http:// ijp.mums.ac.ir
Original Article (Pages: 7045-7054)

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

Enayatollah Kalantar[1], Mohammad Javad Gharavi[2], Shervin Ghaffari Hoseini[3], Ramin Heshmat[4], Mojgan Oshaghi[1], Behnaz Gharegozlou[1], Hamid Asayesh[5], Armita Mahdavi Gorabi[4], Mohammad Esmaeil Motlagh[6], Mehdi Noroozi [7], *Mostafa Qorbani[8], *Roya Kelishadi[9]

[1]Dietary Supplements and Probiotics Research Center, Alborz University of Medical Sciences, Karaj, Iran. [2]Department of Microbiology and Immunology, School of Paramedical Sciences, Iran University of Medical Sciences, Tehran, Iran. [3]Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. [4]Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. [5]Department of Medical Emergencies, Qom University of Medical Sciences, Qom, Iran. [6]Department of Pediatrics, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. [7]Social Determinants of Health Research Center, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran. [8]Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran & Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. [9]Department of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran.

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.

*Please cite this article as: Enayatollah Kalantar, Mohammad Javad Gharavi, Shervin Ghaffari Hoseini, Ramin Heshmat, Mojgan Oshaghi, Behnaz Gharegozlou, et al. Association of Helicobacter Pylori Infection with Cardiometabolic Risk Factors among Iranian Adolescents: the CASPIAN III Study. Int J Pediatr 2018; 6(2): 7045-54. DOI: **10.22038/ijp.2017.24411.2060**

Corresponding Authors:

Mostafa Qorbani, Non-communicable of Disease Research Center, Alborz University of Medical Sciences, Karaj, Iran. AND Roya Kelishadi, Department of Pediatrics, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: mqorbani1379@yahoo.com AND roya.kelishadi@gmail.com
Received date: Oct.15, 2017; Accepted date: Dec.12, 2017

1- INTRODUCTION

In recent decade's prevalence of cardiovascular risk factors rise rapidly in all over the world (1-4). Metabolic syndrome (MetS) and cradiometabolic 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 cardio-metabolic 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 be 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.

8- ACKNOWLEDGMENTS

The authors would like to thank the Alborz University of Medical Sciences, Karaj, Iran, for providing funds for our study. Also we are thankful of the large team working on this study and all participants in different provinces.

9- REFERENCES

1. Abarca-Gómez L, Abdeen ZA, Hamid ZA, Abu-Rmeileh NM, Acosta-Cazares B, Acuin C, et al. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128. 9 million children, adolescents, and adults. The Lancet. 2017; 390(10113):2627-42.

2. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS. Health effects of overweight and obesity in 195 countries over 25 years. The New England journal of medicine. 2017;377(1):13-27.

3. NCD Risk Factor Collaboration. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19· 1 million participants. Lancet (London, England). 2017;389(10064):37

4. NCD Risk Factor Collaboration. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4· 4 million participants. The Lancet. 2016;387(10027):1513-30.

5. Djalalinia S, Kelishadi R, Qorbani M, Peykari N, Kasaeian A, Nasli-Esfahani E, et al. A Systematic Review on the Prevalence of Overweight and Obesity, in Iranian Children and Adolescents. Iranian journal of pediatrics. 2016;26(3): e2599.

6. Azadbakht L, Kelishadi R, Khodarahmi M, Qorbani M, Heshmat R, Motlagh ME, et al. The association of sleep duration and cardiometabolic risk factors in a national sample of children and adolescents: the CASPIAN III study. Nutrition. 2013;29(9):1133-41.

7. Shafiee G, Kelishadi R, Qorbani M, Motlagh ME, Taheri M, Ardalan G, et al. Association of breakfast intake with cardiometabolic risk factors. Jornal de Pediatria (Versão em Português). 2013 Nov 1;89(6):575-82.

8. Khashayar P, Heshmat R, Qorbani M, Motlagh ME, Aminaee T, Ardalan G, et al. Metabolic syndrome and cardiovascular risk factors in a national sample of adolescent population in the middle-east and north Africa: the CASPIAN III study. International journal of endocrinology 2013;2013:1–8.

9. Rahmanian M, Kelishadi R, Qorbani M, Motlagh ME, Shafiee G, Aminaee T, et al. Dual burden of body weight among Iranian children and adolescents in 2003 and 2010: the CASPIAN-III study. Archives of medical science: AMS. 2014;10(1):96.

10. Kelishadi R, Motlagh ME, Bahreynian M, Gharavi MJ, Kabir K, Ardalan G, et al. Methodology and early findings of the assessment of determinants of weight disorders among Iranian children and adolescents: The childhood and adolescence surveillance and prevention of adult Noncommunicable Disease-IV study. Int J Prev Med. 2015 Aug 14;6:77

11. Motlagh ME, Ziaodini H, Qorbani M, Taheri M, Aminaei T, Goodarzi A, et al. Methodology and early findings of the fifth survey of childhood and adolescence surveillance and prevention of adult noncommunicable disease: The caspian-v study. Int J Prev Med. 2017 Jan 23;8:4.

12. Sayehmiri F, Darvishi Z, Sayehmiri K, Soroush S, Emaneini M, Zarrilli R, et al. A Systematic Review and Meta-Analysis Study to Investigate the Prevalence of Helicobacter pylori and the Sensitivity of its Diagnostic Methods in Iran. Iranian Red Crescent Medical Journal 2014;16(6):e12581.

13. Kalantar E, Oshaghi M, Gharegozlou B, Mohammadi S, Heshmat R, Ghaffari Hoseini S, Motlagh ME, Qorbani M, Kelishadi R. Seroprevalence of Helicobacter Pylori Infection in Iranian Adolescents: the CASPIAN-III Study. International Journal of Pediatrics. 2017;5(1):4251-56.

14. Sakr R, Massoud M, Aftimos G, Chahine G. Gastric Adenocarcinoma Secondary to Primary Gastric Diffuse Large B-cell Lymphoma. Journal of gastric cancer. 2017;17(2):180-5.

15. Tsang KW, Lam SK. Helicobacter pylori and extra digestive diseases. Journal of gastroenterology and hepatology. 1999;14(9):844-50.

16. Prelipcean CC, Mihai C, Gogălniceanu P, Mitrică D, Drug VL, Stanciu C. Extragastric manifestations of Helicobacter pylori infection. Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi. 2007;111(3):575-83.

17. Papamichael KX, Papaioannou G, Karga H, Roussos A, Mantzaris GJ. Helicobacter pylori infection and endocrine disorders: is there a link?. World Journal of Gastroenterology: WJG. 2009;15(22):2701.

18. Gunji T, Matsuhashi N, Sato H, Fujibayashi K, Okumura M, Sasabe N, Urabe A. Helicobacter pylori infection significantly increases insulin resistance in the asymptomatic Japanese population. Helicobacter. 2009;14(5):496-502.

19. Li M, Shen Z, Li YM. Potential role of Helicobacter pylori infection in nonalcoholic fatty liver disease. World Journal of Gastroenterology: WJG. 2013;19(41):7024.

20. Naja F, Nasreddine L, Hwalla N, Moghames P, Shoaib H, Fatfat M, et al. Association of H. pylori infection with insulin resistance and metabolic syndrome among Lebanese adults. Helicobacter 2012;17(6):444-51.

21. Sotuneh N, Hosseini SR, Shokri-Shirvani J, Bijani A, Ghadimi R. Helicobacter pylori infection and metabolic parameters: is there an association in elderly population? International journal of preventive medicine 2014;5(12):1537-42.

22. Yang W, Xuan C. Influence of Helicobacter pylori Infection on Metabolic Syndrome in Old Chinese People. Gastroenterology research and practice 2016; 2016: 6951264.

23. Chen TP, Hung HF, Chen MK, Lai HH, Hsu WF, Huang KC, et al. Helicobacter Pylori Infection is Positively Associated with Metabolic Syndrome in Taiwanese Adults: a Cross-Sectional Study. Helicobacter 2015;20(3):184-91.

24. Polyzos SA, Kountouras J. Novel advances in the association between helicobacter pylori infection, metabolic syndrome, and related morbidity. Helicobacter 2015;20(6):405-9.

25. Choi JS, Ko KO, Lim JW, Cheon EJ, Lee GM, Yoon JM. The Association between Helicobacter pylori Infection and Body Weight among Children. Pediatric gastroenterology, hepatology and nutrition 2016;19(2):110-5.

26. Pacifico L, Anania C, Osborn JF, Ferrara E, Schiavo E, Bonamico M, et al. Long-term effects of Helicobacter pylori eradication on circulating ghrelin and leptin concentrations and body composition in prepubertal children. European journal of endocrinology 2008;158(3):323-32.

27. Vo HD, Goli S, Gill R, Anderson V, Stefanov DG, Xu J, et al. Inverse correlation between Helicobacter pylori colonization and obesity in a cohort of inner city children. Helicobacter 2015;20(1):64-8.

28. Kelishadi R, Heshmat R, Motlagh ME, Majdzadeh R, Keramatian K, Qorbani M, Taslimi M, Aminaee T, Ardalan G, Poursafa P, Larijani B. Methodology and early findings of the third survey of CASPIAN study: A national school-based surveillance of students' high risk behaviors. International journal of preventive medicine. 2012;3(6):394.

29. Ahadi Z, Shafiee G, Qorbani M, Sajedinejad S, Kelishadi R, Arzaghi SM, Larijani B, Heshmat R. An overview on the successes, challenges and future perspective of a national school-based surveillance program: the CASPIAN study. Journal of Diabetes & Metabolic Disorders. 2014;13(1):120.

30. Moosazadeh M, Lankarani K, Afshari M. Meta-analysis of the Prevalence of Helicobacter Pylori Infection among Children and Adults of Iran. Int J Prev Med 2016; 7:48-53.

31. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1995; 854:161-262.

32. Li C, Ford ES, Mokdad AH, Cook S. Recent trends in waist circumference and waist-height ratio among US children and adolescents. Pediatrics. 2006;118:e1390–8.

33. Arslan E, Atılgan H, Yavaşoğlu İ. The prevalence of Helicobacter pylori in obese subjects. European journal of internal medicine. 2009;20(7):695-7.

34. Upala S, Jaruvongvanich V, Riangwiwat T, Jaruvongvanich S, Sanguankeo A. Association between Helicobacter pylori infection and metabolic syndrome: a systematic review and meta-analysis. Journal of digestive diseases. 2016;17(7):433-40.

35. Zhu Y, Zhou X, Wu J, Su J, Zhang G. Risk factors and prevalence of Helicobacter pylori infection in persistent high incidence area of gastric carcinoma in Yangzhong city. Gastroenterol Res Pract. 2014;2014:481365.

36. Diomedi M, Stanzione P, Sallustio F, Leone G, Renna A, Misaggi G, et al. Cytotoxin-associated gene-A-positive Helicobacter pyloristrains infection increases the risk of recurrent atherosclerotic stroke. Helicobacter 2008;13:525–31.

37. Hamed SA, Amine NF, Galal GM, et al. Vascular risks and complications in diabetes mellitus: the role of helicobacter pylori infection. J Stroke Cerebrovasc Dis 2008;17:86–94.

38. Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. Gastroenterology. 2007 May 31;132(6):2169-80.

39. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. International journal of molecular sciences. 2014;15(4):6184-223.

40. Cani PD, Bibiloni R, Knauf C, Waget A, Neyrinck AM, Delzenne NM, Burcelin R. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet–induced obesity and diabetes in mice. Diabetes. 2008;57(6):1470-81.

41. Manco M, Putignani L, Bottazzo GF. Gut microbiota, lipopolysaccharides, and innate immunity in the pathogenesis of obesity and cardiovascular risk. Endocr Rev 2010;31:817–44.

42. Haider AW, Wilson PW, Larson MG, Evans JC, Michelson EL, Wolf PA, et al. The association of seropositivity to Helicobacter pylori, Chlamydia pneumoniae, and cytomegalovirus with risk of cardiovascular disease: a prospective study. Journal of the American College of Cardiology. 2002 Oct 16;40(8):1408-13.

43. Wald NJ, Law MR, Morris JK, Bagnall AM. Helicobacter pylori infection and mortality from ischaemic heart disease: negative result from a large, prospective study. BMJ. 1997;315(7117):1199-201.

44. Strandberg TE, Tilvis RS, Vuoristo M, Lindroos M, Kosunen TU. Prospective study of Helicobacter pylori seropositivity and cardiovascular diseases in a general elderly population. BMJ 1997;314:1317–18.

45. Jeon CY, Haan MN, Cheng C, Clayton ER, Mayeda ER, Miller JW, et al. Helicobacter pylori infection is associated with

an increased rate of diabetes. Diabetes care. 2012;35(3):520-5.

46. Folsom AR, Nieto FJ, Sorlie P, Chambless LE, Graham DY. Helicobacter pylori seropositivity and coronary heart disease incidence. Circulation. 1998;98(9):845-50.

47. Strachan DP, Mendall MA, Carrington D, Butland BK, Yarnell JW, Sweetnam PM, et al. Relation of Helicobacter pylori infection to 13-year mortality and incident ischemic heart disease in the caerphilly prospective heart disease study. Circulation. 1998;98(13):1286.

48. Sung JJ, Sanderson JE. Hyperhomocysteinaemia, Helicobacter pylori, and coronary heart disease. Heart. 1996 Oct 1;76(4):305-7.

49. Mendall MA, Patel P, Ballam L, Strachan D, Northfield TC. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. BMJ. 2006;312(7038):1061-65.

50. Patel P, Mendall MA, Khulusi S, Northfield TC, Strachan DP. Helicobacter pylori infection in childhood: risk factors and effect on growth. BMJ. 1994 Oct 29;309(6962):1119-23.