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Does Helicobacter pylori infection have a role in coronary artery disease?

Koroner arter hastalığında Helicobacter pylori enfeksiyonunun rolü var mıdır?

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Bacground/aims: *Various infectious diseases have been linked to coronary artery disease on epidemiological and pathogenic grounds. The aim of this study was to investigate the relationship between Helicobacter pylori infection and coronary artery disease.* ***Methods:*** *A total of 170 consecutive cases undergoing coronary angiography at Ege University Cardiology Department were included in the study. Seroprevalence of Helicobacter pylori infection and antibodies to cagA and plasma levels of fibrinogen, vitamin B_{12}, folic acid and homocysteine were then evaluated.* ***Results:*** *Coronary artery disease was diagnosed in 114 (67.1%) cases by angiography. Anti-Helicobacter pylori IgG was found to be positive in 83 (72.8%) cases with coronary artery disease and in 46 (82.1%) of those without it (p>0.05). Among 129 Helicobacter pylori-positive subjects, antibodies to cagA were detected in 53% (44/83) of the cases with coronary artery disease and in 52.2% (24/46) of those without the disease (p>0.05). Plasma levels of vitamin B12 were significantly lower in coronary artery disease cases than in those without it (224.1±108.5 and 275.8±197.7 pmol/l respectively, p=0.029), while homocysteine levels were significantly higher in coronary artery disease cases than in those without (14.9±5.2 and 12.8±4.8 mmol/l, respectively, p=0.012) it. No significant difference was detected between the cases with and without coronary artery disease in terms of fibrinogen and folate levels and none of the parameters studied showed any significant difference between Helicobacter pylori seropositive and seronegative groups. However, plasma vitamin B_{12} levels were found to be significantly lower in the cagA positive group than in cagA negative cases (209.6±104.2 and 252.9±109.8 pmol/l, respectively, p=0.023).* ***Conclusions:*** *In this study, no significant difference was detected between cases with and without coronary artery disease in terms of Helicobacter pylori and cagA seropositivity rates. The detection of lower vitamin B_{12} and higher homocysteine levels in patients with coronary artery disease suggests the role of vitamin B_{12} deficiency in its pathogenesis. Lower vitamin B_{12} levels found in cagA-positive cases also suggests that infection with cagA-positive Helicobacter pylori strains might contribute to the development of coronary artery disease by decreasing vitamin B_{12} absorption.*

Key words: Helicobacter pylori, coronary artery disease, cagA, fibrinogen, vitamin B_{12}, folic acid, homocysteine.

Amaç: *Çeşitli infeksiyon hastalıkları ile koroner arter hastalığı arasında epidemiyolojik ve patogenetik ilişki kurulmaktadır. Bu çalışmanın amacı, Helicobacter pylori infeksiyonu ile koroner arter hastalığı arasındaki ilişkisinin araştırılmasıdır.* ***Yöntem:*** *Ege Üniversitesi Tıp Fakültesi Kardiyoloji Anabilim Dalı'nda koroner anjiyografileri yapılan ardışık 170 olgu çalışmaya alındı. Helicobacter pylori ve cagA seroprevalansı ile plazma fibrinojen, B_{12} vitamini, folik asit ve homosistein düzeyleri araştırıldı.* ***Bulgular:*** *Anjiyografi ile 114 (%67.1) olguda koroner arter hastalığı saptandı. Koroner arter hastalığı olan 114 hastanın 83'ünde (%72.8) ve koroner arter hastalığı olmayan 56 olgunun 46'sında (%82.1) anti-Helicobacter pylori IgG (+) bulundu (p>0.05). Helicobacter pylori seropozitif bulunan 129 olgudan koroner arter hastalığı olanların %53'ünde (44/83), koroner arter hastalığı olmayanların ise %52.2'sinde (24/46) cagA antikoru pozitif bulundu (p>0.05). Koroner arter hastalığı olan grupta, koroner arter hastalığı olmayanlara göre B_{12} vitamini anlamlı derecede düşük (sırasıyla 224.1±108.5 ve 275.8±197.7 pmol/l, p=0.029), homosistein düzeyi ise anlamlı derecede yüksek (sırasıyla 14.9±5.2 ve 12.8±4.8 mmol/l, p=0.012) bulundu. Fibrinojen ve folik asit düzeyleri açısından iki grup arasında fark saptanmadı. Helicobacter pylori seropozitif ve seronegatif olan gruplarda, incelenen değerlerin hiç biri açısından farklılık saptanmazken, cagA pozitif grupta, negatif olanlara oranla B_{12} vitamini düzeyi anlamlı derecede düşük bulundu (sırasıyla 209.6±104.2 ve 252.9±109.8 pmol/l, p=0.023).* ***Sonuç:*** *Bu çalışmada, koroner arter hastalığı olan ve olmayan olgularda Helicobacter pylori ve cagA seropozitifliği açısından fark bulunmamıştır. Koroner arter hastalığı olan hastalarda B_{12} vitamininin düşük ve homosistein düzeyinin yüksek bulunması, koroner arter hastalığı patogenezinde B_{12} vitamininin eksikliğinin rolünü düşündürmektedir. CagA (+) olgularda da B_{12} vitamininin düşük bulunması, cagA (+) Helicobacter pylori suşlarıyla enfeksiyonun, B_{12} vitamininin emilimini bozarak, koroner arter hastalığının oluşumuna katkıda bulunabileceğini düşündürmektedir.*

Anahtar kelimeler: Helicobacter pylori, koroner arter hastalığı, cagA, fibrinojen, B_{12} vitamini, folik asit, homosistein.

INTRODUCTION

Helicobacter pylori (H.pylori) is the main factor in the development of gastritis and peptic ulcer disease. Many extragastrointestinal disorders of unknown etiology have also been investigated for

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any association with H.pylori infection. Coronary artery disease (CAD), the main cause of death in western countries, has been studied extensively. The exact pathogenic mechanisms of it are not fully known but it has been suggested that CAD may be associated with persistent bacterial or viral agents (1). Several infectious diseases, such as chronic dental infection, cytomegalovirus and chlamydia pneumonia have been linked to CAD on epidemiological and pathogenic backgrounds (2-6). In 1994, Mendall et al. first reported that the H.pylori seropositivity rate was significantly higher in CAD patients than in control cases (7). To date, a number of epidemiological and clinical reports with on the association of CAD and H.pylori infection have been published controversial findings.

Several mechanisms have been suggested as to how H.pylori might increase the risk of CAD. Infection-related chronic inflammation may increase CAD risk by increasing some systemic inflammatory markers (8-10). H.pylori infection can also cause platelet aggregation and induces a procoagulant activity (11). Other suggested mechanisms include changes in circulating lipid profile and immunological cross-reactivity between bacterial and human heat shock proteins (5). Sung and Sanderson also hypothesized that H.pylori gastritis could cause B vitamin deficiency, leading to hyperhomocysteinemia and thus increased risk of CAD (12).

If inflammation-related factors play a role in CAD, more virulent strains of H.pylori would be expected to be more common in CAD patients. Recently, Pasceri et al. suggested that more virulent cagA-positive strains of H.pylori in particular (which cause more inflammatory activity) might be related with CAD (13).

The aim of this study was to determine the seroprevalence of H.pylori infection and antibodies to cagA, an antigen that is expressed by the most virulent H.pylori strains inducing an enhanced gastric inflammatory response, and any relationship with the presence of CAD in patients undergoing coronary angiography. The association of plasma fibrinogen, vitamin B12, folate and homocysteine levels with CAD and H.pylori infection was also investigated.

MATERIALS AND METHODS

A total of 170 consecutive cases admitted to the Department of Cardiology at Ege University Medical School during the first six months of the year 2000 for elective coronary angiography were studied. Written informed consent was obtained from each subject. Cases with previously treated H.pylori infection were excluded. Diagnosis of CAD was based on angiographic findings (>50% diameter stenosis of =>1 major coronary artery). Angiograms were read by experienced cardiologists blinded to the results of H.pylori status.

Fasting venous blood was drawn prior to coronary angiography under standardized conditions. Within 30 minutes, the blood was centrifuged , immediately divided into aliquots, and frozen at –70°C until analysis.

Specific anti-H.pylori and anti-H.pylori cagA IgGs were measured by use of a commercial ELISA (Radim) according to the manufacturer's instructions. Plasma homocysteine levels were assessed by flouresceint polarization immune assay method. Fibrinogen levels were measured by coagulometric method and vitamin B12 and folate with immunoassay.

Parameters of patients with and without CAD and seropositives and negatives for H.pylori and cagA were compared statistically using chi square and student's t tests. p values less than 0.05 were accepted as significant.

RESULTS

Of the total 170 cases, 114 (67.1 %) were diagnosed with CAD by cornary angiography (83 M, 72.8% and 31 F, 27.2%) while there were 56 cases without CAD (38 M, 67.9% and 18F, 32.1%). The mean age was 58.8±10 and 50±14 years in cases with and without CAD respectively. There were no significant difference between groups according to age and gender.

Anti-H.pylori IgG was found to be positive in 83 (72.8%) of 114 cases with CAD and in 46 (82.1%) of 56 without CAD (p>0.05) (Figure 1). Antibodies to cagA protein were positive in 68 (52.7%) of a total of 129 H.pylori-seropositive cases. The cagA positivity rates were 53% (44/83) and 52.2% (24/46) in cases with and without angiographically diagnosed CAD in whom anti-H.pylori IgG antibodies were positive (p>0.05) (Figure 2).

Mean plasma levels of vitamin B_{12} (normal values: 180 - 914 pmol/l) were significantly lower in CAD patients than in those without CAD (224.1±108.5 and 275.8±197.7 pmol/l respectively,

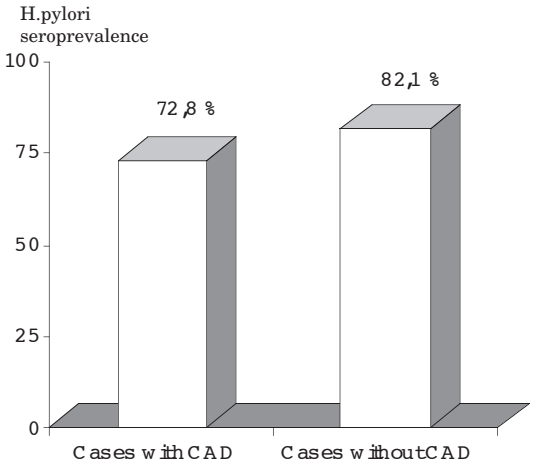

Figure 1. Seroprevalence of H.pylori infection in cases with and without angiographically diagnosed CAD.

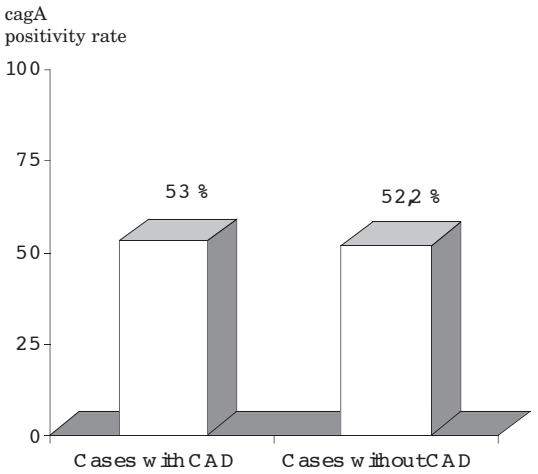

Figure 2. CagA positivity rates in cases with and without CAD.

p=0.029). Plasma vitamin B_{12} levels did not change according to H.pylori status (230.2±108.3 and 246.3±237.7 pmol/l in H.pylori seropositive and negative cases respectively, p>0.05) but it was significantly lower in cagA-positive cases than in cagA-negative ones (209.6±104.2 and 252.9±109.8 pmol/l respectively, p=0.023) (Table 1).

Mean plasma folate levels were 7.3±3.3 and 7.7±3.9 nmol/l in cases with and without CAD respectively. (p>0.05). Mean plasma folate levels of H.pylori seropositive and seronegative cases (7.1±3.4 and 8.1±4.0 nmol/l, respectively) and also cagA-positive and negative cases (7.6±4.1 and 6.6±2.4 nmol/l, respectively) showed no significant difference (Table 2).

Table 1. Mean plasma vitamin B_{12} levels of the case groups.

Case groups	*n*	*Vitamin B_{12} (pmol/l)*
With CAD	114	224.1±108.5 * (26 – 435)
Without CAD	56	275.8±197.7 (99 – 560)
H.pylori-positive	129	230.2±108.3 (26 – 400)
H.pylori-negative	41	246.3±237.7 (53 – 560)
CagA-positive	68	209.6±104.2 ** (26 – 400)
CagA-negative	61	252.9±109.8 (118 –415)
H.pylori-positive CAD cases	83	212.0±90.6 (99 – 400)
H.pylori-negative CAD cases	31	204.4±96.3 (53 – 435)
CagA-positive CAD cases	44	192.8±91 (26 – 380)
CagA-negative CAD cases	39	232.2±87 (118 – 415)

Values are mean±SD. Ranges are given in paranthesis.
* : p=0.029 (cases with CAD vs. without CAD)
** : p=0.023 (cagA-positive vs. cagA-negative cases)

Table 2. Mean plasma folate levels of the case groups.

Case groups	*n*	*Folate (nmol/l)*
With CAD	114	7.3±3.3 (2.58 – 14.46)
Without CAD	56	7.7±3.9 (3.20 – 20.00)
H.pylori-positive	129	7.1±3.4 (3.20 – 14.61)
H.pylori-negative	41	8.1±4.0 (3.30 – 18.10)
CagA-positive	68	7.6±4.1 (3.20 – 14.46)
CagA-negative	61	6.6±2.4 (3.50 – 12.96)
H.pylori-positive CAD cases	83	7.1±3.7 (3.20 – 14.46)
H.pylori-negative CAD cases	31	8.5±4.4 (3.30 – 13.81)
CagA-positive CAD cases	44	7.6±4.5 (3.20 – 14.46
CagA-negative CAD cases	39	6.5±2.5 (3.52 – 11.11)

Values are mean±SD. Ranges are given in paranthesis.

Table 3. Mean plasma homocysteine levels of the case groups.

Case groups	*n*	*Homocysteine (mmol/l)*
With CAD	114	14.9±5.2 * (8.2 – 37.8)
Without CAD	56	12.8±4.8 (6.8 – 20.5)
H.pylori-positive	129	14.5±5.6 (8.2 – 37.8)
H.pylori-negative	41	15.5±7.2 (7.4 – 21.6)
CagA-positive	68	14.6±6.2 (8.3 – 37.8)
CagA-negative	61	14.5+5.0 (7.4 – 23.0)
H.pylori-positive CAD cases	83	15.7±5.8 (8.2 – 37.8)
H.pylori-negative CAD cases	31	14.9±6.6 (7.4 – 21.6)
CagA-positive CAD cases	44	16.6±6.5 (8.3 – 37.8)
CagA-negative CAD cases	39	14.6±5.1 (7.4 – 22.8)

Values are mean±SD. Ranges are given in paranthesis.
* : p=0.012 (cases with CAD vs. without CAD)

DISCUSSION

In 1994, Mendall et al. reported that H. pylori seropositivity was twice as common in CAD patients as in control subjects (59% versus 39% respectively) (7). Since then, a number of studies have been published with controversial results. In some studies, H.pylori infection was found to be associated with an increased risk of developing CAD (3,10,14-16), but in some others no significant difference was detected between cases with and without CAD (17-21). In a review of 20 full or preliminary reports on H.pylori and CAD published between 1994 and 1996, it was concluded that evidence for a causal association between H. pylori and CAD was weak (5).

Proposed mechanisms for how H. pylori might increase CAD risk mainly include elevation of some systemic inflammatory markers. Several studies have reported strong correlations between H. pylori infection and various markers of systemic inflammation, presenting a potential pathophysiological link with CAD (22). These correlations, however, have not been confirmed by other studies and were not found to be significant in a meta-analysis (23).

Mean plasma homocysteine level was 14.9±5.2 mmol/l in CAD cases which was significantly higher than in those without CAD (12.8±4.8 µmol/l) (p=0.012). Plasma homocysteine levels of H.pylori seropositive and seronegative cases were similar (14.5±5.6 and 15.5±7.2 mmol/l, respectively, p>0.05). Also no significant difference was observed between cagA-positive and negative cases by means of plasma homocysteine levels (14.6±6.2 and 14.5±5.0 mmol/l, respectively) (Table 3).

Mean plasma fibrinogen levels (normal values : 200-400 mg/dl) were 358.6±85 mg/dl in cases with CAD and 332.1±77 mg/dl in those without CAD, which was not significantly different. Fibrinogen levels also showed no significant difference between H.pylori and cagA seropositive and negative cases (341.3±68.6 and 352.3±82.0 mg/dl in H.pylori-positive and negative cases; 332.8±60.9 and 350.4±75.9 mg/dl in cagA-positive and negative cases, respectively) (Table 4).

Table 4. Mean plasma fibrinogen levels of the case groups.

Case groups	*n*	*Fibrinogen (mg/dl)*
With CAD	114	358.6±85.2 (196.1 - 551.0)
Without CAD	56	332.1±77.4 (166.2 - 439.2)
H.pylori-positive	129	341.3±68.6 (166.2 - 447.0)
H.pylori-negative	41	352.3±82.0 (217.0 - 489.6)
CagA-positive	68	332.8±60.9 (196.1 - 429.0)
CagA-negative	61	350.4±75.9 (204.3 - 464.0)
H.pylori-positive CAD cases	83	345.9±65 (224.6 - 447.0)
H.pylori-negative CAD cases	31	340.6±70 (229.4 - 454.0)
CagA-positive CAD cases	44	330.7±66 (196.1 - 442.0)
CagA-negative CAD cases	39	361.9±63 (213.0 - 551.0)

Values are mean±SD. Ranges are given in paranthesis.

If H.pylori infection increases the risk of CAD by increasing systemic inflammatory factors, more virulent, cagA-bearing strains of H.pylori would be expected to be more common in CAD patients. The cagA-bearing H.pylori strains have been found to be associated with enhanced virulence and cytotoxin production and were more frequently associated with peptic ulceration and higher grades of gastric inflammation compared with cagA-negative strains (24,25). Evidence from a small case-control study by Pasceri et al. has suggested that the association between H.pylori and CAD might depend on the presence of the more virulent cagA-positive H pylori strains (13). In that study, prevalence of cagA-positive strains was significantly higher in CAD patients than in control subjects (43% and 17%, respectively), whereas no association was seen with cagA-negative strains and CAD. In some other studies the prevalence of cagA-positive H.pylori strains was also found to be higher in CAD patients than control cases. Pieniazek et al. reported that antibody to cagA protein was found to be significantly higher in patients with CAD, diagnosed by coronary angiography, than in healthy controls (47.3% and 28% respectively) (16). In the study of Gunn et al., it was also concluded that the association of chronic H.pylori infection with risk of myocardial infarction appears to be restricted to cagA-bearing strains (26). However, the association of infection with cagA-positive H pylori strains and CAD was not confirmed in some other studies. For example, Koenig et al. assessed the prevalence of infection with H pylori and the anti-cagA antibody in their large case-control study including 312 stable CAD patients and 479 control subjects (27). They found that the prevalence of cagA-positive strains was only slightly higher in patients than in control subjects (27.9% and 21.7%, respectively; p=0.076). They concluded that there was no independent association between more virulent cagA-positive strains of H.pylori and CAD. Murray et al. also found no independant association between cagA-positive H.pylori strains and CAD (28).

In this study, the prevalence of antibodies to H.pylori, and especially to the more virulent strains bearing cagA protein, was not found to be higher in cases with CAD diagnosed by coronary angiography than in those without CAD. In fact, atlhough the difference was not statistically significant, seroprevalence of H.pylori infection was higher in cases without CAD than in those with CAD. This finding does not support the hypothesis that infection with H pylori might be a major risk factor for CAD.

In some studies, higher plasma fibrinogen levels have been found in H.pylori-positive subjects than in H.pylori negative ones (29). Torgano et al. have also reported a significant decrease in plasma fibrinogen levels after antibiotic treatment (30). However, other studies have failed to show any significant difference between H.pylori-positive and negative cases in terms of plasma fibrinogen levels (15,16,27,31-33). In this study, plasma fibrinogen levels did not show any significant difference according to H.pylori or cagA status.

Hyperhomocysteinemia is generally accepted as a novel and independent risk factor for CAD (34-36). Two major hypotheses have been proposed to explain the harmful effects of homocysteine on vessels. It can damage endothelial cells allowing plaque formation and simultaneously interferes with the vasodilatory effect of nitric oxide. Homocysteine also promotes vascular smooth muscle cell hypertrophy and these processes induce vessel occlusion (37). High plasma homocysteine levels have been found in patients with atherosclerosis and coronary, cerebral and peripheral vascular diseases (38-43). Tokgozoglu et al have reported that plasma homocysteine over 15 mmol/l was a significant risk factor for the presence and extent of CAD (44). Plasma homocysteine concentration is determined by genetic and nutritional factors (36). Deficiences of vitamin B_6, B_{12} and folic acid lead to increased plasma homocysteine levels. One of the suggested mechanisms is the elevation of plasma homocysteine levels caused by reduced vitamin B_6, B_{12} and folate absorption due to chronic H.pylori gastritis (12). In the study of Tokgozoglu et al. the mean plasma folate was found to be low and correlated negatively with homocysteine in CAD cases (44). The relationship between plasma homocysteine, folate and vitamin B levels has been investigated in some other studies. Dierkes et al. reported the presence of a weak relationship between plasma homocysteine levels and levels of folate and vitamin B_{12} (45), while Dalery et al. and Turgan et al. found high homocysteine but normal folate and vitamin B_{12} levels in CAD patients (41,43). In this study, higher plasma homocysteine levels and lower vitamin B_{12} levels were found in cases with CAD than in those without CAD. However, mean plasma levels of homocysteine and vitamin B_{12} did

not show any significant difference according to H.pylori serostatus. In addition, no significant difference was observed between homocysteine and vitamin B_{12} levels of H.pylori cagA seropositive and negative cases with CAD. These findings suggest that increased homocysteine and decreased vitamin B_{12} levels are not related with H.pylori infection, but are related with CAD. In this study, the significantly lower plasma vitamin B_{12} levels found in cagA-positive cases compared with cagA-negative cases lead us to speculate that chronic gastritis associated with cagA-positive H.pylori infection could lead to failure of vitamin B_{12} absorption. Endoscopic and histologic examinations must be performed in further studies to clarify this issue. Although vitamin B_{12} levels were lower and homocysteine levels higher in cagA-positive CAD cases than in cagA-negative CAD cases, the differences were not significant, probably due to the small number of cases in the groups.

In conclusion, this study failed to show any association between CAD and H.pylori infection. Higher homocysteine and lower vitamin B_{12} plasma levels were found in CAD cases compared to controls, but this was not related with H.pylori status. Detection of lower plasma vitamin B_{12} levels in cagA-positive cases than in cagA-negative ones suggests that chronic gastritis due to cagA-positive H.pylori strains could contribute to the development of CAD by decreasing vitamin B_{12} absorption. However, larger studies are required to explain this issue.

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