REVIEW

Association of Helicobacter Pylori with Presence of Myocardial Infarction in Iran: A Systematic Review and Meta-Analysis

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OPEN ACCESS

Citation: Yousef Rahmani, Sareh Mohammadi, Mehran babanejad, Alireza Rai. Bahar Zalei, Afshar Shahmohammadi Association of Helicobacter Pylori with Presence of Myocardial Infarction in Iran: A Systematic Review and Meta-Analysis. J Health Sci 2017; 27(4):433. doi: http://dx.doi.org/10.4314/ejhs.v27i4. 15

Received: February 27, 2017 **Accepted** February 28, 2017 **Published:** July 1, 2017 **Copyright:** © 2017 Yousef, R., *et al.* This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. **Funding:** Nil

Competing Interests: The authors declare that this manuscript was approved by all authors in its form and that no competing interest exists.

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ABSTRACT

BACKGROUND: Over the past decade, cardiovascular diseases have been recognized as the leading cause of mortality worldwide. Myocardial infarction (MI) is one of the most prevalent types of cardiovascular diseases that is caused by the closure of coronary arteries and ischemic heart muscle. Numerous studies have analyzed the role of H. pylori as a possible risk factor for coronary artery diseases, in most of which the role of infection in coronary artery disease is not statistically significant.

METHODS: These contradictory findings made us conduct a systematic review to analyze all relevant studies in Iran through a meta-analysis and report a comprehensive and integrated result. All published studies from September 2000 until September 2016were considered

. Using reliable Latin databases like PubMed, Google Scholar, Google search, Scopus, Science Direct and Persian databases like SID, Irandoc, Iran Mede and Magiran. After quality control, these studies were entered into a meta-analysis by using the random effects model. After evaluating

the studies, 11 papers were finally selected and assessed.

RESULTS: A total of 2517 participants had been evaluated in these studies, including 1253 cases and 1264 controls. Based on the results of meta-analysis and using random effects model, an overall estimate of

OR Helicobacter Pylori with Presence of Myocardial Infarction in Iran was *OR=2.53 (CI=1.37-4.67)*.

CONCLUSIONS: The results of this review study show that H. pylori are associated with the incidence of MI so that the odds ratio of MI in the patients with helicobacter pylori is twice greater than that of the people without H. pylori. Future studies are recommended to evaluate the mechanisms associated with relation of H. pylori with MI as well as its association with time.

KEYWORDS: Myocardial infarction, H. pylori, Meta-analysis, Iran

INTRODUCTION

Over the past decade, cardiovascular diseases have been recognized as the leading cause of mortality worldwide. These diseases caused the death of 16 million people (30%) and made 293 million people (11%) disabled in 2010 (1,2). The same as many high-income developed countries over the past century, the low- and middle-income countries currently seem to be at the risk of an increased rate of cardiovascular diseases (3).

Myocardial infarction (MI) is one of the most prevalent types of cardiovascular diseases that is caused by the closure of coronary arteries and ischemic heart muscle (4). Atherosclerosis is a chronic process with various reasons which cause the formation of plaque on the walls of coronary arteries over the years. Accumulation of lipoproteins and oxidation and non-enzymatic glycation changes cause the gradual development and enlargement of plaque. On the other hand, accumulation of phagocytes and macrophages and migration of smooth muscle cells in an inflammatory process cause the development of atherosclerosis. Atherosclerosis plaque injury activates the trombogenesis process, forming a clot on the walls at the lesion site and blocking the coronary artery. Accumulation of plaques and release of thromboxane A2, potent retractors, cause a complete arterial blockage (3.5).

In the United States, one is afflicted with MI every 20 seconds, one dies due to MI every minute and about 50% of patients require rehabilitation and other measures following MI (6). According to the reports of the Ministry of Health and Medical Education in 2010, MI was recognized as the cause of 38% of mortalities. In recent years, the age of heart attack has dropped, affecting the young people too (7).

Many risk factors such as old age, male gender, family history of early atherosclerosis, hyperlipidemia, hypertension, diabetes, smoking and obesity have been identified as causes of myocardial infarction (8). Further, evidence has been found to show the association of inflammatory indicators like CRP and fibrinogen with the risk of coronary artery diseases (9). Infection has been proposed to be involved in the incidence of atherosclerosis in recent years (6). Bacteria such as helicobacter pylori (H. pylori) and chlamydia pneumonia and viruses like cytomegalovirus and herpes have also been found to be involved in the incidence of atherosclerosis (8). Studies have shown that although infectious factors are not directly involved in the incidence of atherosclerosis, they stimulate the inflammatory response of atherosclerosis development and facilitate its complications (10).

Helicobacter pylori are one of the most common human infections, and half of the world population is suffering from this infection. H. pylori have been recognized as the leading cause of several diseases of the upper digestive system since 1984. The incidence of H. pylori is much variable from 15% to 85%. It has been reported to be 20-50% in the developed countries and over 80% in the developing countries (11,12). More than 80% of adults in Japan and Southern America are suffering from this infection, while this rate has been reported to be 40% in the U.K and 20% in Scandinavian countries (12). The incidence of H. pylori in Iran is more than 80%. Although it seems that it declined in the recent years, its incidence is still very high (13).

Numerous studies have analyzed the role of H. pylori as a possible risk factor for coronary artery diseases, in most of which the role of infection in coronary artery disease is not statistically significant. Mandell et al. were the first to study the association of H. pylori with incidence of coronary heart disease (CHD) in 1994 (14). These studies have reported various results; some have shown a strong correlation, some a weak correlation and some lack of correlation between H. pylori and MI diseases. These contradictory findings made us conduct a systematic review to analyze all relevant studies in Iran through a meta-analysis and report a comprehensive and integrated result. Since there are different studies with different results in Iranian population and there was not any comprehensive study in this field to support a definite relationship between helicobacter pylori infection and MI, the present study aimed to determine the association of Helicobacter Pylori

with MI Iranian population during September 2000 to September 2016.

METHODS

In this research, the case-control studies were used to discover the association of H. pylori with MI. All English and Persian articles published from September 2000 to September 2016 were selected for analysis. The case group consisted of patients with MI and control group included participants without MI.

Inclusion criteria: They comprised of the casecontrol and cohort studies reporting the odds ratio of MI due to H. pylori in Iran or providing the possibility of its calculation using the frequency of MI.

Exclusion criteria: They consisted of ecologic and cross-sectional studies and those not reporting H. pylori's corresponding odds ratio (OR) and confidence interval (CI) 95% or not providing the possibility of its computation.

Searching strategy: The articles published in six valid Latin databanks, including Google Scholar, Cochrane, PubMed, Scopus and Science Direct and three Persian databanks, including SID, IranMedex and Magiran were extracted. The articles were searched using the following keywords in Farsi and English "Helicobacter Pylori [MeSH Terms]," "Helicobacter pylori [Title/Abstract]," "H. pylori [Title/Abstract]," "Coronary Disease [MeSH Terms]," "Myocardial infarction [Title/Abstract]," "Myocardial Infarction [MeSH Terms]," ", Iran" and their combinations.

To ensure the correct selection of artciles related to the research topic, two researchers were required to search the articles. In searching the electronic databanks, all artciles were first extracted and the repetitive ones were excluded. If an article was repeated more than once, the article with the highest number of cases was chosen. Next, considering the inclusion and exclusion criteria, all the titles and abstracts and then full texts were checked and the relevant papers were selected for analysis.

All papers were assessed by experts. The data collection and critical quality evaluation of articles

were separately done by two researchers (A. Sh and M.B). After the critical evaluation, the selected articles were checked by both authors.

Data extraction: After evaluating the quality of articles, the data of all the articles selected for analysis were extracted by a pre-prepared checklist. In the checklist for data extraction in the Excel software, the corresponding author's surname, publication year, research location, age or mean age of participants, gender, sample size, number of cases, number of controls and OR (95% CI) were extracted. In studies that provided measurements for both H. pylori IgG and IgA, we extracted the information using IgG as a measurement of H. pylori infection.

The extracted data were imported into Excel software and analyzed by Stata-12 software. Considering the results obtained from the heterogeneity of the studies (using Cochrane's Q-test and Higgins and Thompson's I^2), the fixed and random effect statistical models (95% CI) were applied for data analysis using metan command. Funnel plot was used to evaluate the publication bias, and Egger and Begg tests were used to analyze the funnel plot asymmetry.

RESULTS

The numbers of 11 case-control studies in different areas of Iran were included during 2001-2015. A total of 2517 participants had been evaluated in these studies, including 1253 cases and 1264 controls. The mean age and standard deviation were found to be 56.57 ± 3.47 in the case group and 54.55 ± 3.73 in the control group. Also, from among all participants, there were 655 males and 401 females in the case group and 612 males and 435 females in the control group (Table 1).

Among various studies, the minimum (OR= 0.56, CI=0.21, 1.46) and maximum (OR=13.2, CI= 5.1, 34.3) ORs were reported by Raygan et al (2006) and Sarrafzade et al (2001), respectively (Table 2). Based on the results of meta-analysis and using random effects model, an overall estimate of OR=2.53 (CI=1.37-4.67) was reported for the exposure effect and H. pylori infection and suffering from MI (Table 2).

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Authors' names	Province	Publication year	case	control
Jafarzadeh et al (15)	Rafsanjan	2010	60	60
Honarmand et al(16)	Rasht	2012	100	76
Bazzazi et al (17)	Gorgan	2009	70	70
Sarrafzade et al(18)	Isfahan	2008	57	44
Sarrafzade et al (19)	Isfahan	2001	52	55
Dehghan et al (20)	Qazvin	2015	90	90
Jalali et al (21)	Babol	2003	97	141
Azarkar et al (22)	Birjand	2011	73	78
Khodaiet al (23)	Tehran	2010	500	500
Rahnema et al (24)	Tabriz	2001	104	100
Raygan et al (25)	Kashan	2006	50	50

Table1: Characteristics of included studies

Table2: Pooled results for 11 case-control studies

Study	OR	[95% Conf. Interval]	% Weight
A. Jafarzadeh (2010)	4.64	(1.88, 11.47)	8.79
H. Honarmand (2012)	2.02	(0.96, 4.28)	9.35
H.Bazzazi (2009)	3.03	(1.38, 6.66)	9.22
N. Sarrafzade (2008)	0.83	(0.219, 3.14)	7.19
N. Sarrafzade (2001)	13.22	(5.1, 34.3)	8.61
N.Dehghan (2015)	2.579	(0.94, 7.5)	8.41
F .Jalali (2003)	0.951	(0.57, 1.6)	10.09
Z.Azarka (2011)	1.788	(0.9, 3.6)	9.53
Z.Khodai (2010)	7.765	(5.83, 10.34)	10.61
B.Rahnema (2001)	3.400	(1.73, 6.7)	9.59
F.Raygan (2006)	0.564	(0.22, 1.46)	8.62
D+L pooled OR	2.528	(1.37 , 4.67)	100.00

Heterogeneity chi-squared = 86.59 (d.f. = 10) p = 0.000; I-squared (variation in OR attributable to heterogeneity) = 88.5%; Estimate of between-study variance Tau-squared = 0.9003; Test of OR=1: z= 2.97 p = 0.003

The odds ratios were extracted from various studies according to the number of exposures in the case and control groups. The fixed and random effects models were applied. To detect homogeneity (Cochran's Q-test, Higgins and Thompson's I^2) was applied. The heterogeneity test was used to evaluate the null hypothesis, and all studies were assessed for the similar effect. The effect of heterogeneity was estimated by I^2 square, which provides a measurement of contradiction between studies and determines whether the total percentage of changes within the studies is due to

heterogeneity. Also, $50 < I^2$ indicates lack of homogeneity between studies. In this study, considering the heterogeneity index $I^2=88.5\%$ and p<0.001, the random effect and Der Simonian and Laird methods were used. The mixed OR=2.53 (CI=1.37-4.67) indicates that the odds ratio of MI in the patients with H. pylori was more than that of the control group or the people without H. pylori (p=0.001) (Figure 1). Begg's test suggested no significant publication bias among the studies included in the analysis (all p > 0.05) (Figure 2). Association of Helicobacter Pylori with Presence of Mycardial...

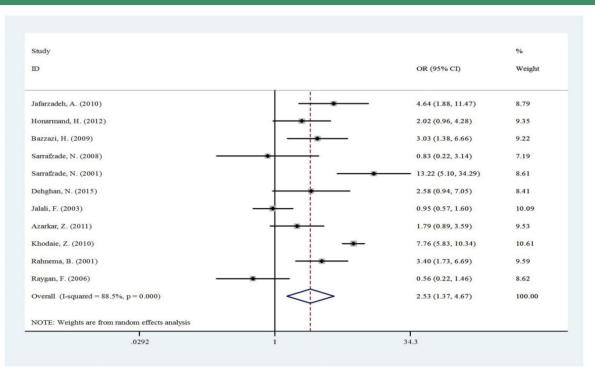


Figure 1: Forest plot for odds ratio

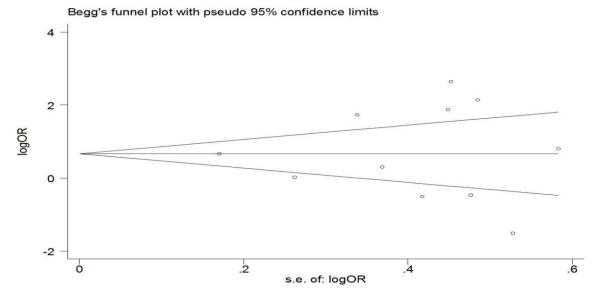


Figure 2: Publication bias estimated by Begg's test

DISCUSSION

The association between H. pylori and MI has not been documented yet. This study is the first systematic review aiming to analyze the association of helicobacter pylori with MI in Iran. The results of the study showed that the OR of MI in case groups with helicobacter pylori infection was higher than that of the control group without the infection. Total OR in the patients with H. pylori was found to be 2.5 times greater than those without this infection, which is indicative of the association of H. pylori with MI.

The results of a systematic review carried out to analyze the association between H. pylori and MI indicated that from among the articles found, the odds ratio of MI in the patients with H. pylori was 1.73 times more than that of the participants without MI. However, this amount was reported to be 2.1 times following the exclusion of the papers with poor quality, which is to a large extent in line with the findings of this study. Nevertheless, in this study, the odds ratio of MI in patients with H. pylori in the Asian countries was 1.75 times greater than that of control group, indicating the higher chance of exposure to helicobacter pylori among the Iranian people than in some Asian countries (26). Moreover, a study in India showed that patients with H. pylori suffered from MI 2.5 times more than those without H. pylori, which is in agreement with the findings of this study (27). Also, several studies reported the association of helicobacter pylori with MI, showing a higher level of infection in case groups than in control groups (28-31).

Although a significant association was reported between H. pylori and MI in the above studies, some of them rejected this relation, reporting a low incidence for H. pylori. Nakic et al. reported the incidence rates of 29% vs. 26% for H. pylori in the case and control groups (32), while Kurshid et al. reported the incidence rates of 45% vs. 47% (33). Moreover, Tsai et al. showed the incidence rates of 69% vs. 72% (34), indicating no statistically significant difference. In some studies like Kahan et al., despite the significant association between H. pylori and MI, the association was not much strong (OR=1.36 CI=1.02-1.82) (35). The contradiction and regarding the presence or lack of relationship between H. pylori and MI was also evident in cohort studies. A meta-analysis performed on cohort studies showed no positive association between H. pylori and coronary artery diseases such as MI (36). However, another recent metaanalysis on cohort studies indicated a significant increase (15%) for the Risk of coronary artery diseases (37).

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The significant association of H. pylori with the risk of MI can be explained in two ways. First, in the study of Reszka et al. carried out on patients with ischemic heart disease, the deoxyribonucleic acid of H. pylori was found in the aortic tissue and atherosclerotic plaque of the patients. This result can be indicative of the direct role of bacteria in the pathogenesis of ischemic heart disease and consequently MI (38). Secondly, this infection may reduce the HDL cholesterol and increase triglyceride level. Furthermore, coagulation parameters and other inflammatory factors like fibrinogen, prothrombin fragments, tumor necrosis factor and interleukin 6 and 8 may increase at serum level. These factors may play a role in the correlation of H. pylori with ischemic diseases (39). On the other hand, H. pylorus is not an independent factor involved in causing the disease in most of the cases; it can play an independent role along with such risk factors as diabetes, hypertension and smoking (32). Some studies have shown the association of H. pylori with low socioeconomic level. The incidence of coronary artery diseases and H. pylori can be due to close correlation of these diseases with socioeconomic status of people (19). Hence, better results can be obtained regarding the correlation of H. pylori with MI by controlling the confounding factors.

The strength of this study is that it is, to the best of the researchers' knowledge, the first study to comprehensively evaluate the correlation of H. pylori with MI in Iran. Also, few studies have addressed this issue via meta-analysis worldwide.

The results of the study show that H. pylori are associated with the incidence of MI so that the odds ratio of MI in patients with helicobacter pylori is twice greater than that of the people without H. pylori. Future studies are recommended to evaluate the mechanisms associated with relation of H. pylori with MI as well as its association with time.

ACKNOWLEDGMENTS

The authors would like to appreciate the personnel of cardiovascular research center of Imam Ali hospital, Kermanshah, for their cooperation in obtaining the required articles.

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