Original Article

The prevalence of *Helicobacter pylori* with hypertension : The Jichi Medical School Cohort Study

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Abstract

Introduction Associations between chronic Helicobacter pylori (*H.pylori*) infection and cardiovascular risk factors have been demonstrated in previous studies. However, the association between *H.pylori* and hypertension is controversial, especially in different age groups.

Methods We conducted this cross-sectional study to reveal the association between *H.pylori* seropositivity and hypertension using the Jichi Medical School (JMS) Cohort Study. Odds ratios (ORs) for hypertension were calculated using multiple logistic regression models.

Results The prevalence of *H.pylori* was significantly higher in subjects with hypertension (56.1%) than those without (52.4%). *H.pylori* seropositivity was not associated with hypertension in overall subjects (adjusted OR : 1.14, 95% confidence interval (CI) : 0.85-1.26, P=0.72). However, *H.pylori* seropositivity was associated with hypertension in subjects aged ≥65 years (adjusted OR : 1.30 (1.01-1.69, P=0.04), but was not in those aged<65 years.

Conclusion There was a significant association between *H.pylori* seropositivity and hypertension only in subjects in the elderly, which implies that longer duration of *H.pylori* infection could be one of the mechanisms of hypertension.

Key Words : *H.pylori* infection, hypertension, cohort study

Introduction

Recently, cardiovascular disease could develop in a person without any of the risk factors, such as hypertension, diabetes mellitus and elevated total cholesterol (TC)[1-3]. Other factors, such as the process of inflammation, especially chronic infection, were speculated to contribute to atherosclerosis[4, 5].

Mendal et al. suggested a possible association between *H.pylori* and cardiovascular disease in 1994[6]. Many studies have since been done to prove the hypothesis that *H.pylori* infection increases the risk of cardiovascular disease. Several mechanisms were pointed out that *H.pylori* infection may contribute to the increased risk of atherosclerosis associated with life-long chronic inflammation that determines increases in C-reactive protein (CRP)[7] or fibrinogen[8].

The association between *H.pylori* and cardiovascular risk factors, such as hypertension[9], was also reported. Hypertension is not only one of the causes of atherosclerosis, but also one of the effects of atherosclerosis. To break this vicious circle between hypertension and atherosclerosis, it is important for us to clarify the association between *H.pylori* infection, which is a treatable disease, and hypertension. However, studies which examine the association between *H.pylori* and blood pressure in Japanese people are few in number[10, 11]. The prevalence of *H.pylori* in Japan was higher in other developed countries[12]. The determinants of hypertension in Japan were different from these countries. For example, weight is one of the determinants of hypertension and the average of weight of Japanese is different from that in other developed countries[13]. It is an important issue for Japanese people to investigate their own epidemiology in order to confirm an association between *H.pylori* infection and hypertension exists or not. It should be also considered in elderly, because the duration of chronic inflammation induced by *H.pylori* infection increases with age.

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The Jichi Medical School（JMS）Cohort Study is a large-scale multicenter study investigating cardiovascular risk factors in rural Japanese community. We examined *H.pylori* IgG antibody to reveal the association between seropositivity and hypertension.

Methods

Subjects

The JMS Cohort Study was conducted to investigate the risk of cardiovascular disease, stroke, and myocardial infarction in a Japanese population[14]. To obtain data for this study, we used a mass screening system for cardiovascular disease, which has been conducted in Japan since 1983 in accordance with the Health and Medical Service Law for the aged.

In 1999, we performed a large-scale cross-sectional survey, as part of the JMS Cohort Study in 6 rural districts：2 towns（Wara in Gifu Prefecture, Akaike in Fukuoka）, 3 villages（Takasu and Kuze in Gifu, Sakuki in Hiroshima）, and 1 island（Aino-shima in Fukuoka）. In each community, a local government office sent personal invitations to all the subjects by mail. All 2,632 subjects agreed to participate in the study and underwent health checkup.

To standardize the methods of data collection, we established a central committee, which was composed of the chief medical officers from all of the participating districts. This committee developed a detailed manual for data collection. Systolic blood pressure（SBP）and diastolic blood pressure（DBP）were measured with a fully automated sphygmomanometer（BP203RV-Ⅱ, Nippon Colin, Komaki, Japan）on the right arm after subjects had rested sitting for 5 min. Hypertension was defined as SBP ≥140mmHg and/or DBP ≥90mmHg. Body mass index（BMI）was calculated as weight（kg）/height^2（m^2）. Lifestyle information was gathered by a questionnaire developed by the committee. Smoking habits were categorized as a current smoker or not. A drinker was defined as a person who regularly consumed alcohol more than 3 days a week. Drinking habits were categorized as drinker or not.

Data Collection

We obtained blood samples before noon after an overnight fast. Blood samples were drawn from the antecubital vein of a seated subject with minimal tourniquet use. Specimens were collected in siliconized vacuum glass tubes containing 1/10 volume of sodium fluoride（blood sugar）, or no additives（lipids）. Tubes were centrifuged at 3,000× g for 15 minutes at room temperature. After separation, plasma samples were stored at 4 ℃ in refrigerated containers if analysis was to be performed within a few days. Otherwise, samples were frozen until analysis. Plasma samples were stored in refrigerated containers with dry ice for a maximum of 6 h, then frozen as rapidly as possible to -80℃ for storage until laboratory determinations were performed at the central laboratory of the Special References Laboratory（SRL）（Tokyo, Japan）, a commercial hematology laboratory. CRP, TC, fasting blood sugar（FBS）and high-density lipoprotein cholesterol（HDL-C）were measured using commercial kits. The serum IgG antibody to *H.pylori* was measured by an enzyme linked immunosorbent assay（ELISA）（HM-CAP, Enteric Products, INC,（EPI）, USA）. IgG to *H.pylori* ≥2.3 was considered positive, 1.8 to 2.2 as pseudopositive, and <1.8 as negative；therefore, we designated a result of ≥2.3 as positive and <2.3 as negative.

The present study was approved by the Institutional Review Board as the Central Committee of the JMS Cohort Study. Study participants gave their informed consent at entry.

Statistical analysis

All data were reported as mean ± standard deviation, or where indicated, median（interquartile range）and percentages. CRP was transformed to natural logarithms because of its skewed distribution. Values in two groups with or without hypertension were compared by an unpaired t-test for consecutive variables and the Chi-squared test or Fisher's exact test for categorical data. Crude and adjusted odds ratios（ORs）were calculated using multiple logistic regression models for hypertension, adjusting for sex, age, TC, HDL-C, FBS, BMI, smoking habits, and alcohol habits, which were known to be potential independent risk factors of hypertension. In addition, ORs were also calculated after these factors plus CRP, which was known to be associated with both hypertension and *H.pylori* seropositivity. ORs were also calculated in subgroup analysis by age ≥65 years or <65 years. A P value of less than 0.05 was considered significant. All statistical analysis were performed using SPSS ver.16.0 for Windows（SPSS Inc., Chicago, Illinois, USA）.

Results

The characteristics of subjects with or without hypertension are shown in Table 1. A total of 877 men and 1,358 women participated in these mass screening examinations. The prevalence of *H.pylori* was significantly higher in subjects with hypertension（56.1%）than those without（52.4%）. The prevalence of hypertension was 31.7%. The prevalence of hypertensive men was larger than that of women. Subjects with hypertension were older than those without hypertension. Their SBP, DBP, BMI, FBS, and CRP levels and *H.pylori* IgG titers were higher and HDL-C levels were lower than those subjects without hypertension. Smoking status was negatively associated with hypertension.

Crude and adjusted ORs for hypertension were shown in Table 2 and 3. Multiple logistic regression analysis showed that *H.pylori* seropositivity was not associated with hypertension after adjustment for sex, age, TC, HDL-C, FBS, BMI, smoking habits, alcohol habits, and CRP（adjustment OR 1.14, 95% CI：0.85-1.26, P=0.72）. In subgroup analysis,

subjects were evaluated separately by age (aged ≥65 or 65< years). Multiple logistic regression analysis showed that *H.pylori* seropositivity in subjects aged ≥65 years was associated with hypertension after adjustment for sex, TC, HDL-C, FBS, BMI, smoking habits, alcohol habits, and CRP (adjusted OR 1.30, 1.01-1.69, P=0.04), but was not in those aged 65<years (adjusted OR 0.84, 0.63-1.13, P=0.84).

Table 1. Characteristics of subjects with or without hypertension

	Hypertension (+) mean ± SD	Hypertension (-) mean ± SD	P value*
men**	310/709 (43.7 %)	567/1526 (37.2 %)	**0.01**
Age (years)	65.1 ± 9.6	59.6 ± 12.3	**<0.001**
SBP (mmHg)	153.9 ± 11.6	118.6 ± 13.4	**<0.001**
DBP (mmHg)	87.8 ± 10.1	69.8 ± 9.5	**<0.001**
BMI	23.6 ± 3.0	22.5 ± 2.9	**<0.001**
TC (mg/dL)	210.5 ± 35.4	203.6 ± 34.2	**<0.001**
HDL-C (mg/dL)	55.6 ± 13.7	57.5 ± 15.3	**<0.01**
FBS (mg/dL)	98.6 ± 16.4	95.6 ± 19.9	**<0.001**
LnCRP	6.24 ± 1.20	5.89 ± 1.30	**<0.001**
Smoking habits**	104/698 (14.9 %)	288/1480 (19.5 %)	**<0.05**
Alcohol habits**	370/705 (43.5 %)	719/1495 (48.1 %)	0.06
H.pylori IgG seropositivity**	397/709 (56.0 %)	799/1526 (52.4 %)	0.11
H.pylori IgG titer†	2.8 (1.1-5.3)	2.4 (0.8-5.1)	**<0.05**

*Variables in two groups with or without hpertension were compared by an unpaired t-test for consective variables and the chi-squared test or Fisher's exact test for categorical data.

**number (percentage).

†median (interquartile range).

H.pylori: *Helicobacter pylori,* SD: standard deviation. SBP: systolic blood pressure. DBP: diastolic blood pressure. BMI: body mass index. TC: total cholesterol. HDL-C: high-density lipoprotein cholesterol. FBS: fasting blood sugar. CRP: C-reactive protein.

Table 2. Odds Ratios for hypertension for *H.pylori* seropositivity and each risk factor

	Univariate			Multivaliate		
variable	OR	95% CI	P value*	OR	95% CI	P value**
H.pylori seropositivity	1.16	0.97-1.40	0.10	1.04	0.85-1.26	0.72
sex (men)	1.31	1.10-1.58	**<0.01**	0.80	0.63-1.02	0.07
Age (years)	1.05	1.04-1.05	**<0.001**	1.05	1.04-1.06	**<0.001**
TC (mg/dL)	1.01	1.00-1.01	**<0.001**	1.01	1.00-1.01	**<0.05**
HDL-C (mg/dL)	0.99	0.99-1.00	**<0.01**	1.00	0.99-1.00	0.23
FBS (mg/dL)	1.01	1.00-1.01	**<0.01**	1.00	1.00-1.01	0.40
BMI	1.13	1.10-1.17	**<0.001**	1.12	1.01-1.16	**<0.001**
Smoking habits	0.57	0.57-0.93	**<0.05**	0.71	0.53-0.95	**<0.05**
Alcohol habits	1.19	1.00-1.43	0.06	1.40	1.12-1.73	**<0.01**
LnCRP	1.25	1.17-1.34	**<0.001**	1.12	1.04-1.22	**<0.001**

OR: odds ratio was calculated with (multiple) logistic regression analysis.
*: logistic regression for hypertension

**: logistic regression for hypertension adjustment for sex, age, total cholesterol, high-density lipoprotein cholesterol, fasting blood sugar, body mass index, smoking habits, alcohol habits, and C-reactive protein.

H.pylori: *Helicobacter pylori, CI: confidence interval.* BMI: body mass index. TC: total cholesterol. HDL-C: high-density lipoprotein cholesterol. FBS: fasting blood sugar. CRP: C-reactive protein.

Table 3. Odds Ratios for hypertension for *H.pylori* seropositivity and each risk factor

	Univariate			Multivaliate		
variable	OR	95% CI	P value*	OR	95% CI	P value**
age≥65 (years)						
H.pylori seropositivity	1.32	1.03-1.69	**0.08**	1.03	1.01-1.69	**0.04**
sex	0.91	0.71-1.16	0.43	0.93	0.68-1.28	0.13
TC (mg/dL)	1.00	1.00-1.01	0.07	1.00	1.00-1.01	0.13
HDL-C (mg/dL)	0.99	0.98-1.00	0.09	1.00	0.99-1.01	0.36
FBS (mg/dL)	1.01	1.00-1.01	0.07	1.00	1.00-1.01	0.57
BMI	1.13	1.08-1.18	**<0.001**	1.10	1.05-1.15	**<0.001**
Smoking habits	0.83	0.61-1.23	0.42	0.82	0.55-1.23	0.33
Alcohol habits	1.27	0.99-1.62	0.06	1.23	0.92-1.64	0.16
LnCRP	1.00	1.00-1.00	0.98	1.15	1.05-1.15	**<0.05**
age<65 (years)						
H.pylori seropositivity	0.92	0.70-1.21	0.54	0.84	0.63-1.13	0.25
sex (men)	0.68	0.51-0.90	**<0.01**	0.61	0.42-0.87	**<0.01**
TC (mg/dL)	1.01	1.01-1.01	**<0.001**	1.01	1.00-1.01	**<0.001**
HDL-C (mg/dL)	0.99	0.98-1.00	**<0.05**	1.00	0.98-1.01	0.36
FBS (mg/dL)	1.01	1.00-1.02	**0.01**	1.00	1.00-1.01	0.32
BMI	1.19	1.13-1.25	**<0.001**	1.13	1.08-1.20	**<0.001**
Smoking habits	0.73	1.51-1.04	0.08	0.48	0.32-0.73	**<0.01**
Alcohol habits	1.42	1.07-1.87	**<0.05**	1.39	1.01-1.92	**<0.05**
LnCRP	1.27	1.14-1.42	**<0.001**	1.14	1.00-1.30	**<0.05**

OR: odds ratio was calculated with (multiple) logistic regression analysis.
*: logistic regression for hypertension

**: logistic regression for hypertension adjustment for sex, total cholesterol, high-density lipoprotein cholesterol, fasting blood sugar, body mass index, smoking habits, alcohol habits, and C-reactive protein.

H.pylori: *Helicobacter pylori, CI: confidence interval.* BMI: body mass index. TC: total cholesterol. HDL-C: high-density lipoprotein cholesterol. FBS: fasting blood sugar. CRP: C-reactive protein.

Discussion

We showed that *H.pylori* seropositivity was associated with hypertension in subjects aged ≥65 years, but was not in those aged<65 years in the JMS Cohort Study.

The association between *H.pylori* infection and hypertension has been reported. Mbenza et al. used logistic regression models adjusted for age, childhood living conditions, diabetes mellitus, smoking and excessive alcohol intake, and reported that seropositivity for *H.pylori* predicted independently both hypertension in the total study population and in men[9]. Kopacova et al. found marked differences between age groups in how *H.pylori* positivity was related to SBP and DBP[15]. They showed a relatively strong positive effect on blood pressure in subjects over 65 years. Moreover, we showed that *H.pylori* seropositivity in subjects aged ≥65 years was associated with hypertension using multiple logistic regression models after adjustment for conventional hypertension risk factors plus CRP.

The association of *H.pylori* with evaluations of serum CRP has also been reported[7]. Indeed, when compared by an unpaired t-test, CRP in *H.pylori* seropositive subjects (mean ± standard deviation Ln CRP : 6.03 ± 1.27) was higher than that in seronegative subjects (Ln 5.92 ± 1.28) in our study (P=0.03). Inducing a high inflammatory response, *H.pylori* infection may result in the development of atherosclerosis. Hypertension was considered to be an inflammatory process and associated with increased expression of the systemic markers of inflammation, such as CRP[16] and fibrinogen[17]. Thus, CRP was considered to be one of the confounding factors in the association between *H.pylori* infection and hypertension. We found a correlation between *H.pylori* seropositivity and hypertension in subjects aged ≥65 years, independent of CRP. The association was likely to be explained by respective underlying mechanisms.

Not only the process of inflammation but also its duration was speculated to contribute to atherosclerosis. We found an association between *H.pylori* seropositivity and hypertensives aged ≥65 years, but not aged<65 years. *H.pylori* is acquired during early childhood in most individuals and the infection lasts several decades as a chronic infection throughout life, unless specifically treated. Our study suggested that the duration of *H.pylori* infection is important for the association between this infection and hypertension. Moreover, hypertension not only promoted atherosclerosis, but was also followed by atherosclerosis, which supports the association between the untreated chronic *H.pylori* infection and hypertension.

On the other hand, some studies, including meta-analysis[18], showed that *H.pylori* was not associated with hypertension. Kopacova et al. reported that there were several methodological differences in carrying out studies to determine the possible relationship between *H.pylori* infection and raised blood pressure and that several other factors must

be considered（weight gain, salt intake, aging, co-morbidity, antihypertensive therapy, and compliance of patients）[15]. So far, these papers are difficult to compare as they differ in individual studies, design and number of subjects, diagnostic methods used（serology, 13C-urea breath test, stool antigen tests）, and come from both developed and developing countries[15].

We had some limitations. First, we determined *H.pylori* infection status by a serology test. Serology has been shown to be less sensitive and specific than compared with techniques that measure active *H.pylori* infection such as the urea breath test, stool antigen assay, or gastric biopsy. *H.pylori* serologies in this setting have been shown to have a sensitivity of 91.1% and a specificity of 82.5% compared with results of the 13C-urea breath test[19]. The serology test we used had acceptable sensitivity and specificity. Second, we did not check *H.pylori* cytotoxin-associated antigen A（Cag-A）status. Cag-A positive *H.pylori* has been demonstrated to be closely associated with atherosclerosis[20]. Because Cag-A positive *H.pylori* infections are common in Japan[21], the lack of data would not affect our results. Finally, we did not know whether subjects were taking medication for hypertension or not. In baseline data of the JMS Cohort Study, the proportion of subjects with hypertension who were being medicated was 34.3%[22], and they were younger than our study subjects；therefore, we may have underestimated the prevalence of hypertension.

Recently, eradication therapy for *H.pylori* has spread in the world and its effects on the association between *H.pylori* and hypertension are also controversial. Further studies are needed to clarify the association between *H.pylori* and hypertension.

We showed a significant association between *H.pylori* seropositivity and hypertension only in subjects in the elderly, which implies that longer duration of *H.pylori* infection could be one of the mechanisms of hypertension.

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ヘリコバクター・ピロリ感染症と高血圧症：JMS コホート研究

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要　　約

ヘリコバクター・ピロリ感染症と心血管危険因子の関連性が指摘されている。高血圧症との関連性についても指摘されているが，一定の見解は得られていない。

われわれは，日本の地域一般住民におけるヘリコバクター・ピロリ感染症と高血圧症との関連性を調べるため，自治医科大学（JMS）コホート研究の一環として，横断調査を行った。

ヘリコバクター・ピロリ抗体陽性率は，高血圧症群では56.1%，非高血圧症群では52.4% であった。多重ロジスティック解析では，ヘリコバクター・ピロリ抗体陽性は，高血圧症と関連していなかった（一般的な心血管危険因子で調整したオッズ比：1.14，95% 信頼区間：0.85-1.26，P=0.72）。65歳以上では，ヘリコバクター・ピロリ抗体陽性は高血圧症と関連があり（1.30，1.01-1.69，P=0.04），65歳未満では，関連していなかった。

われわれは，地域一般住民において，65歳以上ではヘリコバクター・ピロリ感染症が高血圧症と関連し，65歳未満では関連していないことを示した。

（キーワード：ヘリコバクター・ピロリ感染症，高血圧症，コホート研究）

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