Insulin has been shown to promote colorectal carcinogenesis (Corpet et al., 1997; Tran et al., 1996) and several studies have shown an increased risk of colon or colorectal cancer with diabetes (Weiderpass et al., 1997; Wideroff et al., 1997; Hu et al., 1999). Diabetes mellitus has also been shown to be associated with an increased risk of colon adenoma development (Kono et al., 1998; Nishii et al., 2001; Marugame et al., 2002). It is thus naturally of interest whether the metabolic syndrome is related to colorectal carcinogenesis. In this paper, we therefore examined links between the metabolic syndrome and colorectal adenoma, a well-established precursor lesion for colorectal cancer (O'Brien et al., 1990), in a population of middle-aged Japanese men.

Materials and Methods

Subjects

Study subjects were male officials in the Self-Defense Forces (SDF) who received a preretirement health examination at the SDF Fukuoka Hospital from January 1995 to March 2002 or at the SDF Kumamoto Hospital from May 1996 to March 2002. The preretirement health examination is a nationwide program offering a comprehensive medical examination to those retiring from the SDF, details of which have been described elsewhere (Kono et al., 1999; Toyomura et al., 2004). Colonoscopy was a routine procedure among others during a 5-day admission. The study was approved by the ethical committee of Kyushu University.

The present investigation included 756 cases of histologically confirmed colorectal adenomas and 1751 controls with no polyps among 3552 men who underwent total colonoscopy successfully. In a consecutive series of 4219 men during the above-mentioned period, 8 refused to participate in the survey, and 659 did not undergo successful total colonoscopy (no colonoscopy, 126; poor results, 11; and partial colonoscopy, 522). Of the 3552 undergoing total colonoscopy, 324 were excluded because of a history of colectomy (n = 20), colorectal polypectomy (n = 283), malignant neoplasms (n = 36), or inflammatory bowel disease (n = 3). In the remaining 3228 men, colonoscopic findings were classified as colorectal cancer (n = 2), polyp (n = 1471), non-polyp benign lesions such as diverticula (n = 207), and normal (n = 1548). Of the 1755 controls with normal or non-polyp benign lesions, 1751 were used as controls after exclusion of 4 men for whom the waist was not measured. Of the 1471 men with colorectal polyps, 756 were found to have adenomas without in situ or invasive carcinoma, and they were used as cases for the present study.

Numbers of cases having adenomas of the proximal colon alone, distal colon alone, and rectum alone were 258, 294, and 79, respectively. Proximal colon included cecum, ascending colon and transverse colon. A total of 125 cases had adenomas at multiple sites. Cases with adenomas sized of <5, 5–9, and ≥10 mm (the largest size for multiple adenomas) numbered 460, 243, and 49, respectively. Size of adenoma was not recorded with 4 cases. In the present study, adenomas of 5 mm or greater diameter was classified as large, while lesions measuring less than 5 mm in diameter were defined as small adenomas.

Clinical and Laboratory Data

Venous blood was drawn after an overnight fast for the determination of serum lipids and other biochemical measurements. Serum triglycerides and HDL-cholesterol were assayed enzymatically at each hospital laboratory using reagents from different sources. Plasma glucose levels were assayed by the glucose oxidase method using a commercial kit (Shino Test, Co. Ltd., Tokyo) at each hospital laboratory. A single blood pressure reading on the first day of admission was used for the present study. Waist and hip circumferences were measured in the horizontal plane at the level of the umbilicus and at the largest circumference around the buttocks, respectively. Medical history and current medication were ascertained by ward nurses and physicians.

Definition of the Metabolic Syndrome

In accordance with the diagnostic criteria proposed by the Japanese Committee of the Metabolic Syndrome Diagnostic Criteria (2005) and the International Diabetes Federation (Alberti et al., 2005), the metabolic syndrome was defined as the combination of abdominal obesity with any two of the following conditions: elevated triglycerides (≥150 mg/dL); lowered HDL cholesterol (<40 mg/dL); elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg); and raised fasting glucose (≥110 mg/dL). Medication for hypertension and treatment for diabetes mellitus were taken as evidence of raised blood pressure and fasting glucose, respectively. Of the cases and controls combined, 300 (12.0%) were under antihypertensive medication, 109 (4.3%) were under dietary or drug treatment for diabetes mellitus. It has been recommended by the International Diabetes Federation (Alberti et al., 2005) that cutoff points for abdominal obesity take account of the ethnicity and sex, and a waist circumference of ≥ 85cm has been adopted as the definition for abdominal obesity for Japanese men (≥ 90cm for Japanese women). However, cutoffs of 90 cm for men and 80 cm for women have already been specified for Chinese and South Asians (Alberti et al., 2005). The clinical significance of the different cutoffs remains uncertain at the present, and therefore we applied both 85 cm and 90 cm (for men), as the Japanese and Asian definitions, respectively, for the present analysis.

Statistical Analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were obtained by logistic regression analysis; the 95% CI was derived from the standard error for the logistic regression coefficient. Statistical adjustment was made for age (continuous variable), hospital, and rank in the SDF. Two-sided P values less than 0.05 were regarded as statistically significant. All computations were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC).

Table 1. Relation of Each Component of the Metabolic Syndrome to Colorectal Adenomas

Variable/category	Number (%)		OR (95% CI) [a]
	Cases	Controls	
Waist circumference (cm)			
<85	377 (50)	1034 (59)	1.00 (referent)
85-89	199 (26)	417 (24)	1.31 (1.06-1.61)
≥90	180 (24)	300 (17)	1.66 (1.33-2.06)
Triglycerides (mg/dL)			
<150	491 (65)	1201 (69)	1.00 (referent)
≥150	265 (35)	550 (31)	1.18 (0.98-1.41)
HDL (mg/dL)			
≥40	702 (93)	1605 (92)	1.00 (referent)
<40	54 (7)	146 (8)	0.85 (0.61-1.18)
Elevated blood pressure [b]			
(–)	287 (38)	729 (42)	1.00 (referent)
(+)	469 (62)	1022 (58)	1.16 (0.98-1.39)
Raised fasting glucose [c]			
(–)	613 (81)	1435 (82)	1.00 (referent)
(+)	143 (19)	316 (18)	1.06 (0.85-1.32)

OR, odds ratio; CI, confidence interval.
[a] Adjusted for age, hospital, and rank in the Self Defense Forces.
[b] Either systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or medication for hypertension.
[c] Either fasting plasma glucose ≥110 mg/dL or treatment for diabetes mellitus.

Results

Ages ranged 49-57 years for the cases and 44-59 years for the controls, with 99% in the range of 50-55 years in both groups. Abdominal obesity defined by the Japanese criterion (≥85cm in waist circumference) was observed with 50% of of the cases and 41% of the controls. Abdominal obesity based on the Asian criterion (≥90 cm) was much less frequent, but was also more prevalent in the cases (Table 1). Prevalent odds of colorectal adenoma progressively increased with higher values for waist circumference. Adjusted ORs for colorectal adenoma with abdominal obesity as classified by the Japanese (≥85 cm versus <85 cm) and Asian (≥90 versus < 90 cm) criteria were 1.45 (95% CI 1.22-1.73) and 1.52 (95% CI 1.23-1.87), respectively. Hypertriglyceridemia, lowered HDL cholesterol, raised blood pressure, and raised fasting glucose were evident in 31%, 8%, 58%, and 18%, respectively, for the control group. None of these four components of the metabolic syndrome was measurably associated with colorectal adenoma.

Table 2. Risk of Colorectal Adenomas in Relation to the Metabolic Syndrome

Metabolic syndrome	Number (%)		OR (95% CI) [a]
	Cases	Controls	
Japanese criteria			
(–)	563 (74)	1403 (80)	1.00 (referent)
(+)	193 (26)	348 (20)	1.38 (1.13-1.69)
Asian criteria			
(–)	657 (87)	1588 (91)	1.00 (referent)
(+)	99 (13)	163 (9)	1.48 (1.13-1.93)

OR, odds ratio; CI, confidence interval.
[a] Adjusted for age, hospital, and rank in the Self Defense Forces.

The prevalence rates for the metabolic syndrome as defined by the Japanese criteria were 26% in the cases and 20% in the controls. The corresponding values on the basis of the Asian criteria were 13% and 9% (Table 2). The adjusted OR for colorectal adenomas was moderately but statistically significantly increased in individuals with the metabolic syndrome, independent of the criteria applied. When the analysis was conducted by tissue site (Table 3), the ORs associated with metabolic syndrome were consistently increased for proximal colon adenomas. A less evident increase in the OR of distal colon adenoma associated with metabolic syndrome was statistically significant only when the Japanese definition was used, while a statistically non-significant increase in the OR of rectal adenoma was more pronounced with the Asian definition.

A positive association with metabolic syndrome was observed almost exclusively for large adenomas (Table 4). Of the cases with proximal colon adenoma alone (n = 258), 85 cases were classified as having large adenomas, and adenomas of the remaining 173 cases were classified as small. Cases of large proximal colon adenoma with the metabolic syndrome defined by the Japanese and Asian criteria numbered 27 and 12, respectively, resulting in an OR of 1.90 (95% CI 1.18-3.04) for the Japanese definition and an OR of 1.70 (95% CI 0.90-3.20) for the Asian definition. The ORs for small proximal adenomas were 1.42 (95% CI 0.99-2.03) and 1.61 (95% CI 1.02-2.55), respectively.

Discussion

The present study revealed a statistically significant

Table 3. Risk of Adenomas of the Proximal Colon, Distal Colon and Rectum in Relation to the Metabolic Syndrome

Metabolic syndrome	Proximal colon		Distal colon		Rectum	
	No [a]	OR (95% CI) [b]	No [a]	OR (95% CI) [b]	No [a]	OR (95% CI) [b]
Japanese criteria						
(–)	186	1.00 (referent)	218	1.00 (referent)	60	1.00 (referent)
(+)	72	1.56 (1.16-2.10)	76	1.41 (1.06-1.88)	19	1.27 (0.75-2.16)
Asian criteria						
(–)	221	1.00 (referent)	259	1.00 (referent)	67	1.00 (referent)
(+)	37	1.64 (1.11-2.40)	35	1.33 (0.90-1.96)	12	1.75 (0.92-3.31)

OR, odds ratio; CI, confidence interval. [a] Number of adenoma cases. [b] Adjusted for age, hospital, and rank in the Self Defense Forces.

Table 4. Risks of Colorectal Adenoma in Relation to the Metabolic Syndrome by Size of Adenoma

Metabolic syndrome	Small adenomas		Large adenomas	
	No[a]	OR (95% CI)[b]	No[a]	OR (95% CI)[b]
Japanese criteria				
(−)	352	1.00 (referent)	209	1.00 (referent)
(+)	108	1.24 (0.97-1.59)	83	1.60 (1.21-2.12)
Asian criteria				
(−)	407	1.00 (referent)	247	1.00 (referent)
(+)	53	1.26 (0.90-1.75)	45	1.83 (1.28-2.62)

OR, odds ratio; CI, confidence interval.
[a] Number of adenoma cases.
[b] Adjusted for age, hospital, and rank in the Self Defense Forces.

increase in the risk of colorectal adenoma associated with the metabolic syndrome, most prevalent for the proximal colon rather than the distal colon or rectum, and particularly for large adenomas. We were unable to rule out a small increase in the risk of distal colon or rectal adenoma associated with metabolic syndrome, however. It should be noted that the findings were consistent with both the Japanese and Asian criteria for abdominal obesity.

Previously, to our knowledge, only one study has examined the relation between a cluster of metabolic abnormalities and colorectal cancer (Trevisan et al., 2001). The focus was on abnormal values for triglycerides, HDL cholesterol, and fasting glucose (each defined by the highest or lowest quartile) and hypertension (systolic pressure ≥140 mmHg and/or ≥90 mmHg). Abdominal obesity was not taken into account, but the cluster of metabolic abnormalities was associated with a statistically significant 3-fold increase in mortality from colorectal cancer (Trevisan et al., 2001).

The present findings are in agreement with the previous observations regarding diabetes mellitus and colon adenomas in the SDF Health Study. In earlier analyses (Nishii et al., 2001; Marugame et al., 2002), based on some of the subjects included in the present analysis, diabetes mellitus was associated with increased risks of both proximal and distal colon adenomas, but was more strongly associated with proximal colon adenoma and with large adenomas (≥5 mm in diameter). The finding that the metabolic syndrome might also be more strongly associated with large adenomas indicates that hyperinsulinemic status may be responsible for growth of adenomas. Insulin may exert a proliferative effect on colonic tumor cells directly (Corpet et al., 1997; Tran et al., 1996) or via the insulin-like growth factor pathway indirectly (Yu and Rohan, 2000). Furthermore, increased production of proinflammatory cytokines and decreased production of an anti-inflammatory adiponectin in adipocytes may be relevant to the growth of adenomas (Eckel et al., 2005). Recently, high plasma levels of adiponectin were shown to be inversely related to the risk of colon cancer (Wu et al., 2005). However, it is not clear why the metabolic syndrome or diabetes mellitus should be most strongly associated with proximal colon adenoma. Subsite differences in the association with diabetes mellitus has also been observed as regards colorectal cancer. At least three studies have examined the relation of diabetes mellitus to subsite-specific colorectal cancer risk. One of these studies showed an increased risk associated with diabetes mellitus for proximal colon cancer exclusively (Limburg et al., 2005), and the other two found a more evident increase in the risk of proximal colon cancer (Weiderpass et al., 1997; Hu et al., 1999). However, central obesity has been reported to increase the risk in both proximal and distal sites (Moore et al., 2004) and dietary zinc, protective against diabetes, has been linked with reduction in both sites (Lee et al., 2004).

The present study features methodological advantages in that total colonoscopy was performed almost non-selectively in a defined population and that the absence of polyp lesions could thereby be confirmed in the controls. However, the study subjects were not representative of Japanese men in the general population. Thus the present findings may not be generalized. Another important aspect is that a fairly large number of the subjects (n = 283) had previously undergone colorectal polypectomy, and consequently cases with small adenoma accounted for a large proportion of the total adenoma cases. If the metabolic syndrome is most relevant to the growth of adenomas, the observed association may have been underestimated.

In the present study, physical activity and other factors associated with colorectal adenoma and cancer were not taken into consideration. Physical inactivity is one of the most important lifestyle factors related to the metabolic syndrome, as well as to colon cancer development (Moore et al., 1998b). In addition, moderate alcohol use is related to increased insulin-sensitivity (Facchini et al., 1994; Davies et al., 2002) while smoking exerts an opposite effect (Facchini et al., 1992). Both alcohol use and cigarette smoking are associated with increased risk of colorectal adenoma (Giovannucci et al., 1993; Giovannucci and Martinez 1996; Toyomura et al., 2000). Adjustment for these factors (except alcohol) probably causes overadjustment which necessarily tends to mask any association between the metabolic syndrome and colorectal adenoma. In fact, analysis allowing for physical activity, alcohol use, and cigarette smoking only attenuated the association to a limited extent with our subjects; ORs for adenomas at the colorectum, proximal colon, distal colon, and rectum with the Japanese definition were thus 1.31 (95% CI 1.07-1.61), 1.47 (95% CI 1.09-1.99), 1.34 (95% CI 1.00-1.79), and 1.16 (0.68-1.99), respectively. It could be argued that controlling for such factors is not appropriate when the aim is to address the role of the metabolic syndrome per se in the occurrence of colorectal adenomad.

In summary, the present reasonably large cross-sectional study in a population of middle-aged Japanese men showed an increased risk of colorectal adenomas, particularly of proximal colon adenomas and of large adenomas, associated with the metabolic syndrome. Thus the metabolic syndrome can be considered an important entity with regard to prevention of colorectal cancer as well as circulatory disease and type 2 diabetes.

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Prevalence of Atopic Dermatitis and Serum IgE Values in Nursery School Children in Ishigaki Island, Okinawa, Japan

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Abstract

There have been many studies of the prevalence of atopic dermatitis (AD), but few population-based epidemiologic studies measure the prevalence in Japan among children aged 5 years and younger. We examined the prevalence of AD, serum total IgE levels and specific IgE antibodies to 10 common allergens among children in Ishigaki Island, Okinawa, Japan in 2001. We also obtained information on the predictability of the U.K. Working Party diagnostic questionnaire criteria for AD in this population. Five hundred and sixty five children aged 5 years and younger were enrolled in this study with informed consent from their parents. The questionnaire of the U.K. Working Party diagnostic criteria for AD was translated into Japanese, and the parents completed the questionnaire sheet. Physical examination and blood sampling were done for all children. Thirty-nine out of the 565 (6.9%) children were diagnosed with AD by physical examination. The total and specific IgE levels were significantly higher in the children with AD than in those without AD. High levels of total IgE were found in 33.3% of the children with AD. A specific IgE to one or more allergens was detected in 64.1% of children with AD. However, a substantial population of children without AD also had high levels of total IgE (12.7%) and a specific IgE to one or more allergens (30.2%), and the increment of total and specific IgE levels was significantly associated with age. The percentage of positive answers to the questionnaire of the U.K. Working Party diagnostic criteria for AD was significantly higher in children with AD (59.0%) than in children without AD (5.3%) ($P<0.0001$). Its specificity was 94.7%. The false negative rate was 41%. In conclusion, the prevalence of AD was relatively low in children in Ishigaki Island. High levels of total IgE were found in only one third of children with AD under 5 years of age. The Japanese translated form of the questionnaire of the U.K. Working Party diagnostic criteria for AD should be refined to improve its sensitivity.

Abbreviation: AD; atopic dermatitis

Key words: atopic dermatitis; epidemiology; questionnaires; immunoglobulin E

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease that is characterized by relapsing itch and eczema. It is a major skin disease of children that is increasing in both developed (1–3) and developing counties (4). A similar trend has been documented in Japan (5); however, one study has reported that AD is no longer increasing (6). There have been many studies of the prevalence of AD (6–13), but few population-based epidemiologic studies that measure the prevalence in Japan

Table 1. The prevalence of atopic dermatitis (AD) in children aged 5 years and under in nursery schools in Ishigaki City, Okinawa, Japan, in 2001

Age (years)	Boys		Girls		Total	
	Numbers examined	AD Cases (%)	Numbers examined	AD Cases (%)	Numbers examined	AD Cases (%)
1	47	2 (4.3)	41	4 (9.8)	88	6 (6.8)
2	57	3 (5.3)	56	3 (5.4)	113	6 (5.3)
3	78	5 (6.4)	52	8 (15.4)	130	13 (10.0)
4	65	5 (7.7)	68	4 (5.9)	133	9 (6.8)
5	55	4 (7.3)	46	1 (2.2)	101	5 (5.0)
Total	302	19 (6.3)	263	20 (7.6)	565	39 (6.9)

among children aged 5 years and younger.

The first set of standardized diagnostic criteria for AD arose from the work of Hanifin and Lobits, and it was revised by Hanifin and Rajka (14, 15). The Japanese Dermatological Association criteria for the diagnosis of AD were established in 1995 (16). In order to set more useful criteria for mass-screening, the United Kingdom (U.K.) Working Party furthered the development of a standardized questionnaire defining the diagnostic criteria for AD (17). This questionnaire was composed of only 5 questions that were easy to answer by parents.

The aim of the present study was to determine the prevalence of AD, serum total IgE, and specific IgE antibodies among children aged 5 years and younger living in a relatively isolated area, Ishigaki Island. An additional aim of the study was to obtain information on the predictability of the questionnaire of the U.K. Working Party diagnostic criteria for AD when used in combination with physical examination in a Japanese population.

Methods

Study population

A large-population, long-term study of residents of the Yaeyama District of Okinawa, Japan for hepatitis B virus markers has been ongoing since 1968 (18–20). The present study was done as a part of the above-mentioned epidemiologic study in 2001. We visited 15 nursery schools in Ishigaki Island, which has a population of 45,000, in the Yaeyama District of Okinawa Prefecture, Japan. Approval for the study was obtained from the Ethics Committee of Kyushu University Hospital as well as from the directors and class teachers of the schools. Informed consent to allow participation of the children was obtained from the parents and guardians. The yearly average temperature and humidity were 25.4°C and 76% on Ishigaki Island.

Six hundred and five children were originally enrolled in the study. There were 40 exclusions because of insufficient physical and laboratory examination or incomplete answers to questionnaires. The remaining 565 children were 302 boys and 263 girls, with a mean age of 3.1 years, and represented 13.7% of the 4,112 kindergarten pupils in Ishigaki City. Physical examinations with questionnaires concerning histories of symptoms and family history were completed, and venous blood samples were obtained between July 30 and August 3, 2001.

Physical and laboratory examination

The medical examinations for all children were done by two dermatologists from the Department of Dermatology at Kyushu University Hospital. AD was diagnosed according to the Japanese Dermatological Association criteria for the diagnosis of AD (16). All children were tested for total and specific IgE antibodies. Total IgE level was determined by a radioimmunoassay with a detection limit of 20 IU/ml (Shionoria IgE, Shionogi & Co., Ltd. Japan). A total IgE

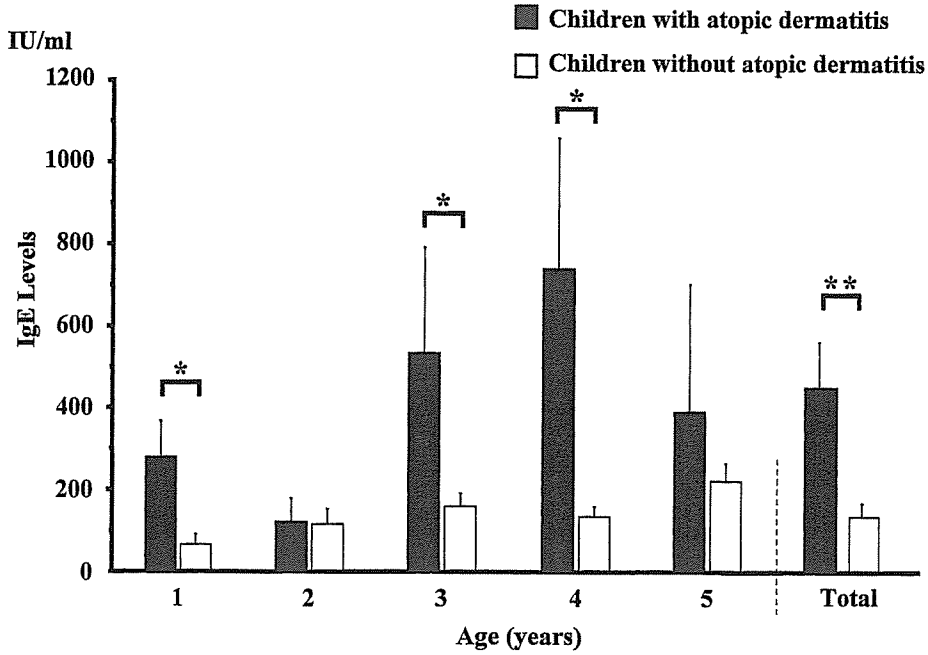

Fig. 1. Levels of total IgE in children 5 years of age and younger in nursery schools, Ishigaki City, Okinawa, Japan, in 2001.
The black bar (■) indicates children with AD and the open bar (□) shows children without AD. The standard deviations are shown by the thin, vertical bars and statistical significance is indicated by the "*" ($P<0.05$) and "**" ($P<0.001$).

Table 2. Comparison of the rates of abnormal total IgE levels between children with and without atopic dermatitis (AD) in Ishigaki City, Okinawa, Japan, in 2001

Age (years)	With AD		Without AD	
	No. tested	Abnormal IgE No. #(%)	No. tested	Abnormal IgE No. #(%)
1	6	3 (50.0)	82	3 (3.7)**
2	6	1 (16.7)	107	7 (6.5)**
3	13	3 (23.1)	117	23 (19.7)**
4	9	5 (55.6)	124	15 (12.1)**
5	5	1 (20.0)	96	19 (19.8)**
Total	39	13 (33.3)*	526	67 (12.7)

#A total IgE level of over 230 IU/ml was considered abnormal.
*A statistically significant difference was found between children with and without atopic dermatitis ($P=0.0029$)
**$P=0.0007$, calculated by use of the Cochran Armitage test.

level over 230 IU/ml was considered abnormal for statistical analysis. Specific IgE antibodies against aeroallergens such as house dust, Japanese cedar pollen, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Candida*, *Malassezia*, and food allergens, such as chicken egg white,

Table 3. Comparison of positive specific IgE antibody responces of children in Ishigaki City, Okinawa, Japan, in 2001, with and without atopic dermatitis (AD)

Specific IgE antibody	AD children (n=39) Positive No. (%)	Non-AD children (n=526) Positive No. (%)	P value*
house dust	17 (43.6)	115 (21.9)	0.0038
Japanese cedar pollen	0 —	0 —	—
D. pteronyssinus	19 (48.7)	122 (23.2)	0.0008
D. farinae	19 (48.7)	98 (18.6)	<0.0001
Candida	2 (5.3)	2 (0.4)	0.0255
Malassezia	0 —	1 (0.2)	—
chicken egg white	10 (25.6)	57 (10.8)	0.0167
cow's milk	9 (23.1)	68 (12.9)	0.1233
rice	1 (2.6)	0 —	—
soy	2 (5.3)	2 (0.4)	0.0255
one or more antibodies	25 (64.1)	159 (30.2)	<0.0001

*P values represent the result of statistical comparison of children with and without atopic dermatitis.

D. pteronyssinus, Dermatophagoides pteronyssinus; D. farinae, Dermatophagoides farinae

Table 4. Comparison of positive rates for one or more specific IgE antibodies in children with and without atopic dermatitis (AD) in Ishigaki City, Okinawa, Japan, in 2001 by age

Age (years)	with AD		without AD	
	No. tested	Abnormal No. (%)	No. tested	Abnormal No. (%)
1	6	3 (50.0)	82	21 (27.6)**
2	6	5 (83.3)	107	29 (27.1)**
3	13	5 (38.5)	117	36 (30.8)**
4	9	9 (100.0)	124	32 (25.8)**
5	5	3 (60.0)	96	41 (42.7)**
Total	39	25 (64.1)*	526	159 (30.2)

*A statistically significant difference was found between children with and without atopic dermatitis (P<0.0001)

**P=0.0394, calculated by use of the Cochran Armitage test.

cow's milk, rice, and soy were tested with the Pharmacia Enzyme CAP procedure (Pharmacia CAP System Specific IgE FEIA, Pharmacia Diagnostics AB, Sweden). A level of specific IgE antibodies over 0.7 UA/ml was considered abnormal for statistical analysis.

Questionnaire

The questionnaire of The U.K. Working Party diagnostic criteria for AD was translated into Japanese by a staff member of Kyushu University Hospital. The questionnaire has 5 questions regarding the present and past history of skin conditions (17). Each one-page questionnaire was completed by parents on behalf of their children. Children with suitable positive answers were diagnosed as AD using the same evaluation method proposed by the U.K. Working Party (17).

Table 5. Responses to the United Kingdom Working Party questionnaire for children with and without AD diagnosed by clinical examination

Questionnaire		Physical examination: AD N=39	Physical examination: Non-AD N=526
AD	N=51	23 (59%)	28 (5.3%)
Non-AD	N=514	16 (41%)	498 (94.7%)

Statistical analysis

Continuous data were expressed as mean values ± standard deviation (SD) or standard error (SE) of the mean. Unpaired t-test and Mann-Whitney U-test were used to compare the means of samples between the two groups. The chi-square test or Fisher's exact test was used for categorical variables for comparisons between the two groups. The Cochran-Armitage test was used to determine the relationship between the increase or decrease in the prevalence rate of AD or the IgE abnormality rate. $P<0.05$ was considered statistically significant.

Results

Prevalence of AD

Table 1 shows the overall prevalence of AD in the study population. Out of 565 children, 39 (6.9%) were diagnosed with AD by physical examination. The prevalence peaked at age 3 (10%), and was lowest at age 5 (5%); however, the age-related difference was not statistically significant ($P=0.7146$ by the Cochran-Armitage test). No significant differences were found when boys (19 of 302, 6.3%) and girls (28 of 263, 7.6%) were compared for disease prevalence.

Total IgE levels

The mean (± SE) total IgE levels were significantly higher in children with AD (451.1 ± 120.4 IU/ml) than in those without AD (139.2 ± 14.7 IU/ml) ($P<0.001$ by Mann-Whitney U-test) (Fig. 1). The total IgE levels were quite variable in each age group, and significant differences in mean IgE levels were found at ages 1, 3, and 4 between children with and without AD (1 year old, $P=0.0026$; 3 years old, $P=0.0272$; and 4 years old, $P=0.0037$, by Mann-Whitney U-test) (Fig. 1). As shown in Table 2, the occurrence of abnormal total IgE levels of over 230 IU/ml was significantly higher in children with AD (13 of 39, 33.3%) than in those without AD (67 of 526, 12.7%) ($P=0.0029$ by the chi-square test). Interestingly, the rate of abnormal total IgE levels in children with AD did not significantly increase with age, however; the rate of abnormal total IgE levels in children without AD significantly increased with age ($P=0.0007$ by the Cochran-Armitage test) (Table 2).

Positivity of specific IgE antibodies against aeroallergens and food allergens

Antigen-specific IgE antibodies against aeroallergens and food allergens, as indicated by values over 0.7 UA/ml, were found in 184 (32.6%) of the total of 565 children. Table 3 shows the differences in specific IgE antibody between children with and without AD. A positive response for one or more specific IgE antibodies was significantly higher in children with AD (64.1%) than in those without AD (30.2%) ($P<0.0001$). Specific IgE antibody positivities, with the exceptions of Japanese cedar pollen, *Malassezia*, cow's milk and rice, were significantly higher in children with AD than those without AD (Table 3). The percentage positivity of specific IgE antibodies in children with AD did not significantly differ according to age (Table 4) (38.5% to 100%, $P=0.3618$ by the Cochran-Armitage test). However, the percentage positivity of specif-

ic IgE antibodies significantly increased with age in children without AD (Table 4) (25.8% to 42.7%, P=0.0394 by the Cochran-Armitage test).

Questionnaire

We determined the sensitivity and specificity of the translated questionnaire of the U.K. Working Party diagnostic criteria for AD (Table 5). Fifty-one out of 565 children (9%) fulfilled the criteria for AD by the questionnaire. When compared to the actual diagnosis by physical examination, the sensitivity was 59% (23 out of 39), and the specificity was 94.7% (498 out of 526). The false positive and negative rates were 5.3% and 41%, respectively (Table 5).

Discussion

Symptoms of AD began during the first year of life in 65% of the children and in 85% during the first 5 years (21); it is thus worthwhile to determine the prevalence in children under the age of 5 years. In 2000 to 2002, the research team of the Japanese Ministry of Welfare (chief researcher; Dr. S. Yamamoto) performed physical examinations of 39,755 children living in Asahikawa, Iwate, Tokyo, Gifu, Osaka, Hiroshima, Kochi, and Fukuoka (22). They reported that the national average prevalence rate of AD was 12.8% in 4-month-old children, 9.8% in 18-month-old, 13.2% in 3-year-old, 11.8% in 6- to 7-year-old, and 10.6% in 11- to 12-year-old children. In our study, the prevalence of AD (6.9%) in children aged 5 years and younger in Ishigaki Island, which is located in the subtropical zone of Japan, was lower than the average rate on the mainland of Japan. It is also interesting that the present result, like Yamamoto's study, showed that the prevalence peaked at age 3. A worldwide survey has reported that AD is increasing in the developed countries in cooler climates (8). Japanese investigators also reported that the prevalence (17.3%) of AD was significantly higher in the cooler climate of Gifu than in the warmer climate of Itoman, Okinawa (3.4%), even after controlling for genetic and environmental factors (9, 10). The reason for the lower prevalence in Okinawa (Itoman and Ishigaki) remains to be elucidated.

IgE levels have been reported to be elevated in 80 to 85% of children who developed AD (23, 24). In the present study, the total IgE levels were significantly higher in children with AD than in those without disease. The children with AD also had higher positive rates of most specific IgE antibodies against aeroallergens and food allergens than the children without AD. However, the positive percentage was lower than expected (high levels of total IgE; 33.3%, one or more specific IgE; 64.1%). None of the children had specific IgE antibody to Japanese cedar pollen, probably because there are no cedars in Ishigaki. Approximately 20% of children with AD have been reported to show allergic reactions to food constituents (25). In infancy allergic sensitization is predominantly to food. In later childhood, allergic sensitization to aeroallergens, such as house dust mites and pollen, is common (26). We also confirmed that the major allergens (specific IgE positive rates) were house dust mites, egg white, and milk in children with AD in Ishigaki. It should be emphasized that high serum levels of IgE ware detected in 12.7% (67/526) of children without AD, and that 30.2% of these non-atopic children had one or more positive specific IgE antibodies to common allergens in our study. House dust mites, milk, and egg white were also the major antigens for specific IgE production even in the non-atopic children. It is also very interesting that both the total and specific IgE levels significantly increased with age in children without AD. The tendency of age-related accumulation of total and specific IgE was not observed in the children with AD, because it had already reached high levels as early as at age 1. Nolles et al.(27) reported a similar age-related increase of IgE antibodies. These results suggest (1) that the total and specific IgE levels increase with age probably with cumulative exposure to common al-

lergens even in non-atopic individuals, and (2) that earlier and higher increases in total and specific IgE antibodies are associated with AD.

The prevalence of AD has been studied in a variety of populations throughout the world (6–13), but comparisons of prevalence is difficult because of differences in study populations and study methods. Some investigators have measured point prevalence (28, 29), while others have measured 12 months prevalence in different age groups (8). The variation problem of study designs was addressed by the International Study for Asthma and Allergies in Childhood (ISAAC) (8). The methodology was subsequently standardized by the use of a questionnaire based on the U.K. Working Party definition of AD (17). A previous validity study suggested that the questionnaire might slightly overestimate the true prevalence (30). In the present study, we translated the questionnaire of the U.K. Working Party into Japanese and analyzed the sensitivity and specificity of the translated questionnaire. Although the specificity of the translated questionnaire for AD was 94.7%, its sensitivity was only 59%. This low sensitivity may be due to some incomprehensibility in the Japanese translation and to insufficient parent cooperation. It is critical that we refine the translation to improve the parents' understanding of the translated questionnaire.

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Association between chronic *Helicobacter pylori* infection and acute ischemic stroke: Fukuoka Harasanshin Atherosclerosis Trial (FHAT)

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Abstract

Helicobacter pylori (*H. pylori*) have been associated both epidemiologically and pathogenetically with coronary atherosclerosis, but data on the relationship between chronic *H. pylori* infection and stroke are lacking. Therefore, we investigated the relationship between *H. pylori* infection and acute ischemic stroke in 62 patients with their first stroke and 143 controls. The stroke patients were all admitted to Harasanshin General Hospital (Fukuoka, Japan) and the controls were asymptomatic age-matched outpatients with hyperlipidemia who did not have cardiac disease or infections. All patients underwent cranial CT scanning and/or brain magnetic resonance imaging, duplex ultrasonography of the extracranial carotid arteries, and transthoracic echocardiography. *H. pylori* infection was diagnosed by detection of anti-*H. pylori* IgG antibodies, the ^{13}C-urea breath test, and histology. Conditional logistic regression analysis was performed to analyze the data. The 62 stroke patients and 143 controls were aged from 41 to 92 years. Chronic *H. pylori* infection was associated with a higher risk of stroke due to small artery occlusion (odds ratio: 9.68; 95% CI: 3.56–33.08, $P < 0.001$) and a lower risk of cardioembolic stroke (odds ratio: 0.27; 95% CI: 0.03–1.53). Chronic *H. pylori* infection still showed an overall association with ischemic stroke (odds ratio for all subtypes combined: 2.57; 95% CI: 1.09–6.08) after adjusting for major cardiovascular risk factors. These results suggest that chronic *H. pylori* infection may be a triggering factor that increases the risk of acute ischemic stroke.
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Keywords: *Helicobacter pylori*; Ischemic stroke; Stroke subtypes; Carotid atherosclerosis

1. Introduction

Atherosclerosis is a highly prevalent disease, and is currently the greatest cause of morbidity and mortality in developed societies. Many risk factors are involved in the development of atherosclerosis, which manifests as coronary artery disease (CAD) and myocardial infarction (MI), including hyperlipidemia, hypertension, smoking, and diabetes mellitus [1], but much of the risk remains unexplained. The pathogenesis of atherosclerosis involves the processes of vascular injury, inflammation, degeneration, and thrombosis, but the stimulus that triggers the inflammatory response is largely unclear.

The pulse wave velocity can be used as an indicator of arterial stiffness [2,3], and it is regarded as a marker of vascular damage [4,5]. An instrument was recently developed that can measure the branchial-ankle pulse wave velocity (baPWV) by the volume rendering method. Yamashina et al. have reported a high validity and reproducibility of baPWV measurements, suggesting that this parameter may be an acceptable indicator of vascular damage and may be suitable

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for screening large populations to detect vascular disease [6].

Chronic infection with *Helicobacter pylori* (*H. pylori*) has been seroepidemiologically linked to CAD and atherosclerosis [1,7]. Ischemic stroke comprises a heterogeneous mixture of different stroke subtypes caused by atherosclerotic as well as non-atherosclerotic mechanisms [9]. Although stroke is pathogenetically related to coronary atherosclerosis, data about the association between chronic *H. pylori* infection and cerebrovascular disease are limited [9–14]. It appears that the first paper regarding ischemic cerebrovascular disease and *H. pylori* was published in 1998 [14], and it was only a small study. To make a valid and reliable assessment of the role of chronic *H. pylori* infection in cerebrovascular disease, the underlying mechanism of ischemic stroke must be taken into consideration by stratifying the subjects into different etiologic subtypes. Because direct detection of *H. pylori* in the cerebral vasculature would require samples of cerebral vessels, which are not clinically available, surrogate markers such as the anti-*H. pylori* antibody titer must be used to assess the association between stroke and infection with this organism.

The present case-control study was performed to investigate whether *H. pylori* infection was an independent risk factor for various etiologic subtypes of ischemic stroke.

2. Methods

2.1. Subjects and methods

All of the patients with acute cerebrovascular disease admitted to the Division of General Medicine at Harasanshin General Hospital (Fukuoka, Japan) during the year 2002 were considered eligible for the present study. Between July 1 and December 31, 2002, a total of 62 patients who suffered their first ischemic stroke were registered for this study.

2.2. Selection of stroke patients

Patients with their first stroke were enrolled in the study if they met the following criteria: (a) first ischemic stroke, (b) admission to hospital for treatment, and (c) admission within 72 h of the onset. Stroke was defined according to World Health Organization criteria [15]. Cerebral infarction was diagnosed on the basis of the initial CT and MRI data. All patients underwent ultrasonography of the neck and intracranial arteries. The carotid arteries were assessed by color flow B-mode Doppler ultrasound (SONOS 5500, PHILIP) according to the standard method [16,17]. The vertebrobasilar system was evaluated as described by Bartels [18]. In some cases, the ultrasound images were unsatisfactory, so MRI angiography was performed to determine the presence/absence of atherosclerotic lesions.

Patients without clinical or imaging evidence of atherosclerosis who had atrial fibrillation and/or echocardiographic findings suggestive of possible cardiogenic embolism were classified as having thromboembolic stroke. The other patients were diagnosed as having large artery stroke if there was >50% stenosis of the extracranial carotid or an intracranial artery, small artery occlusion if they had a clinical lacunar syndrome associated with appropriate CT changes or a typical clinical syndrome despite normal CT scans, or undefined stroke if their condition was not due to either of these mechanisms [8]. The present study only included patients with large vessel stroke and cardioembolic stroke, while the other subtypes were excluded because both atherosclerotic and non-atherosclerotic mechanisms might be involved.

During hospitalization, neurological evaluation was always done by one neurologist who applied the specified study criteria for classification of the patients. All evaluations were performed at the Department of Neuroradiology.

2.3. Selection of controls

The control subjects were chosen from among asymptomatic age-matched outpatients with hyperlipidemia who did not have cardiac disease or infections. The absence of atherosclerosis in the control subjects was assessed as follows: normal 12-lead ECG, normal echocardiography findings, <25% stenosis of the carotid arteries on Doppler ultrasonography, and normal lower limb arteries on physical examination. A history of cardiac disease meant exclusion from the control group.

2.4. Baseline evaluation

Data were collected by interview, physical examination, and neurological examination performed by trained health professionals, detailed review of all available medical records, and laboratory tests of fasting blood samples. Stroke patients were evaluated on day 7 after the onset of symptoms, while blood samples were taken within 24 h of admission (86% of the blood samples were obtained within 48 h after stroke onset). Control subjects were evaluated in the same manner as the stroke patients at the Stroke Prevention Clinic of the Department of Neurology between July 2002 and January 2003. Patients and control subjects were defined as hypertensive if they had a diastolic blood pressure >90 mmHg and a systolic blood pressure >140 mmHg or if they had been treated with antihypertensive therapy for at least 1 year. Patients were classified as diabetic if they had a fasting glucose level >126 mg/dL on two occasions or if they had been treated with antidiabetic drugs for at least 1 year. Patients were defined as smokers if they reported daily smoking of >10 cigarettes for at least 1 year during the last 10 years, and they were considered to be hyperlipidemic if the total cholesterol level was >220 mg/dL or if they had been treated with lipid-lowering drugs for at least 1 year. The BMI (kg/m^2) was calculated as a measure of obesity. All subjects reporting previous *H. pylori* eradication therapy were excluded from the study. The stroke patients

and controls lived in the same geographic area (Fukuoka City).

The type of ischemic stroke was classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria into large artery atherosclerosis, cardiogenic embolism, small artery occlusion, other etiologies, and undefined. Classification was performed by one neurologist on the basis of clinical findings and the results of standardized diagnostic tests, including CT or MRI, vascular imaging, and ECG or echocardiography.

2.5. Laboratory tests

All samples were stored at −80 °C and were analyzed simultaneously by technicians who were unaware of whether each sample belonged to a patient or a control.

2.6. IgG antibody to H. pylori

Serum IgG antibody to *H. pylori* was detected by ELISA [19] according to the manufacturer's instructions. Samples were tested in duplicate and results were expressed in arbitrary units. The reference limits were previously determined in our laboratory using serum samples from persons with or without *H. pylori* infections. A value >7.5 U was defined as positive, whereas values <3.0 U were negative (sensitivity and specificity >95%). Values between 3.0 and 7.5 U were defined as borderline and were excluded from the study.

2.7. ^{13}C-urea breath test

Each patient underwent a ^{13}C-urea breath test (UBT) by drinking 100 mg of ^{13}C-urea in water after an overnight fast. Breath samples were collected before and 20 min after the administration of ^{13}C-urea. The $^{13}CO_2/^{12}CO_2$ ratio ($\Delta^{13}CO_2$) in the breath bag was analyzed by a small infrared spectrometer (UBiT-200; Otsuka Electronics Co., Hirakata, Japan) and the results were expressed as the percent excess (parts per thousand) of $^{13}CO_2$ ($\Delta^{13}CO_2$). This method has been shown to have an excellent correlation (r = 0.996) with mass spectrometric measurement of $^{13}CO_2$ [20,21]. ^{13}C-UBT values below 3.5% were considered negative for *H. pylori*.

2.8. Brachial-ankle pulse wave velocity (baPWV)

The baPWV was measured using a volume plethymograph (PWV/ABI; Colin, Co., Ltd., Komaki, Japan), which simultaneously recorded the PWV, blood pressure, electrocardiogram, and heart sounds [6]. Each subject was examined in the supine position, with the electrocardiographic leads on both wrists, a microphone for detecting heart sounds taped at the left sternal edge, and cuffs on both arms and ankles. The cuffs were connected to a plethymographic sensor that determined the pulse volume waveform and to an oscillometric pressure sensor that measured the blood pressure. Pulse volume waveforms were recorded using a semiconductor pressure sensor with the acquisition frequency set at 1200 Hz. Waveforms for the arm and ankle were stored in 10 s batches with automatic gain analysis and quality adjustment. In this study, baPWV data were obtained after at least 5 min of rest. The coefficient of variation for reproducibility of baPWV values in healthy subjects was reported to be 2.4% for the interobserver coefficient of variation (n = 15) and 5.8% for the intraobserver coefficient of variation (n = 17) [22].

2.9. Detection of H. pylori infection

H. pylori infection was identified by histologic examination, the ^{13}C-UBT, and serologic evaluation. Patients in whom at least one of these three tests was positive were classified as *H. pylori*-positive and those in whom all three tests were negative were considered to be *H. pylori*-negative.

2.10. Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of ischemic stroke associated with *H. pylori* infection were estimated by univariate analysis, as well as by multiple logistic regression analysis with adjustment for age, sex, smoking history, diabetes, and hypertension.

Because C-reactive protein (CRP) values do not show a normal distribution, a non-parametric test (the Mann–Whitney U-test) was used to compare this variable between groups. All analyses were performed with SPSS software (ver. 8). When not otherwise stated, data are presented as the mean ± S.D. and P = 0.05 (two-tailed) was considered to indicate statistical significance.

2.11. Ethics

The design of this study was approved by the Ethics Committee and the Data Protection Committee of Harasanshin General Hospital (Fukuoka, Japan). Informed consent for the collection of blood was obtained from all patients (or their closest relatives).

3. Results

One hundred and three patients with stroke and 281 control subjects were considered for the study, but 51 patients and 138 control subjects were excluded for the following reasons: unclassified stroke subtype (13 patients), refusal to participate in the study (19 patients and 38 control subjects), previous *H. pylori* eradication therapy (9 patients and 21 control subjects), abnormal ECG (27 control subjects), abnormal echocardiography findings (31 control subjects), and asymptomatic carotid stenosis (21 control subjects). Therefore, 62 patients and 143 control subjects were investigated further.

Table 1
Characteristics of the subjects

	Stroke patients ($n = 62$)	Controls ($n = 143$)	P value
Age [years, mean ± S.D.]	71.5 ± 11.3	69 ± 9.3	N.S.
Male sex [%]	40 (65%)	48 (34%)	$P < 0.001$
Blood pressure [mean ± S.D., mmHg]			
Systolic	161.4 ± 31.4	132 ± 20.4	$P < 0.001$
Diastolic	84.2 ± 13.5	78.1 ± 11.1	$P < 0.01$
Smoking [%]			
Ever	31 (50%)	65 (46%)	N.S.
Never	31 (50%)	78 (55%)	N.S.
History [%]			
Hypertension	55 (89%)	47 (33%)	$P < 0.001$
Diabetes mellitus	26 (42%)	16 (11%)	$P < 0.001$
IMT [mean ± S.D., mm]	1.22 ± 0.35	1.13 ± 0.41	N.S.
baPWV [mean ± S.D., cm/s]	2,292.8 ± 665.1	1,527.4 ± 314.8	$P < 0.001$

3.1. Characteristics of the subjects

The clinical characteristics of the stroke patients and control subjects are displayed in Table 1. The mean age of the 62 stroke patients was 71.5 years (S.D. 11.3), and 40 of them (65%) were men. Their average systolic blood pressure and diastolic blood pressure was 161.4 and 84.2 mmHg, respectively. Among the 62 patients, 50% were recent or former smokers, 89% had a history of hypertension, and 42% had diabetes. The mean carotid intima/media thickness (IMT) was 1.22 mm and baPWV was 2292.8 cm/s.

3.2. Prevalence of chronic H. pylori infection

Table 2 shows the prevalence of seropositivity to *H. pylori* and *H. pylori* infection. Infection was detected in 48/62 stroke patients (77%) compared with 64/143 controls (45%) and the difference was significant ($P < 0.0001$). When analyzed for sex, 34/40 male stroke patients (85%) were infected by *H. pylori* compared with 18/48 controls (38%) ($P < 0.0001$). Among the women, 14 out of 22 stroke patients (64%) were infected compared with 46 out of 95 controls (48%) ($P < 0.05$). Chronic *H. pylori* infection was found in 40 patients (89%) with small artery occlusion, 6 patients (67%) with large artery atherosclerosis, and 2 patients (25%) with cardiogenic embolism.

Table 2
Crude prevalence of chronic *H. pylori* infection in each group

	Stroke patients ($n = 62$)	Controls ($n = 143$)	P value
All	48 (77%)	64(45%)	$P < 0.0001$
Age (years)			
<70	19 (74%)	31(40%)	$P < 0.01$
≥70	29 (81%)	33(50%)	$P < 0.01$
Sex			
Male	34 (85%)	18(38%)	$P < 0.0001$
Female	14 (64%)	46(48%)	$P < 0.05$
Stroke subtype			
Small artery occlusion	40 (89%)		
Large artery atherosclerosis	6 (67%)		
Cardioembolic	2 (25%)		

3.3. ORs for H. pylori infection in stroke patients and controls after adjustment for possible confounding factors (Table 3)

Chronic *H. pylori* infection showed an overall association with ischemic stroke when all of the stroke subtypes were combined. There was no significant difference in the prevalence of chronic *H. pylori* infection between patients with cardiogenic embolism and the control subjects, whereas the prevalence of infection was significantly higher in the patients with small artery occlusion than in the controls (univariate analysis showed OR: 9.68 and CI: 3.56–33.08 ($P < 0.0001$)). However, there was no significance difference in the prevalence of chronic *H. pylori* infection between the patients with large artery atherosclerosis and the control subjects.

3.4. ORs for association between chronic H. pylori infection and stroke subtypes

Conditional logistic regression analysis (Table 4) showed that chronic *H. pylori* infection was significantly associated with a higher risk of stroke due to small artery occlusion and large artery atherosclerosis. In contrast, there was a significant inverse correlation between chronic *H. pylori* infection and cardiogenic embolism (adjusted OR: 0.137; 95% CI: 0.0236–0.796). Despite these differential associations with the stroke subtypes, chronic *H. pylori* infection also showed an overall association with ischemic stroke (all subtypes combined).

3.5. C-reactive protein (CRP)

Measurement of CRP was performed in all stroke patients and control subjects. The CRP level was 1.13 ± 2.03 mg/dL in the stroke patients (all subtype combined) and 0.32 ± 0.87 mg/dL in the control subjects, showing a significant difference ($P < 0.001$). There was no significant difference of CRP between the patients with cardiogenic embolism and the control subjects, whereas the CRP level was significantly higher in patients with small artery occlusion and large

Table 3
Odds ratios for *H. pylori* infection after adjustment for possible confounding factors

	Ischemic stroke				Stroke subtype											
	(all subtypes)				Small artery occlusion				Large artery atherosclerosis				Cardioembolic			
	OR	RR	95%	CI	OR	RR	95%	CI	OR	RR	95%	CI	OR	RR	95%	CI
Age (years)																
<70	0.62	0.72	0.32	1.18	0.74	0.79	0.36	1.52	0.27	0.28	0.03	1.47	0.99	0.99	0.18	5.47
≥70	0.61	1.40	0.85	3.09	1.35	1.26	0.66	2.78	4.10	3.90	0.76	41.41	1.01	0.18	5.59	6.18
Male sex	3.57	2.42	1.84	7.09***	3.49	2.66	1.66	7.61**	2.77	2.66	0.57	17.59	1.34	1.33	0.24	7.43
Smoking	1.20	1.14	0.63	2.28	0.89	0.91	0.43	1.81	1.44	1.42	0.30	7.48	3.55	3.41	0.62	36.72
Hypertension	15.8	7.93	6.53	44.4***	9.90	6.56	3.86	30.31***	8.61	8.08	1.12	388.17*				
Diabetes mellitus	5.67	2.80	2.62	12.67***	2.45	1.94	1.07	5.48*	15.78	13.58	2.85	161.89**	4.15	3.88	0.74	23.33
large IMT	1.68	1.43	0.88	3.20	1.31	1.24	0.64	2.69	4.36	4.13	0.80	44.01	1.19	1.18	0.22	6.57
high baPWV	5.84	2.77	2.56	13.82***	6.07	3.43	2.62	14.34***	1.36	1.34	0.13	7.57	1.59	1.57	1.15	9.42
high CRP	21.39	4.88	8.60	59.67***	11.31	5.16	4.94	26.90***	5.14	4.71	1.05	27.21*	4.02	3.77	0.72	22.57
H. pylori infection	4.20	2.85	2.06	9.03***	9.68	6.64	3.56	33.08***	1.69	1.66	0.35	10.77	0.27	0.28	0.03	1.53

* $P < 0.05$.
** $P < 0.001$.
*** $P < 0.0001$.

artery atherosclerosis than in the controls (univariate analysis showed OR: 11.31 and CI: 4.94–26.90 ($P < 0.0001$); OR: 5.14 and CI: 1.05–27.21 ($P < 0.05$), respectively) (Table 3).

4. Discussion

4.1. Main findings

In the present case-control study, *H. pylori* infection was associated with an increased risk of ischemic stroke due to small artery occlusion or large artery atherosclerosis versus a decreased risk of stroke caused by cardiogenic embolism. There was also a strong association between *H. pylori* infection and the overall risk of stroke. Moreover, we found no difference in the prevalence of *H. pylori* infection among patients with two different stroke subtypes (large artery and small artery stroke) and controls. Our study showed that the presence of *H. pylori* infection might be increased in patients with stroke that is due to large artery and small artery disease but not in patients with cardiogenic embolism.

Although CRP (a sensitive marker of systemic inflammation) was increased in both groups of stroke patients compared with control subjects, the *H. pylori*-positive patients showed significantly higher CRP levels than the *H. pylori*-negative patients.

4.2. Chronic H. pylori infection and stroke subtype

Our findings were consistent with the results of some previous studies that have addressed the relationship between chronic *H. pylori* infection and ischemic stroke.

Markus and Mendall [14] reported elevated levels of IgG antibody for *H. pylori* in patients with lacunar stroke, which is comparable to small artery occlusion [8]. The adjusted OR was 2.51 (95% CI: 1.19–5.28), which was compatible with our findings (OR: 9.68; 95% CI: 3.56–33.08). The classic lacunar hypothesis is that lipohyalinosis of small arteries caused by diabetes mellitus and hypertension represents the underlying pathogenesis of this stroke subtype [21]. In recent years, however, evidence has been obtained that lacunar infarcts also share the mechanisms involved in atherosclerotic disease [23]. Similar trends were demonstrated for stroke caused by large artery atherosclerosis in the study performed by Markus and Mendall [14] and the present study (adjusted OR: 2.17; 95% CI: 1.11–4.21 and adjusted OR: 1.69; 95% CI: 0.35–10.77, respectively), although the association did not reach statistical significance in our study, possibly because of the small number of patients with this stroke subtype.

Unfortunately, comparison of the role of *H. pylori* in cardioembolic stroke could not be performed between the two studies because Markus and Mendall [14] combined their data for stroke due to cardiogenic embolism and stroke due to undefined causes. Since cardioembolic stroke is mainly caused by disorders such as atrial fibrillation that lead to thromboembolic occlusion of the cerebral arteries [8], our

Table 4
Odds ratios for association of chronic *H. pylori* infection with ischemic stroke subtypes

	Unadjusted OR[a]			Adjusted OR[b]		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Ischemic Stroke (all subtypes)	2.22	1.04–4.72	$P < 0.05$	2.57	1.09–6.08	$P < 0.05$
Stroke Subtypes						
Small artery occlusion	1.00		$P < 0.05$	1.00		$P < 0.05$
Large artery atherosclerosis	0.215	0.0430–1.07		0.215	0.0430–1.07	
Cardioembolic	0.137	0.0236–0.796		0.137	0.0236–0.796	

ORs and 95% CIs were calculated by conditional logistic regression analysis.
[a] Matched for age and sex.
[b] Matched for age, sex, smoking, hypertension, and diabetes.

findings are consistent with a positive association between chronic *H. pylori* infection and ischemic stroke caused by cerebral atherosclerosis. When stroke is defined as a non-homogeneous condition and stratified analysis of various stroke subtypes is performed, this often results in a small number of patients in each subgroup. Therefore, the lack of a significant association with large artery atherosclerosis needs further investigation in a larger population. Furthermore, it is possible that the apparent association of stroke with *H. pylori* infection was attributable to residual confounding factors related to socioeconomic status, although we tried to control them. This might be of particular relevance with regard to reports of *H. pylori* infection as a marker of lower socioeconomic status [24], which seems to be an independent risk factor for vascular disease [25].

4.3. Chronic H. pylori infection and mechanism of atherogenesis

In recent years, it has been hypothesized that only certain *H. pylori* strains, which express the cytotoxin-associated gene A (Cag A) encoding the Cag A protein, may have a link with atherosclerosis. Several mechanisms have been hypothesized, including inflammation, hyperhomocysteinemia, immune-mediated vascular damage, and direct bacterial invasion of atherosclerosis plaques [26]. Although we did not investigate antibody for Cag A protein, Maeda et al. have reported that most *H. pylori* strains in Japan are capable of producing Cag A protein [27]. Compared with *H. pylori*-negative patients, the *H. pylori*-positive patients showed more evidence of systemic inflammation (higher CRP levels), which gives some support to the hypothesis that *H. pylori* infection may induce generalized inflammation, a recognized risk factor for atherosclerosis [7]. The strong non-specific inflammatory response to acute tissue ischemia associated with stroke may well have minimized a pre-existing difference of chronic inflammation between the patients with and without *H. pylori* infection. Other mechanisms may also be suggested that could link infection with *H. pylori* to atherosclerotic stroke.

Amerisco et al. [26] recently reported that *H. pylori* might be present in carotid plaques because chronic *H. pylori* infection elicits a strong local inflammatory response; it is possible that the presence of bacteria may contribute to plaque instability and the onset of acute ischemic stroke through a local vascular effect.

In any case, our data suggest that infection with *H. pylori* represents a risk factor for the development of atherosclerotic stroke.

4.4. Limitations

The main limitation of the present study was its case-control design. Although care was taken to avoid potential biases, it is well known that prospective studies are often unable to confirm the associations detected in case-control studies, so further prospective studies are needed to confirm our findings.

In addition, the cross-sectional nature of the present study did not allow us to establish whether or not *H. pylori* played a causative role in atherosclerotic stroke. Furthermore, given the wide prevalence of *H. pylori* infection, it is possible that unknown factors having an independent association with both this organism and ischemic stroke may have produced a spurious association in our study. Finally, our control subjects were not representative of the general population and the enrollment criteria may have led to selection of a population with a low risk of *H. pylori* infection. However, it should be noted that the subjects with and without ischemic stroke showed almost identical rates of *H. pylori* infection.

5. Conclusion

The present study suggested that *H. pylori* infection might be associated with ischemic cerebrovascular disease due to an increased prevalence of this organism in patients with ischemic stroke. The pathophysiological mechanism underlying this association seems likely to be a chronic inflammatory response to bacterial infection.

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多嚢胞性卵巣症候群

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Polycystic ovary syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by chronic unovulation, hyperandrogenism and polycystic change in ovary. Hyperinsulinemia is so often accompanied with PCOS that insulin resistance may play important roles in pathogenesis of PCOS. Recent studies reported the effectiveness of insulin-sensitizing drugs on treatment of patients with PCOS. Thiazolidinedione, an agonist of PPARγ receptor, improves not only insulin sensitivity but also hyperandrogenism and ovulatory dysfunction in patients with PCOS. Insulin-sensitizing drugs such as thiazolidinediones are expected to be a novel therapy for PCOS, although further studies on the effectiveness and safety should be required.

Key words: polycystic ovary syndrome (PCOS), insulin resistance, PPARγ, thiazolidinedione, insulin-sensitizing drug

はじめに

多嚢胞性卵巣症候群(polycystic ovary syndrome: PCOS)は，月経異常，高アンドロゲン血症，卵巣の多嚢胞性変化などを特徴とする症候群である．しばしばインスリン抵抗性を伴い，PCOSの病因との関連が注目されている．近年，PCOSの治療にインスリン抵抗性を改善するPPARγ受容体のアゴニストであるチアゾリジン誘導体が有用であることが報告された．

本稿ではその臨床成績を中心に概説する．

1. 多嚢胞性卵巣症候群(PCOS)の病態とインスリン抵抗性

PCOSは無月経，多毛，肥満および両側卵巣の嚢胞性腫大を呈する疾患として，1935年SteinとLeventhalにより報告されたが，今日では多彩な症状と全身的な内分泌異常を呈する症候群と考えられている．日本産婦人科学会のPCOS診断基準(1993年)[1]では，①月経異常(無月経，稀発月経，無排卵周期症など)，②LHの基礎分泌値高値，FSHは正常範囲，③超音波断層検査で多数の卵胞の嚢胞状変化が認められること，の3つの必須項目を満たす場合，

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