Research Square

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The Role of *Helicobacter Pylori* Infection on Atherosclerosis in Diabetic Patients

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Abstract

Background: In this study, the aim was to investigate the effect of *Helicobacter pylori* (Hp) presence on intima-media thickness, which is an early sign of atherosclerosis in type 2 diabetic patients.

Methods: This study is a retrospective study conducted with type 2 diabetic patients who were followed up in the gastroenterology and diabetes outpatient clinic. The relationship between the presence of Hp and laboratory findings, demographic and clinical characteristics, intima-media thickness and pathology findings were analyzed in patients who underwent endoscopy for dyspepsia.

Results: A total of 73 cases meeting the exclusion criteria, 32 males (43.8%) and 41 females (56.2%), between 42 and 83 years with an average age of 59 ± 10 years were included in the study. Of the cases, 31 (42.4%) were found to be Hp positive. The presence of Hp and accompanying diseases, drug treatments used, demographic characteristics, biochemical parameters, endoscopy and pathology results, and intima-media thicknesses were compared. ALT value was found to be higher in Hp negative cases ($p<0.005$). The presence of Hp was found to increase the carotid intima-media thickness by 0.092 units (p: 0.018) at 95% significance level on the left and 0.060 units at 90% significance level on the right (p: 0.063). There was no significant difference for other variables.

Conclusion: It was shown that the presence of Hp increases the carotid intima-media thickness in patients with type 2 diabetes. Similarly, LDL and age were shown to have an increasing effect on intima-media thickness.

Introduction

Diabetes mellitus (DM) is a metabolism disease resulting from insulin deficiency or reduced insulin effect [1]. Among chronic complications, coronary artery disease (CAD) is the most important cause of mortality and morbidity in diabetic patients [2]. Type 2 diabetics have 2-4 times higher risk of CAD than the normal population and most die due to macrovascular events [3]. Atherosclerosis is a chronic inflammatory process characterized by thickening and stiffening of vein walls and causes diseases with high morbidity like myocardial infarction and stroke [4, 5].

Diabetes, hypertension and hyperlipidemia disrupt the endothelial integrity of veins and begin this inflammatory process [4]. Atherosclerosis begins to form at early ages in diabetics and more widespread involvement occurs [1]. It is thought that chronic inflammation and disruption of the venous structure occurring with *Helicobacter pylori* (Hp) infection forms a risk for atherosclerosis [6]. Carotid intima media thickness (CIMT) is accepted as a noninvasive and good marker of early atherosclerotic changes [7]. In this study, CIMT measurements were used with the aim of researching the effect on atherosclerosis of Hp infection in diabetic patients.

Material And Method

Our retrospective study included type 2 diabetes patients aged 18 years and older attending the gastroenterology and diabetic clinics with gastroscopy performed for dyspeptic complaints and carotid Doppler examination. Clinical records of patients were assessed; those younger than 18 years, pregnant cases, with Hp eradication performed, with DM diagnosis other than type 2 DM and with cardiovascular, cerebrovascular or peripheral artery

disease were excluded from the study. Patient age, gender, body mass index (BMI), smoking habit, duration of diabetes, comorbid chronic diseases and medications used were recorded.

Blood samples were taken after 8-hours fasting. Complete blood count levels were measured using an automatic hematology analyzer (Beckman Coulter, Brea, CA, USA). Serum glucose measurements were identified using the enzymatic route with the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). HbA1c levels were measured with a COBAS 311 analyzer using the particle-supported immunoturbidometric method (Roche Diagnostics GmbH, Mannheim, Germany). HbA1c results are stated as percentage of total Hb in accordance with the Diabetes Control and Complication Trial/ National Glycohemoglobin Standardization Program (DCCT/NGSP). Serum cholesterol, triglyceride and HDL-C levels were measured with kits using the enzymatic colorimetric method (COBAS 311, Roche Diagnostics GmbH, Mannheim, Germany). LDL-C was calculated according to the Fridewald formula (LDL-C = total cholesterol – (VLDL + HDL), VLDL = TG/5). CRP was measured with the particle-supported immunoturbidometric method with a Behring Nephelometer BN-100 (Behring Diagnostic, Frankfurt, Germany). Estimated glomerular filtration rate (eGFR) was calculated with the CKD-EPI method (GFR=141 X min (Scr/κ,1) Ó X max(Scr/κ,1)−1.209 X 0.993yaş X 1.018 (female) X 1.159 (Black), Scr=serum creatinine (mg/dL), κ=for women 0.7 and for men 0.9, α= for women -0.329 and for men -0.411. Min=Scr/k minimum or 1, Max=Scr/k maximum or 1). Spot urine albumin/creatinine (mg/g) ratio was measured using levels in first morning urine.

The gastroscopy procedure was performed with a Fujinon endoscopy device by a single gastroenterologist. Endoscopy results were categorized as gastritis, ulcer, hernia and esophagitis. The presence of Hp was researched with endoscopic biopsy and pathological assessment used the Sydney protocol; with inflammation, atrophy, intestinal metaplasia and Hp positivity stated.

Doppler ultrasonography was performed using a Toshibo Aplio 500 device and 14 Hz surface probe. Right and left carotid intima media thicknesses were measured in millimeters as the distance between the anterior edge of the lumen intimal interface to the anterior edge of the media adventitia interface of the distal wall. The presence of plaque was researched.

STATISTICAL ANALYSES

Descriptive statistics were used to define continuous variables (mean, standard deviation, minimum, median, maximum). With the aim of investigating the effect of independent variables on continuous dependent variables, multiple linear regression analysis was applied. Comparison of two continuous independent variables with normal distribution used the Student t test, while comparison of two independent variables without normal distribution used the Mann Whitney U test. With the aim of investigating correlations between categoric variables, the chi-square (or if appropriate, Fisher exact test) was used. Statistical significance level was determined as 0.05. Analyses were completed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Results

As shown in Table 1, there were no statistically significant differences between the age, DM duration, BMI, gender and smoking habit of cases according to the presence of Hp ($p>0.05$). According to the presence of Hp, cases were not identified to have statistically significant differences in fasting blood sugar, HbA1c, total cholesterol,

triglycerides, HDL, LDL, non-HDL, Hb, albumin/creatinine, GFR and CRP measurements (p>0.05) (Table 2). As shown in Table 3, 31.5% of cases (n=23) were smokers, while 42.5% (n=31) were Hp positive.

Table 1
Description of patients according to presence of *Helicobacter pylori* (basic characteristics)

Hp		**Negative**		**Positive**		
		N=42		**N=31**		
		Mean±SD		**Mean±SD**		**P**
		Med. (Min.-Max.)		**Med. (Min.-Max.)**		
Age (years)		60±11		58±10		0,366[2]
		60 (42-83)		58 (44-83)		
DM duration (years)		13±7		11±6		0,223[1]
		11 (2-26)		10 (3-31)		
BMI (kg/m2)		28±2		29±2		0,246[2]
		28 (23-34)		28 (26-35)		
		N (%)		**N (%)**		**p[3]**
Gender	Male	18	42.9	14	45.2	1.000
	Female	24	57.1	17	54.8	
Smoking	No	31	73.8	19	61.3	0.312
	Yes	11	26.2	12	38.7	
Hypertension	No	13	31.0	11	35.5	0.802
	Yes	29	69.0	20	64.5	
Hyperlipidemia	No	23	54.8	14	45.2	0.482
	Yes	19	45.2	17	54.8	
COPD/Asthma	No	38	90.5	28	90.3	1.000
	Yes	4	9.5	3	9.7	
Hypothyroidism	No	37	88.1	30	96.8	0.232
	Yes	5	11.9	1	3.2	
CRD	No	40	95.2	26	83.9	0.127
	Yes	2	4.8	5	16.1	

Statistical significance at p<0.05. Abbreviations: Hp: *Helicobacter pylori*, DM: diabetes mellitus, BMI: body mass index, COPD: chronic obstructive pulmonary disease.

Table 2
Laboratory parameters of patients with type 2 diabetes mellitus, according to presence of Hp.

Hp	Negative N=42	Positive N=31	
	Mean±SD Med. (Min.-Max.)	Mean±SD Med. (Min.-Max.)	P
FPG (mg/dl)	146±55 132 (68-320)	153±61 131 (74-282)	0.620[1]
HbA1c (%)	7.8±1.8 7.6 (5.4-14.7)	8.2±2.9 7 (5.4-19)	0.517[2]
Total Cholesterol	183±42 178 (103-285)	180±58 163 (99-337)	0.818[1]
Triglyceride (mg/dl)	149±71 128 (52-364)	159±95 146 (47-400)	0.615[1]
HDL-C (mg/dl)	45±12 45 (24-68)	41±11 39 (24-79)	0.174[1]
LDL-C (mg/dl)	111±32 100 (52-191)	108±47 97 (35-226)	0.333[2]
Non-HDL-C (mg/dl)	134±37 129 (68-226)	134±55 128 (58-300)	0.554[2]
Hb (gr/dl)	11.9±2 12 (7.8-15)	11.6±2.1 11.5 (6.4-15.4)	0.668[1]
Spot urine albumin/creatinine (mg/gr)	48.32±70.94 16 (0.1-257)	988.31±2543.88 27.55 (1.8-11912)	0.105[2]
EPI-GFR	84±27 88 (3-122)	78±28 87 (21-115)	0.354[1]
CRP (mg/dl)	33.48±58.84 5.7 (1.9-193)	16.67±33.27 3.95 (2.2-142)	0.325[2]

[1]*Student t test*, [2]*Mann-Whitney U test*. Statistical significance ate p<0.05. Abbreviations: Hp: *Helicobacter pylori*, FBG: fasting blood glucose, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, Non-HDL-C: Non high density lipoprotein cholesterol, Hb: hemoglobin, CRP: C- reactive protein.

Table 3: The assessment of Carotid Intima Media Thickness according to presence of Hp, smoking status and plaque distribution

	Mean	±SD	Median	Min.	Max.
Intima Media Left (mm)	0.7	±0.2	0.7	0.5	1.7
Intima Media right (mm)	0.7	±0.1	0.7	0.5	1.3

		N	%
Hp	No	42	57.5
	Yes	31	42.5
Smoking	No	50	68.5
	Yes	23	31.5
Plaque	No	40	54.8
	Yes	33	45.2

Of those participating in the study, 45.2% (n=33) had plaque identified, with mean left intima media thickness of 0.7±0.2 mm and mean right intima media thickness of 0.7±0.1 mm. When medication used, endoscopic findings and pathology results are compared according to the presence of Hp, there were no statistically significant differences identified (p>0.05). The multiple linear regression model took left and right intima media thickness as the dependent variables and fasting blood sugar, HbA1c, BMI, LDL, age and Hp presence as independent variables and used the backward variable selection method. When left intima media thickness is fixed, a 0.092 mm increase in thickness occurred with Hp presence at 95% significance level; a 1 unit increase in age caused 0.009 mm increase at 95% significance level; and a 1 unit increase in LDL caused a 0.001 mm increase at 95% significance level. When right intima media thickness is fixed according to other variables, the presence of Hp caused 0.060 mm increase in thickness at 90% significance level; 1 unit increase in age caused 0.007 mm increase at 95% significance level; and 1 unit increase in LSL caused 0.001 mm increase at 95% significance level (Table 4).

Table 4: Factors Affecting CIMT

LEFT	R^2	Corrected R^2	Durbin-Watson	Significance level p	F Value
Model	0.331	0.301	2.165	<0.001	11.054

	Unstandardized β	Standard deviation	Standardized β	t value	Significance level p	VIF
Fixed	0.015	0.131		0.116	0.908	
Hp presence	0.092	0.038	0.244	2.421	**0.018**	1.015
Age	0.009	0.002	0.496	4.896	**<0.001**	1.029
LDL-C	0.001	0.000	0.306	3.040	**0.003**	1.016

RIGHT	R^2	Corrected R^2	Durbin-Watson	Significance level P	F Value
Model	0.243	0.210	**2.118**	**<0.001**	7.184

	Unstandardizedβ	Standard deviation	Standardized β	t value	Significance level p	VIF
Fixed	0.252	0.109		2.306	0.024	
Hp presence	0.060	0.032	0.203	1.892	**0.063**	1.015
Age	0.007	0.002	0.457	4.238	**<0.001**	1.029
LDL-C	0.001	0.000	0.196	1.833	**0.071**	1.016

Statistical significance at p<0.05. CIMT = carotid intima media thickness, Hp: *helicobacter pylori,* LDL-C: low density lipoprotein cholesterol.

Discussion

There are many studies showing the prevalence and correlation of Hp in diabetic patients [8, 9, 10, 11, 12]. Studies by Ciortescu et al. [9] and Demir et al. [10] showed a significant increase in Hp prevalence in diabetic cases compared to the normal population. Gulcelik et al. reported Hp prevalence increased in another study of diabetic patients and that this may be due to slowed stomach emptying and bacterial increases as a result of diabetic-linked autonomic neuropathy [13]. Along with studies showing Hp infection is more common in men [14, 15, 16, 17, 18, 19], a study by Lu et al. did not show a significant difference between gender and Hp presence [16], overlapping with our study.

In the literature there are many studies showing the correlation between Hp and atherosclerosis [6, 17, 18]. Some studies showed that Hp infection caused microvascular injury which triggers the initial stage of atherosclerosis [13, 18]. A study by Franceschi et al. reported that the interaction between Hp antibody and vein wall antigens may play a role in atherosclerosis development [19]. Another study of diabetic patients by Hamed et al. identified that the increase in intima media thickness in Hp infection may play a role in development of atherosclerosis and CAD by causing atherosclerotic plaque formation through invasion of the vein wall [14].

There are many studies researching the relationship between Hp and lipid profile in the literature. A study by Rahman et al. compared lipid profiles between Hp positive cases with and without CAD and identified no significant changes in total cholesterol, triglyceride and LDL cholesterol values, but HDL cholesterol was low in both groups [20]. A study by Laurila et al. [21] found similar results with high total cholesterol and triglyceride values and similar HDL cholesterol values in Hp positive cases compared to negative cases. Another study [22] showed lower HDL cholesterol value in Hp positive cases compared to negative ones. A different study identified LDL cholesterol values were high in Hp positive individuals [23]. Vafaeimanesh et al. [24] found no significant difference in lipid parameters in Hp positive or negative cases, similar to our study. This result may be linked to the low number of participants in the study and patients who attended regular clinical follow-up beginning lipid-lowering treatment in the early period.

A study by Su et al. showed the effect of BAG and BGT on endothelial dysfunction [25]. Another study identified a reduction in plasma glucose levels with Hp eradication treatment [26]. While there are studies showing higher fasting plasma glucose in Hp positive cases compared to negative cases [15, 26], our study showed no significant effect of Hp positivity on fasting plasma glucose. This result may be linked to the use of medications effective on insulin resistance at similar rates in Hp positive and negative cases participating in the study and patients regularly attending clinical check-ups.

There are studies showing a relationship between microalbuminuria, an early clinical marker of diabetic nephropathy, with endothelial dysfunction and subclinical atherosclerosis [27, 28]. A study by Chung et al. identified that Hp positivity was independently associated with the presence of microalbuminuria and urine albumin creatinine ratio had positive correlation with severity [29]. In our study, we showed the presence of Hp had no significant effect on albumin creatinine ratio and GFR level. Different from these studies, this result may be linked to the Hp positive and negative cases included in the study having similar risk factors for microvascular complications. In the study, Hp positive and negative cases did not have significant differences between diabetic duration and RAS blocker use so the actual effect on albumin creatinine ratio and GFR level may be inferred to be RAS blocker use and diabetic duration, rather than Hp.

The inflammation parameter of CRP was shown to increase CAD risk in many studies [30, 31]. A study by Jackson et al. compared the CRP levels of Hp positive and negative cases and showed Hp positive vases had higher CRP level [32]. Similar to our study results, Vafaeinmanesh et al. identified no significant effect of Hp presence on CRP elevation [24].

There are studies showing Hp positivity in adults is positively correlated with disrupted glucose tolerance [33, 34]. In this context, the study by Chen et al. [35] identified a significant relationship between Hp positivity in diabetic patients with HbA1c elevation. A study by Dai et al. identified higher HbA1c levels in type 1 diabetic patients with Hp positivity but reported there was no significant effect of Hp positivity on HbA1c levels in type 2 diabetic patients [33]. In our study, Hp presence was not shown to have a significant effect on HbA1c levels, supporting the findings of a study completed by Horikawa et al. [34].

In the literature, there are studies showing increased intima media thickness with BMI, a marker of obesity [36]. When considered in terms of the presence of Hp, there was a positive significant correlation reported between Hp positivity and BMI [37] and BMI of Hp positive patients was higher compared to negative patients [38]. In our study, the presence of Hp had no significant effect on BMI.

Atherosclerosis is an inflammatory disease beginning in the early periods of life progressing with arterial vein wall deformation. Arterial wall thickness is an early marker of atherosclerosis and may be easily assessed with Doppler ultrasound. There are many studies showing Hp positivity causes an increase in intima media thickness [14, 27]. A study by Zhang et al. in China showed presence of Hp had a positive effect on CIMT in men under 50 years of age; however, there was no significant effect in women and men over 50 years of age [39]. In our study, similar to the study by Zhang et al., we observed Hp positivity significantly increased CIMT.

In the literature, there are many studies showing Hp infection increases plaque formation in the carotid artery [40, 41]. Hu et al. showed high HbA1c value accompanying Hp positivity was closely associated with plaque formation in the carotid artery [41]. In our study, Hp positivity did not have a significant effect on plaque formation. This result leads to consideration that the basis of plaque formation in the carotid artery is not the presence of Hp, but is associated with the elevation in HbA1c. In fact, patients with increased plaque formation in the carotid artery were reported to differentiate not just in terms of the presence of Hp but also in terms of HbA1c elevation in the study by Hu et al. [41]. In our study, the reason for the lack of observation of a significant correlation between Hp presence and carotid artery plaque formation may be the similar HbA1c levels in both groups.

Limitations of our study include the lack of prospective study and the low number of patients. However, strong aspects of our study include research of the presence of Hp with endoscopic methods and detailed knowledge of medications used by participants.

Conclusion

In our study, Hp infection in type 2 diabetes patients with similar risk factors for atherosclerosis was independently shown to increase CIMT. This result leads to consideration that eradication of Hp in patients with atherosclerosis risk factors may reduce the atherosclerosis progression. Assessment of CIMT after Hp eradication in a prospective study of groups with similar characteristics will assist in answering this question.

Declerations

Ethics approval and consent to participate: The research was completed with permission from the Clinical Research Ethics Committee dated 27.10.2020 decision number 2020/514/188/4.
Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Competing interests: Authors state that there is no conflict of interest in this study.
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Authors' contributions: BB designed the study, supervised the work, reviewed and edited the article. RNA, EK collected samples and clinical data. RNA and BB researched the data. SA, RNA and HE wrote the manuscript. All authors have read and approved the final manuscript.
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