

Association of Helicobacter Pylori Infection with Cardiometabolic Risk Factors among Iranian Adolescents: the CASPIAN III Study

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Abstract

Background: At least half the world's population is colonized the stomach by Helicobacter pylori (H. pylori) which are a key constituent of the human microbiome. The aim of this study was to investigate the association of cardiometabolic risk factors with H. pylori infection in Iranian adolescents.

Materials and Methods: The current study was conducted along with the third survey of a national school-based surveillance system in Iran, entitled "Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable Disease" (CASPIAN) study. Detailed questionnaires on demographic, socioeconomic, dietary, and health-related information of the participants were filled by one of the parents under supervision of trained health-care workers. Trained healthcare professionals measured anthropometric indices, blood pressures according to standard protocols. Fasting venous blood was examined for fasting blood sugar and lipid profile.

Results: Overall 882 serum samples were suitable for testing. H. pylori antibody was found in 643 serum samples (72.9%). Among cardiometabolic risk factors, only the mean weight of participants was different between two groups (44.6 ± 11.8 in H. pylori positive and 42.8 ± 11.3 in H. pylori negative group; $p=0.04$). Overall, 5.1% of adolescents with positive H. pylori tests were overweight or obese, while 1.7% of negative ones were so ($p=0.02$). In the multivariate regression model, H. pylori seropositivity increased the risk of overweight (OR, 3.3; 95% CI, 1.2-9.3; $p=0.03$). In the multivariate model, association of other cardiometabolic risk factors with H. pylori infection was not statistically significant ($p>0.05$).

Conclusion: Results of present study showed that H. pylori infection was associated with excess weight in adolescents. H. pylori eradication may be decrease the risk of obesity.

Key Words: Adolescent, Helicobacter pylori, Iran, Metabolic Syndrome.

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1- INTRODUCTION

In recent decade's prevalence of cardiovascular risk factors rise rapidly in all over the world (1-4). Metabolic syndrome (MetS) and cardiometabolic risk factors in childhood is associated with adverse health consequences in adulthood (1). Previous studies in Iran documented a significant increase in rates of MetS and cardiometabolic risk factors in children and adult population (5-7). According to previous national studies in Iranian children and adolescents, approximately 20% of children were overweight or obese and 2.5-5% had MetS (8-11).

Helicobacter pylori (*H. pylori*) infection is the most prevalent chronic infection globally, affecting more than 50% of the world population. Its distribution closely parallels the socioeconomic status of the people; rate of infection reaches 80% in low- and middle-income countries, while it is 20% to 80% in high-income countries. The rate of *H. pylori* infection is high in Iranian children, with a distribution of 20 to 75% in different studies (12,13). *H. pylori* chronically infect gastric mucosa and are the causal agent of atrophic and non-atrophic gastritis and peptic ulcer. It has an etiological association with primary gastric B-cell lymphoma and gastric adenocarcinoma (14).

Recently many researchers have focused on extra-digestive complications of chronic *H. pylori* infection because of proven systemic effects of this disease (15). In the last few years, numerous studies have proposed an association between *H. pylori* infection and some cardio-metabolic risk factors including metabolic syndrome and its components i.e. insulin resistance, hyperlipidemia, overweight / obesity, high blood pressure, non-alcoholic fatty liver disease, and cardiovascular disease (CVD) (16-19). This might be due to the common pathogenic pathways shared between *H. pylori* infection and MetS. *H. pylori* causes

systemic inflammation with increased levels of pro-inflammatory and vasoactive mediators and acute phase proteins, release of reactive oxygen species, and platelet activation and aggregation which all are underlying causes of MetS and atherosclerosis (15). MetS and its final consequences are highly distributed in all communities, even extending to the adolescents and young adults, as is *H. pylori*; thus if the etiologic relationship between them becomes established, eradication of *H. pylori* would be valuable as a risk factor reduction intervention for CVD. However in this regard, results of studies are inconsistent; while some report no association between *H. pylori* infection and components of MetS (20-21); others propose direct positive relation between them (22, 23).

Moreover, in many of those studies there is no adjustment for potential cofounders which influence the prevalence of MetS, such as socio-economic status and nutritional habits of the contributors which disturbs the proposed causal relationship between *H. pylori* infection and MetS (24). The majority of the studies in Iran have examined association of *H. pylori* infection and cardio-metabolic risk factors in adult population, and studies including children and adolescents are scarce (25-27). This study aimed to investigate the association of *H. pylori* infection with cardio-metabolic risk factors in a representative sample of Iranian adolescents.

2- MATERIALS AND METHODS

2-1. Study Design and Population

The current study was conducted along with the third survey of a national school-based surveillance system in Iran, entitled "Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable Disease" (CASPIAN) study (2009-2010) (28, 29).

2-2. Sampling Method

In the CASPIAN III, 5,528 students aged 10-18-year-old were selected by multistage random cluster sampling from 27 provinces of Iran (28). In each province, equal clusters at the level of school were included. Eligible school was selected using information bank of the Ministry of Education. Stratification was done according to the age, sex, and place of residence (urban/rural). Detailed questionnaires on demographic, socioeconomic, dietary, and health-related information of the participants were filled by one of the parents under supervision of trained health-care workers. In this project 882 subjects were randomly selected and included from database of CASPIAN III study. Sample size was determined according to previous study in Iran and by considering the prevalence of *H.pylori* infection 54 %, the alpha error 5%, and a precision of 3.3% (30).

2-3. Inclusion and exclusion criteria

Student with Iranian nationality (having Iranian identity card) were eligible to participate in this study. Having a known chronic disease and consumption of medication for a chronic disease were exclusion criteria in this study.

2-4. Anthropometric measures and blood pressure

Cardiometabolic risk factors including anthropometric measures (weight, height, and waist circumference), blood pressure, and relevant biochemical were measured in the CASPIAN III survey. Briefly, body weight, height, and waist circumference (WC) were measured by trained health care experts under standard protocol and by using calibrated instruments and body mass index (BMI) was calculated and categorized according to the WHO growth curves (31). Weight was recorded with lightly dressed condition with 0.1 kg accuracy and standing height was measured without shoes with 0.1 cm

accuracy. WC was measured by a tape to the nearest 0.2 cm at the end of expiration at the midpoint between the top of iliac crest and the lowest rib in standing position. Abdominal obesity was defined as waist to height ratio more than 0.5 (32). Arterial blood pressure was measured manually using a mercury sphygmomanometer with a suitable cuff size for children after a 5- min rest in the supine position. The onset and disappearance of the tapping Korotkoff sound was determined as systolic blood pressure (SBP) and diastolic blood pressure (DBP). Average of three measures of blood pressure was recorded as actual value. SBP and DBP above the 90th percentile for their age, sex, and height from the National Heart, Lung, and Blood Institute's considered as high blood pressure.

2-5. Serological methods

A venous blood was obtained from each participant after 12 hours fasting to measure serum levels of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood sugar (FBS), Aspartate transaminase (AST), and alanine aminotransferase (ALT); tests were performed in central provincial laboratories that met the standards of the National Reference laboratory, a WHO-collaborating center in Tehran using standard kits (Pars Azmoun, Iran). All collection tubes were centrifuged at 2500–3000 ×g for 10 minutes. Immediately after centrifugation, serum samples were aliquot into 200µL tubes and stored at –70°C. All samples were transferred by cold chain to laboratory. Serum anti- *H. pylori* antibodies Immunoglobulin G (IgG) was measured using an Enzyme Linked Immunosorbant Assay (ELISA) method which supplied by ChoRus Company (Italy). In present study for increase of test accuracy results was tested twice. Serum

anti- H. pylori antibodies IgG values above 12AU/ml, was considered as positive result.

2-6. Ethical considerations

The ethical committees of Isfahan and Tehran University of Medical Sciences approved the CASPIAN III study. The current study was also approved by the Ethic committee of Alborz University of Medical Sciences. Protocols and objectives were fully described to the students and their parents and written informed consent was obtained from one of the parents to use their data and serum samples in scientific projects.

2-7. Statistical analysis

The statistical analysis was performed using STATA package (state statistical software: Release 12, STATA Corporation 2011, and College Station, TX, USA). The quantitative variables were presented as mean and standard deviation (SD) and the qualitative variables as number and percentage. Association of Helicobacter Pylori IgG Seropositivity with continuous and categorical variables was assessed using T-test and Chi-square test respectively.

Association of cardiometabolic risk factors and liver enzymes with H. pylori infection was assessed using different logistic regression models. In model I the crude association was assessed; in model II age, gender and living area was adjusted and in model III, socioeconomic status and family history of CVD additionally was adjusted in the model. Results of logistic regression are presented as odds ratio (OR) and 95 % confidence interval (CI). $P < 0.05$ was considered as statistically significant.

3- RESULTS

From 900 randomly selected enrollees, 882 serum samples were suitable for

testing. H. pylori antibody was found in 643 serum samples (72.9%). The mean age of seropositive and seronegative children were nearly the same (14.8 ± 2.8 vs. 14.7 ± 2.6 years old, respectively; $P=0.52$). Overall, 51.7% of students were boys and 61.52% were from urban area. Totally, 31.75%, 46%, 41.72% and 26.53% were in elementary, secondary and high school levels, respectively.

Table.1 represents the distribution of cardio-metabolic risk factors in H. pylori IgG Seropositive and seronegative group. The H. pylori IgG seropositivity in girls (76.3%) was significantly higher than boys (69.7%) ($P= 0.03$). Among cardio-metabolic risk factors, only the mean weight of participants was different between two groups (44.6 ± 11.8 in H.pylori positive and 42.8 ± 11.3 in H.pylori negative group; $P=0.04$). Overall, 5.1% of adolescents with positive H.pylori tests were excess weight (overweight or obese), while 1.7% of negative ones were excess weight ($P=0.02$).

Association of cardiometabolic risk factors with H. pylori infection in logistic regression model are presented in **Table.2**. In the crude model, only the excess weight was associated with H.pylori infection with the odds of 3.1 (95% confidence interval [CI], 1.1-8.9; $P=0.03$). In the multivariate model, H. pylori IgG seropositivity increased the risk of excess weight by 3.3, independent of other cardio-metabolic risk factors (OR: 3.3; 95%CI, 1.2-9.3; $P= 0.03$) (**Table.2**).

In the multivariate model, association of other cardiometabolic risk factors (high FBS, high BP, abdominal obesity, high TG, low HDL, high LDL, High TC) and liver enzymes (ALT and AST) with H. pylori IgG seropositivity was not statistically significant ($P>0.05$).

Table-1: The comparison of studied parameters in participants with and without helicobacter pyloriat the baseline examination

Variables	Total (882) Mean (SD)	With H.pylori infection (n=643) Mean(SD)	Without H.pylori infection (n= 239) Mean(SD)	P-value
Age (year)	14.8 (2.7)	14.8(2.8)	14.7(2.6)	0.52
Weight (kg)	44.1(11.7)	44.6(11.8)	42.8(11.3)	0.04
Height (cm)	153.4 (13.5)	153.9(13.4)	152.1(13.7)	0.06
BMI(kg/m ²)	18.4 (2.9)	18.5(2.9)	18.2(2.8)	0.14
Waist(cm)	66.9 (22.1)	66.5(10.1)	68.1(39.1)	0.37
Waist to height ratio	0.4 (0.1)	0.4(0.1)	0.4 (0.2)	0.16
SBP(mmHg)	102.2 (14.7)	102.8(13.9)	100.5(16.6)	0.07
DBP(mmHg)	65.2 (10.3)	65.8(10.3)	63.8(10.4)	0.01
TC(mg/dl)	144.1 (27.7)	143.2(28.2)	146.4(26.3)	0.19
TG(mg/dl)	90.1 (33.7)	90.5(33.3)	89.2 (34.9)	0.66
LDL-c (mg/dl)	80.1 (25.8)	79.6(25.7)	81.1(26.1)	0.59
HDL-c(mg/dl)	47.7 (15.5)	47.4(15.4)	48.4(15.9)	0.51
FBS (mg/dl)	82.9 (8.8)	83.1(8.7)	82.6 (9.1)	0.52
AST (U/L)	26.3 (13.3)	26.4(14.2)	26.1 (11.2)	0.81
ALT (U/L)	16.8 (10.3)	17.2 (11.5)	15.9(6.8)	0.24

BMI: body mass index; BP: blood pressure; SBP: systolic blood pressure; DBP: Diastolic blood pressure; FBS: fasting blood sugar; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TC: total cholesterol; TG: triglyceride; AST: Aspartate transaminase; ALT: alanine aminotransferase; MetS: metabolic syndrome. Data are presented as mean (SD) and compare with independent sample T-test; SD: standard deviation.

Table-2: Association of cardiometabolic risk factor and liver enzymes with H. pylori infection in logistic regression analysis

Variables	Model 1		Model 2		Model 3	
	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)
Excess weight	0.03	3.3(1.2,9.3)	0.03	3.2(1.1,9.5)	0.03	3.1(1.1,8.9)
High SBP	0.80	0.9(0.4,1.9)	0.81	0.9(0.4,1.9)	0.85	0.9(0.4,1.9)
High DBP	0.34	1.6(0.6,4.3)	0.34	1.6(0.6,4.3)	0.32	1.6 (0.6,4.4)
High TG	0.28	1.2(0.8,1.8)	0.29	1.2(0.8,1.8)	0.33	1.2(0.8,1.7)
Low HDL	0.99	1.0(0.7,1.5)	0.98	1.0(0.7,1.5)	0.98	1.1(0.7,1.5)
High BP	0.94	0.9(0.5,1.9)	0.94	0.9(0.5,1.9)	0.96	1.1(0.5,1.9)
High TC	0.85	0.9(0.3,2.4)	0.83	0.9(0.3,2.4)	0.68	0.8(0.3,2.2)
High LDL	0.51	0.8(0.4,1.5)	0.51	0.8(0.4,1.5)	0.49	0.8(0.4,1.5)
Abdominal obesity	0.58	1.2(0.7,1.9)	0.58	1.2(0.7,1.9)	0.64	1.1(0.6,1.8)
High ALT	0.17	0.7(0.4,1.2)	0.16	0.7(0.4,1.2)	0.14	0.7(0.4,1.1)
High AST	0.21	0.7(0.4,1.2)	0.19	0.7(0.4,1.2)	0.16	0.7(0.4,1.2)

SBP: systolic blood pressure; DBP: Diastolic blood pressure; TG: triglyceride; AST: Aspartate transaminase; ALT: alanine aminotransferase; BP: blood pressure; HDL: High-density lipoproteins; LDL: Low-density lipoprotein.

4- DISCUSSION

To our knowledge, this is the first largest nationwide study in Iranian children to document the association of H. pylori with cardiometabolic risk factors. Results of present study show that in the crude model, only the excess weight was associated with H. pylori infection with the odds of 3.1 (95% CI, 1.1-8.9; P=0.03). In the adjusted model this association remain significant (OR: 3.3; 95%CI, 1.2-9.3; P=0.03) which was concordant with some previous studies (33, 34).

A systematic review and meta-analysis shows that H. pylori infection is positively associated with higher BMI; the mean of BMI was higher (standardized mean difference: 0.30, 95%CI 0.01–0.58) in H. pylori positive group compare to H. pylori negative group (34). In contrary to our findings, in other study, there was no significant difference between the obese and non-obese subjects (35).

The possible mechanism that can justify the positive association of H. pylori infection and weight disorders is inflammation or dyspepsia. Previous studies demonstrate that infection with H. pylori is associated with higher level of inflammatory markers (36, 37) which are markers of inflammation in weight disorders (38, 39). Furthermore, previous studies show that the presence of H. pylori in the gut microbiota leads to inflammation, metabolic endotoxemia and obesity (40, 41). Association of H. pylori IgG seropositivity and cardiometabolic risk factors is contradictory (42- 44). In present study we could not detect any association between H. pylori IgG seropositivity and cardiometabolic risk factors (high FBS, high BP, and abdominal obesity, high TG, low HDL, high LDL and high TC) which was consistent with previous studies (42-44). In an elderly cohort, seropositivity of H. pylori was not associated with increased risk for cardiovascular diseases (41). In the other

hand Jeon et al. study show that in a prospective cohort study, H. pylori seropositivity increased the risk of diabetes (45). Moreover in some large studies, H. pylori infection was not associated with the increased risk of cardiovascular and ischemic heart disease mortality and morbidity (43, 46, 47). Our study results in contrary to some cross-section studies do not support a strong association between H. pylori infection and risk of cardiometabolic risk factors (48, 49). This discrepancy in findings can be justified by SES confounding effect, study participant and type of outcome. Although we adjusted SES in our study, the residual confounding effect of socioeconomic status (SES) due to different method of SES calculation make difficult to interpret associations of H. pylori and cardiometabolic risk factors in population based studies (50). Moreover in present study we studied association of H. pylori infection and risk of cardiometabolic risk factors in adolescents while majority of studies assess the relationship between H. pylori infection and risk of cardiovascular diseases in adult population (48, 49).

4-1. Limitations of the study

The main limitation of this study is the nature of cross-sectional design which precludes causality inference. We were not able to include all students aged 6 - 9-year-old which restrict study generalizability. Another limitation of the study was depletion of some serum samples from a number of provinces. However this nationwide study with representative samples from adolescents in several provinces of Iran that provides the possibility of assessing relationship between H. pylori infection and cardiometabolic risk factors.

5- CONCLUSION

In conclusion, results of present study show that H. pylori infection was

associated with excess weight in adolescents. In addition the risk of H. pylori IgG seropositivity in girls was higher compared to boys. H. pylori eradication may decrease the risk of weight disorders in children and adolescents. Large cohort studies are necessary to depict clear picture of association between H. pylori seropositivity and cardiometabolic risk factors in children and adolescents.

6- AUTHORS' CONTRIBUTION

All authors contributed equally to this paper.

7- CONFLICT OF INTEREST: None.

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