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ORIGINAL ARTICLE – OPEN ACCESS

The Relationship Between Premature Coronary Atherosclerosis and *Helicobacter pylori* Infection

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ABSTRACT

Objective: *Helicobacter pylori* infection (HPI) might potentially lead to chronic infection and cancer development in the gastric mucosa. However, previous studies have shown that coronary artery disease might also be associated with this infection. On the other hand, this causal association has not been previously documented in the context of premature coronary atherosclerosis (PCA). In our study, we aimed to investigate the potential relationship between HPI and PCA.

Materials and Methods: All consecutive patients (≤40 years of age) (between the years 2009 and 2018) undergoing coronary angiography and gastroduodenoscopy were included in the study (n=199). Patients were divided into two groups (PCA and control). The statistically considered significant p value is <0.05.

Results: One hundred ninety nine patients included those with PCA [n=61 (30%)] (51% male, average age 35 years old). HPI was detected in 70% of patients with PCA (n: 43). Statistically significant independent relationship between HPI and PCA was observed in the logistics regression analysis (p<0.001).

Conclusion: HPI may be an independent risk factor for PCA.

Keywords: Atherosclerosis, coronary, *Helicobacter pylori*, infection, premature

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INTRODUCTION

Helicobacter pylori (HP) are a gram-negative bacterium that can lead to chronic infection and cancer development, especially in the gastric mucosa. As long as it is not properly managed after entering the organism, it perpetuates its life span. In previous studies, it has been known to be associated with increased coronary artery disease (CAD) frequency (1, 2). Recent studies have shown that atherosclerosis is associated with a variety of infectious pathogens (including HP) (3–6). In particular, the decrease in preventive factors with increased coagulability and endothelial dysfunction due to chronic inflammation might lead to an increased risk for premature coronary atherosclerosis (PCA) (6–10). In addition, both HP infection (HPI) and CAD are associated with the socioeconomic state of patients and both increase with age (7–9).

Traditionally, PCA is defined as an existing CAD (noncritical or critical stenosis) in patients <40 years of age (also below the ages of 30 or 50 in some studies) (11). In clinical assessment, PCA is strongly related to acute myocardial infarction (AMI), which may cause increased heart failure in adults and risk of death (10). In time, the hypothesis has been suggested that the significant decrease in the annual death rate caused by AMI may be associated with decrements in the rates of duodenal peptic ulcer and HP (10, 12). In addition, according to a recent study, the eradication of HP might be regarded as a preventive action against the development of primary and secondary CAD (13). However, the literature data is still controversial regarding the relationship between CAD and HPI (1, 14).

Meta-analysis of clinical researches has shown a stronger relationship between HPI and the risk of acute coronary syndrome (ACS) (10). However, its relationship with PCA has not been absolutely confirmed. In our study, we aimed to investigate the relationship between HPI and PCA, which has not been previously investigated.

MATERIALS and METHODS

Our study was planned as an observational, cross-sectional, retrospective and single-centered. Prior to the study, permission was obtained from the Local Ethics Committee (Trakya University Faculty of Medicine-Clinical Research Ethics Commitee, Date: 01.10.2018, ID: 16/09). Informed consent was obtained from all individual participants included in the study.

In the determination of volunteers, all consecutive coronary angiography (CAG) results between 2009 and 2018 were evaluated in our angiography laboratory, and the central archive records were examined by identifying PCA patients (≤40 years of age in patients).

Table 1. Baseline demographic parameters of the study population

Variables	PCA group (n=61)	Control group (n=138)	p
Age	35 (32.5–39.5)	36 (31–40)	0.322
Gender			0.001
Female	30 (49.18%)	100 (72.46%)	
Male	31 (50.82%)	38 (27.54%)	
HT	54 (88.52%)	88 (63.76%)	<0.001
DM	31 (50.81%)	42 (30.43%)	0.006
Smoking	37 (60.55%)	25 (18.11%)	<0.001
Hyperlipidemia	36 (59.01%)	40 (28.98%)	<0.001
Obesity	3 (4.91%)	4 (2.89%)	0.476
Urease positivity	43 (70.49%)	55 (39.85%)	<0.001
LVEF (%)	58 (54–61)	60 (55–66)	0.015
LDL (mg/dL)	116 (88–144)	115 (81–143)	0.733
Triglycerides (mg/dL)	149 (107–203)	119 (84–167)	0.003
Total cholesterol (mg/dL)	184 (156–215)	182 (140–215)	0.547
HDL (mg/dL)	40 (32–48)	46 (37–56)	0.001

PCA: Premature coronary atherosclerosis; HT: Hypertension; DM: Diabetes mellitus; n: Number; LVEF: Left ventricular ejection fraction; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

CAD diagnosis was determined as the detection of atherosclerotic stenosis (noncritical <50% or critical ≥50%) in any coronary artery. Thereafter, all consecutive patients with gastroduodenoscopy (gastroenterological indications) were identified in the PCA group within the last 1 year, and HP urease test or hematoxylene-eosin and giemsa staining density in gastric biopsy were evaluated (as HPI positive or negative). Patients with normal coronary arteries in CAG during the same cross-sectional period and negative gastroduodenoscopy/urease test were labeled as the control group.

Exclusion criteria were as follows: >40-year old and <18-year old patients, malignancy history, connective tissue disease, inflammatory intestinal disease, Kawasaki disease, rheumatic valve disease, and pregnancy. Demographic characteristics of patients in patient files and central archive [age, gender, hypertension (HT) (blood pressure >140/90 mmHg), diabetes mellitus (DM) (fasting blood glucose >126 mg/dl), smoking, obesity (body mass index >30 kg/m2)], and laboratory results [total cholesterol, triglyceride (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL)] were recorded. Transtoracic echocardiographic (TTE) examination, 2.5–3.5-MHz transducer was obtained with parasternal and apical images was measured (Vivid 7 Pro, General Electric Medical System, Milwaukee, Winconsin) and left ventricular ejection fraction (LVEF), by using the Simpson method.

Statistical Analysis

The normal distribution was evaluated harnessing the Shapiro—Wilk test. Regarding the comparison of the two groups, Student's t-test was harnessed for variables that were concordant with the normal distribution; whereas, Mann—Whitney U test was harnessed for variables that were not. Pearson chi-square test analyzed the potential association among qualitative variables.

The PCA risk factors were uncovered with the use of univariate and multivariate stepwise binary logistic regression analyses. The mean and standard deviation were harnessed for the variables which were concordant with the normal distribution; whereas, the quarters and median were harnessed for the variables which were not. Percentage and frequency values were noted in the setting of qualitative variables. The level of significance was considered as 0.05 in the evaluation of all statistical tests. All the analyses were performed with the use of TURCOSA statistical software (Turcosa Analytics Ltd. Co, Kayseri, Türkiye).

RESULTS

The demographic characteristics of the participants are shown in Table 1. HDL levels were significantly lower in the PCA group compared to controls, and TG levels were significantly higher. As expected, the incidents of traditional risk factors, including DM, HT, smoking, hyperlipidemia, and gender, were significantly different between the two groups (more prevalent in the PCA group). In addition, the incidence of HPI was significantly higher in the PCA group (Table 1).

HPI-positive group was found to have a higher PCA incidence (p<0.001) (Table 2). When the angiography indications were evaluated, it was observed that ACSs were more frequent in the PCA group (p/0.023). In the evaluation of coronary artery lesions, all the coronary arteries except LMCA were more likely to be involved in the HPI group (Table 2). In addition, the average LVEF value in the HPI group was significantly higher compared to the control group (Table 2).

Clinical factors such as gender, HT, age, smoking, HDL, total cholesterol, and HP urease positivity (potentially associated) were evaluated in stepwise binary logistic regression analysis. The HPI was identified as an independent risk factor for PCA development (OR: 6.01, 95% confidence interval (CI): 2.52–14.3, p<0.001) (Table 3).

Table 2. Angiographic parameters of the study population

Variables	HP urease positive (n=98)		HP urease negative (n=101)		p
	n	%	n	%	
Indications for angiography					
Generally					0.023
Elective	69	70.40	85	84.15	
ACS	29	29.59	16	15.84	
CCS angina	26	26.53	33	32.67	
MPS positivity	22	22.44	25	24.75	
Exercise test positivity	17	17.34	21	20.79	
Low LVEF	4	4.08	6	5.94	
Anterior MI	6	6.12	1	0.99	
Inferior MI	5	5.10	3	2.97	
Lateral MI	–	–	–	–	
NSTEMI	7	7.17	5	4.95	
USAP	11	11.22	7	6.93	
Premature CAD	43	43.87	18	17.82	<0.001
Coronary artery lesions					
LMCA	3	3.06	1	0.99	0.298
LAD	33	33.67	14	13.86	<0.001
CX	21	21.42	11	10.89	0.043
RCA	20	20.40	10	9.90	0.038
SB	13	13.26	3	2.97	0.008
Coronary ectasia	8	8.16	7	6.93	0.465
Coronary calcification	2	2.04	2	1.98	0.810
Coronary anomaly	4	4.08	5	4.95	0.983
LVEF (%)	59 (54.5-61.5)		57 (51-61)		0.036

HP: *Helicobacter pylori*; ACS: Acute coronary syndrome; CCS: Canadian cardiovascular society; MPS: Myocardial perfusion scintigraphy; LVEF: Ejection fraction; MI: Myocardial infarction; NSTEMI: Non-ST elevation myocardial infarction; USAP: Unstable angina pectoris; CAD: Coronary artery disease; LMCA: Left main coronary artery; LAD: Left anterior descending coronary artery; CX: Circumflex coronary artery; RCA: Rig coronary artery; SB: Side branch coronary artery; n: Number

DISCUSSION

In our study, a significant relationship was found between PCA and HPI. Finding a causal relationship between PCA and HPI might potentially play an important role in the improvement of young age morbidity and mortality associated with PCA. HP can be screened for its effective treatment. It will also encourage the development of quick and cost effective new test kits as a scanning method. There also exists a potential feasibility of developing a vaccine (administered during childhood) against HPI.

Previous studies examining the CAD and HPI relationship have harnessed various criteria to describe CAD presence (14–16). In our study, we used angiographic verification to determine the presence or absence of CAD both in cases and controls. In addition, in our study, to identify HPI most accurately, a combination of diagnostic urease test and gastroduodenoscopic biopsy was used.

In patients with PCA, the fact that the lesions in all coronary arteries are more common in the HPI group in patients with PCA potentially suggests the roles of coagulability and endothelial dysfunction due to chronic inflammation in young patients. In a previous study by Umit et al. (17), the authors found the frequency of HPI in the Thrace region as 52.8%. In our study, this was 49.3% demonstrating a significant variation between those with and without PCA. In addition, the only nucleotide polymorphisms (such as angiotensin II A1166c gene polymorphism) associated with environmental factors and chronic inflammation might be considered as one of the fundamental mechanisms of PCA evolution (18). Based on these results, HPI prevalence might have a significant role in the propagation of PCA.

However, the mechanism by which HPI affects the prevalence of PCA needs to be clarified. Torisu et al. (19) demonstrated that in patients with atrophic gastritis (AG), HPI that is diagnosed by serum pepsinogenic test method, which is an early preclinical marker of atherosclerosis, was found to be significantly higher compared with healthy subjects. Moreover, the levels of serum strikes that may be protective against atherosclerosis were reported to be significantly lower in AG-positive

Table 3. Stepwise binary logistic regression analysis of risk factors on premature coronary atherosclerosis

	Univariate binary logistic regression*			Multivariate stepwise binary logistic regression**		
Variable	**OR**	**95% CI**	**p*** **	**OR**	**95% CI**	**p*** **
Gender (female)	0.36	0.19–0.68	0.001	0.07	0.02–0.27	<0.001
Age	1.03	0.98–1.08	0.202	1.18	1.07–1.31	<0.001
HT	4.38	1.95–11.21	<0.001	3.38	1.07–10.63	0.037
Smoking	6.96	3.60–13.86	<0.001	7.04	2.99–16.61	<0.001
DM	2.36	1.27–4.40	0.006	–	–	–
TC	0.99	0.99–1.01	0.783	1.00	0.99–1.01	0.143
HDL	0.95	0.92–0.97	0.001	0.94	0.90–0.98	0.014
LDL	0.99	0.99–1.01	0.552	–	–	–
TG	1.00	1.00–1.01	0.009	–	–	–
Urease positivity	3.60	1.91–7.01	<0.001	6.01	2.52–14.33	<0.001

*: Univariate binary logistic regression; **: Multivariate stepwise binary logistic regression; ***: Significance value <0.05; HT: Hypertension; DM: Diabetes mellitus; TC: Total cholesterol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglyceride; OR: Odds ratio; CI: Confidence interval

subjects (20, 21). Also, Kutluana et al. (22) previously reported that AG, which was diagnosed through a histological method, might elicit hyperhomocysteinemia that might serve as an independent risk factor for the evolution of atherosclerosis in the general population. In this report, carotis intima-media thickness in AG subjects was found to be thicker compared with controls. When these findings are analyzed globally, it seems reasonable that HPI might have a significant impact on the evolution of premature atherosclerotic changes in coronary arteries.

Our study has some limitations. Our study has a retrospective, observational and cross-sectional design. Moreover, mediators including tumor necrosis factor-alpha, interleukin-6 homocysteine, lipoprotein A, and ghrelin (that all might be associated with atherosclerosis) have not been assessed in details.

CONCLUSION

Our results suggest that HPI may be an independent risk factor for PCA. However, further large-scale studies are needed to establish this causal relation.

Ethics Committee Approval: The Trakya University Clinical Research Ethics Committee granted approval for this study (date: 01.10.2018, number: 16/09).

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