic children with positive endoscopic or laboratory results in our trial.

In the study of Abbas et al, the most common symptoms of H. Pylori infection were 25.5% nausea, 24.5% abdominal pain, and 20.2% heartburn. Based on our study the most common presentations were 92.7% abdominal pain, 80.5% polydipsia, and 75% halitosis. Nausea was ranked as the sixth most common symptom based on our results (56.1%). The differences could be related to different demographic characteristics such as race, age, and also different sample sizes [24].

In the study of Okuda et al, the most common endoscopic finding of h.pylori among children and adolescents was nodular gastritis which is also common in Crohn's disease and celiac, etc. Therefore, such diseases should be ruled out by pathological study in patients with nodular gastritis, even if H.pylori infection has been confirmed [25]. Based on our results, none of the children with h. Pylori infection had a normal endoscopic view. The most common endoscopic views were 75.6% pangastritis and 70% nodular gastritis.

On one hand, It is noteworthy to mention that endoscopic reports are thoroughly operator-dependent; hence, the differences in frequency of each endoscopic view could be expected in various pieces of research.

On the other hand, as h.pylori colonization initially occurs in the gastric antrum, nodular gastritis would be the first endoscopic view of h.pylori infection especially if endoscopy is performed in early phases of infection. However, progressive long-term h.pylori infection would probably be ended up with pangastritis. Hence, it seems that the cases of our study were mostly at the advanced stage of infection in which pangastritis has been diagnosed in 75.6% of cases [5,26].

A study by Gurbuz et al performed in Istanbul-Turkey concluded similar results to ours in terms of endoscopic view. They reported pangastritis and nodular gastritis as the two most common endoscopic views in H. Pylori infection, respectively [27]. The similarity of results might be due to the geographic and cultural similarities between Iran and Turkey which seem to have similar foods, diets, analogous spices, and equivalent ingredients for foods.

Gastric atrophy, gastroduodenal ulcer, and intestinal metaplasia are rare pathologies in children compared with adolescents. These pathologies are mostly related to the chronicity of H. Pylori infection and require long-term infection; therefore, they are unlikely to be formed in children [28,29]. Due to our results, the most common finding of the gastric pathology was moderate gastritis with activity and the most common duodenal pathology was mild duodenitis. None of our cases had gastric or duodenal ulcers. 10% (5 out of 50) had gastric metaplasia in duodenum which was a red flag for chronic and long-term h.pylori infection.

Various articles have emphasized the role of homocysteine accumulation on cardiovascular diseases regarding to Vitamins B6, B9 and B12 deficiency resulting from malabsorption following chronic h.pylori infection [18,26,30,31]. Furthermore, there are various articles expressing the relationship of endothelial disorders and h.pylori infection due to increased level of inflammatory cytokines(IL-6, IL-1β) and CRP [32,33].

A clinical trial in 2011 pointed out that treatment of h.pylori infection has ended with the improvement of CIMT, ankle-brachial index, and FMD three months after admission. This study has concluded that h.pylori eradication would result in the prevention of atherosclerosis and cardiac diseases [34]. Moreover, another article in 2005 concluded that H. Pylori infection is directly correlated with systemic inflammation and endothelial disorders [30].

Li A et al in 2018 reported that the average FMD increases in both females and males approximately beyond 13 and 14 years old, respectively; however, the rate of increase is higher in the female group [35]. Based on our results, the average of FMD was higher in the females which could be related to hormonal effects such as estrogen. Nevertheless, we could not find any statistical correlation between age and FMD which might be due to the small sample size or h. Pylori infection among our cases.

The average FMD in the study of Li A was 8.2% which was similar to our results at the time of admission (8.2%) [35]. The average of FMD improved to 9.2% after 1.5 months and 9.5% after three months during our trial.

A similar study on British children has estimated an average of 8% for FMD[35]. Hence, the differences in FMD among different groups of children seem to be related to racial and genetic varieties. However, further trials are needed to be done.

An Iranian article in 2019 on 2-16-year-old children has found that the risk of endothelial disorders increases in case of positive h.pylori infection [36].

On the other hand, the study on 7-17-year-old Turkish children has concluded that there was no statistical difference between children with and without a history of h.pylori infection in terms of lipid profile, CRP, and serum homocysteine level [37]. It is noteworthy to mention that this article has divided the groups of children based on the h.pylori IgG, not the presence of h.pylori infection at the time of study. In other words, the H. Pylori infection had not been confirmed by UBT or stool Ag. In addition, h.pylori IgG resists after treatment for a while and it might be positive in the absence of h.pylori infection. Therefore, it seems that our results would be more reliable due to the h.pylori infection confirmation by stool Ag, and UBT.

Based on our results, the vessel diameter at rest hyperemic state and also FMD had significant improvement following h.pylori four-drug regimen. However, IMT after three months of h.pylori eradication had minimal improvement (almost 0.01 mm of decrease) which was not clinically significant. It might be due to the more time-consuming process of IMT improvement in comparison with other above-mentioned parameters.

There are several documents in parallel with our claim that justify the longer process of IMT improvement, such as exome-mediated mechanisms, increased level of homocysteine, increased level of CRP, and YKL-40 factor resulting from h.pylori infection which all have negative effects on endothelial healing process. Therefore, treatment of H.Pylori infection inhibits the production of inflammatory factors and induces the healing process [38-40].

Limitations and Suggestions

This study has several limitations, including a small sample size of 50 children, which may affect the generalizability of the findings. The dropout rate during follow-up, particularly due to the COVID-19 pandemic, reduced the number of participants analyzed at later stages, potentially impacting the robustness of the results. Additionally, the quasi-experimental design lacked a control group, limiting causal conclusions about the effects of H. pylori eradication on endothelial dysfunction. Future research should involve larger sample sizes and randomized controlled trials with a control group to enhance validity. Long-term studies assessing the impact of H. pylori treatment on cardiovascular health, as well as investigations into genetic and lifestyle factors influencing outcomes, would provide further insights into this important area of pediatric health.

CONCLUSION

Regarding our results, h.pylori eradication would lead to improvement of cardiac parameters (FMD, vessel diameter at rest, and hyperemic state).
Our study had various limitations such as a small sample size and poor compliance of some cases in follow-up visits due to the COVID-19 pandemic. Hence, further clinical trials with larger sample sizes are recommended.

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