Original Article

Risk Factors for and the Prevalence of Peripheral Arterial Disease and its Relationship to Carotid Atherosclerosis: The Kyushu and Okinawa Population Study (KOPS)

Hachiro Ohnishi¹, Yasunori Sawayama², Norihiro Furusyo^{1,2}, Shinji Maeda², Shoji Tokunaga³, and Jun Hayashi^{1,2}

¹Department of Environmental Medicine and Infectious Diseases, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan

²Department of General Internal Medicine, Kyushu University Hospital, Fukuoka, Japan

³Department of Medical Informatics, Kyushu University Hospital, Fukuoka, Japan

Aim: Peripheral arterial disease (PAD) is associated with cerebrovascular disease, ischemic heart disease, and other cardiovascular disease. We investigated the prevalence of and factors related to PAD to clarify the relationship between PAD and carotid atherosclerosis in a cross-sectional population-based study.

Methods: The study included 2,402 (900 males and 1,502 females; mean $\pm$ SD = 64.9 ± 10.9 years) of 3,862 residents of two Japanese rural areas who reported for a free health examination in 2005 or 2006. An ankle brachial index value ≤ 0.9 was considered to be PAD. The carotid artery intima-media thickness (CA-IMT) was measured by carotid ultrasound.

Results: The prevalence of PAD was 1.71% ($n=41$) of all participants. The risk factors independently associated with a significantly higher risk of PAD, identified by multivariate analysis, are as follows: For males, age, dyslipidemia, and CA-IMT, and for females, age, waist circumference, and dyslipidemia.

Conclusion: The prevalence of PAD in Japan was confirmed to be lower than that of similar studies performed in other countries. PAD was strongly correlated with age and dyslipidemia in both sexes, carotid atherosclerosis in males, and abdominal fat in females.

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Key words; Carotid atherosclerosis, Epidemiology, Intima-media thickness, Peripheral arterial disease, Waist circumference

Introduction

Japanese lifestyle changes have led to the recent increase of atherosclerosis, which is related to hypertension, dyslipidemia, glucose intolerance, and obesity, which are also increasing¹⁻³. Many risk factors are involved in the occurrence of atherosclerosis, which manifests as cerebrovascular disease, coronary artery disease, and peripheral arterial disease (PAD)^{4,5}.

The signs and symptoms of PAD are usually thought to progress slowly in the natural progression of atherosclerosis. Atherosclerosis disease of the peripheral arteries is considered to be a particularly serious problem for patients because of reduced physical activity and quality of life, and shortened lifespan. PAD is associated with the occurrence of coronary artery disease, and stroke⁵⁻⁷. Thus, PAD should be detected and treated as early as possible.

Many large-scale clinical research trials for arteriosclerosis have been performed, and reports of epidemiological surveys about PAD can be found from the United States, Europe and Asia^{5, 8-11}), however, there have been few published epidemiological studies of PAD in Japan¹²⁻¹⁴.

Address for correspondence: Jun Hayashi, M.D., Ph.D., Professor, Department of General Internal Medicine, Kyushu University Hospital, Fukuoka, 812-8582, Japan
E-mail: hayashij@gim.med.kyushu-u.ac.jp

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Measurement of carotid artery intima-media thickness (CA-IMT) by high-resolution B-mode carotid ultrasound examination has been used as a non-invasive method for detecting early carotid atherosclerosis. We have examined and reported on CA-IMT in a number of areas of southwestern Japan^{2, 3)}. In previous studies, CA-IMT has been associated with cardiovascular disease and stroke and has shown significant associations with PAD^{5, 6, 15-17)}; however, little is known about the relationship between PAD and CA-IMT of Japanese¹⁴⁾.

The aim of this study was to investigate the prevalence of and factors related to PAD and to clarify the risk factors for PAD using data gathered at routine health examinations and CA-IMT in southwestern Japan.

Materials and Methods

Participants

The basic demographics of the two rural studied areas can be summarized as follows: Iki City, with about 31,400 residents, is an isolated island in southwestern Japan where fishing and farming are the main economic activities¹⁸⁾. Hoshino Village, with about 3,400 residents, is a rural, mountainous, agriculture village in Fukuoka prefecture that is relatively isolated from other communities¹⁹⁾. The lifestyle in these areas does not differ much from that of other parts of Japan. The participants were residents notified by newspaper and public announcements of a free health examination given by the Department of General Internal Medicine, Kyushu University.

The study included 2,402 (900 male and 1,502 female, age range 40–93, mean $\pm$ SD = 64.9 $\pm$ 10.9 years) of 3,862 Iki City and Hoshino Village residents who reported for a free health examination in 2005 or 2006. In 2005, the data of 1,417 residents of Iki City were available for analysis, (506 male and 911 female, age 40–93 years, mean $\pm$ SD = 64.5 $\pm$ 12.5 years), and in 2006, the data of 985 residents of Hoshino Village were available for analysis, (394 male and 591 female subjects, age 40–92 years, mean $\pm$ SD = 65.3 $\pm$ 11.7 years). Excluded were 1,281 residents who did not complete all of the required examinations or who did not return the questionnaire, 156 who were under 40 years of age, 13 with TG levels >400 mg/dL, 8 with missing ABI measurements, and 2 with ABI >1.50. Exclusion was because of possible measurement artifacts reflecting the presence of rigid or calcified arterial walls^{5, 7)}.

To ensure the validity of the data, all doctors participating in the study were members of the General

Internal Medicine Department of Kyushu University who were briefed on the study protocol and trained in the medical techniques necessary for the study. The design of this study was approved by the Kyushu University Hospital ethics committee. Informed consent was obtained from all participants before the examination.

Medical History

At the baseline examination, anthropometry and blood pressure were measured by public health nurses. Body mass index (BMI) and waist circumference (WC) were adopted as indicators of obesity. Height and weight were measured with light clothes and without shoes. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. WC was measured in the horizontal plane at the umbilical level. Smoking behavior was assessed by questionnaire, and the subjects were classified as smokers (current or past smokers) or non-smokers. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at rest in a sitting position. SBP above 140 mmHg and/or DBP above 90 mmHg or a subject taking anti-hypertensive agents were defined as hypertension (HT). Fasting plasma glucose (FPG) above 110 mg/dL and/or treatment for diabetes was defined as glucose intolerance. Total cholesterol (TC) above 220 mg/dL, triglycerides (TG) above 150 mg/dL, and/or high-density lipoprotein cholesterol (HDL-C) below 40 mg/dL, and/or low-density lipoprotein cholesterol (LDL-C) above 140 mg/dL or lipid-lowering drug administration were defined as dyslipidemia. Chronic kidney disease (CKD) was defined as an estimated creatinine clearance (eCcr) <60 mL/min/1.73 m² (CKD stages 3–5)²⁰⁾. Estimation of the glomerular filtration rate (eGFR) by the Cockcroft-Gault method was adjusted by the body surface area (BSA) and was used to evaluate kidney function²⁰⁾. The equations are as follows:

Cockcroft-Gault (CG) equation:

$$\text{CG-eGFR (mL/min/1.73 m}^2\text{)} = \text{Ccr} \times (1.73/\text{BSA})$$

$$\text{Ccr (mL/min)} = ((140 - \text{age}) \times \text{weight}) / (72 \times \text{serum creatinine}) \times (0.85, \text{ if female})$$

$$\text{BSA (m}^2\text{)} = 0.007184 \times \text{height (cm)}^{0.725} \times \text{weight (kg)}^{0.425}$$

Assay Methods

Blood samples were collected from all participants after overnight fast and stored at -20°C until analysis. The following parameters were measured: FPG, high sensitive C-reactive protein (hs-CRP), serum creatinine and serum levels of TC, TG and HDL-C. The LDL-C level was calculated using the

Table 1. Prevalence of PAD by sex and age

Age group	Male		Female		Male and Female	
	N. tested	PAD+ (%)	N. tested	PAD+ (%)	N. tested	PAD+ (%)
40–49	112	---	156	---	268	---
50–59	152	---	306	1.0	458	0.7
60–69	256	0.4	486	1.7	742	1.2
70–79	313	3.2	456	1.8	769	2.3
80+	67	9.0	98	5.1	165	6.7
<i>p</i> for trend		< 0.001		0.008		< 0.001
Total	900	1.89	1,502	1.73	2,402	1.71

Friedewald formula²¹⁾. Subjects with TG levels >400 mg/dL were excluded ($n = 13$).

Diagnosis of Peripheral Arterial Disease

The ankle brachial index (ABI) value is useful for the diagnosis of PAD^{5, 22)}. ABI is measured by the ratio of SBP at the ankle and at the arm on each side. Subjects with ABI ≤ 0.9 on either side or on both sides were considered to have PAD²²⁾. The ratio of SBP in the leg to that in the arm was determined using a new device, the form PWV/ABI: BP-203RPEII (Omron Healthcare Co., Ltd, Japan). This device has been used in other Japanese epidemiological studies^{12–14)}.

Ultrasonographic Measurement

CA-IMT and plaques were measured by carotid ultrasound. High-resolution B-mode ultrasound examination was performed with a 7.5 MHz mechanical sector transducer on the Aloka SSD-2000 (Aloka Co. Ltd., Tokyo, Japan) by four specially trained ultrasound technicians^{2, 3)}. CA-IMT was defined as the distance between two echogenic lines separated by a hypoechoic or anechoic space, with the outer line corresponding to the medial-adventitial border and the inner line representing the luminal-intimal border. CA-IMT was measured at points 20, 25, and 30 mm proximal to the flow divider on the far wall of the right and left common carotid arteries at the end of the diastolic phase. The CA-IMT was the higher of the values for the right or left carotid artery; thus, we defined the maximum-IMT as CA-IMT. Plaque thickness was incorporated into CA-IMT, and CA-IMT above 1.1 mm was defined as abnormal^{2, 3)}.

Statistical Analysis

The Mann-Whitney U-test and Fisher's exact test were used to analyze the characteristics of the PAD and non-PAD groups. Values are expressed as the

mean $\pm$ standard deviation (SD). A two-tailed $p < 0.05$ was considered significant.

The odds ratio (OR) and 95% confidence interval (CI) for the possible risk factors of PAD were estimated by age-adjusted and multivariate-adjusted logistic regression analysis. The multiple logistic regression model was selected by the backward stepwise method. The significance level for addition and removal was set as 0.05 and 0.10, respectively. Because of the strong association between BMI and WC, these variables were inserted in the separate models as candidate variables; thus, the stepwise model was selected in two ways for each sex.

We further estimated the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) using the above models for males and females. The confidence intervals for AUC were estimated by the exact method. All analyses were performed using Stata ver 10.

Results

The prevalence of PAD in the general population of the two Japanese areas studied is shown by sex and age in **Table 1**. PAD was found in 41 (1.71%) of 2,402 participants. The prevalence of PAD in males (1.89%) and females (1.73%) was not significantly different. The prevalence of PAD increased with advancing age in both sexes.

To clarify the effect of cardiovascular risk factors on PAD and to determine predictive markers for patients with PAD, the conventional risk factors and subject characteristics were compared by sex between participants with and without PAD (**Table 2**).

In a comparison with non-PAD participants, age ($p < 0.0001$), prevalence of HT ($p = 0.03$) and CKD ($p < 0.0001$), and CA-IMT values ($p < 0.0001$) were significantly higher in male PAD patients. Otherwise, age ($p < 0.01$), WC ($p < 0.01$), prevalence of glucose

Table 2. Basic characteristics of male and female study participants by PAD status

Variables	Male			Female		
	PAD (<i>n</i> =17)	Non-PAD (<i>n</i> =883)	<i>p</i> -value	PAD (<i>n</i> =24)	Non-PAD (<i>n</i> =1,478)	<i>p</i> -value
Age (years)	77.5 ± 5.2	64.9 ± 11.0	<0.0001*	71.0 ± 9.0	64.6 ± 10.7	<0.01*
Study area (Iki, %)	76.5	55.8	0.14 [†]	45.8	60.9	0.14 [†]
BMI (kg/m ²)	22.2 ± 3.1	23.1 ± 2.9	0.27*	24.2 ± 3.9	22.8 ± 3.2	0.06*
Waist circumference (cm)	85.0 ± 7.3	83.9 ± 7.8	0.41*	85.0 ± 12.6	77.8 ± 9.0	<0.01*
Current + Past smoking (%)	64.7	64.3	1.00 [†]	4.2	4.0	1.00 [†]
Current smoking (%)	11.8	27.0	0.27 [†]	4.2	2.4	0.45 [†]
HT (%)	76.5	49.2	0.03 [†]	50.0	49.1	1.00 [†]
Glucose intolerance (%)	35.3	18.6	0.11 [†]	29.2	10.4	0.01 [†]
Dyslipidemia (%)	64.7	41.1	0.08 [†]	79.2	54.7	0.02 [†]
CKD (%)	47.1	10.8	<0.001 [†]	12.5	7.0	0.24 [†]
hs-CRP (mg/dL)	0.12 ± 0.16	0.09 ± 0.12	0.16*	0.12 ± 0.15	0.07 ± 0.10	<0.01*
CA-IMT (mm)	2.21 ± 0.84	1.23 ± 0.71	<0.0001*	1.16 ± 0.52	1.03 ± 0.49	0.07*

Abbreviations: BMI: body mass index, HT: hypertension, CKD: chronic kidney disease, hs-CRP: high sensitive C-reactive protein, CA-IMT: carotid artery intima-media thickness

*Mann-Whitney U analysis [†]Fisher's exact test

Table 3. Odds ratios for PAD by age-adjusted and stepwise multivariate-adjusted logistic regression analysis

Variables ^a	Male				Female					
	Age-adjusted		Multivariate-adjusted *, **		Age-adjusted		Multivariate-adjusted *		Multivariate-adjusted **	
	OR (95% C.I.)	<i>p</i> -value	OR (95% C.I.)	<i>p</i> -value	OR (95% C.I.)	<i>p</i> -value	OR (95% C.I.)	<i>p</i> -value	OR (95% C.I.)	<i>p</i> -value
Age (per 10 years)			6.07 (2.61, 14.12)	<0.0001			1.76 (1.10, 2.81)	0.02	1.71 (1.08, 2.73)	0.02
Study area (Iki vs. Hoshino)	2.56 (0.81, 8.15)	0.11			0.66 (0.29, 1.50)	0.32				
BMI (kg/m ²)	1.00 (0.83, 1.21)	0.96			1.15 (1.03, 1.28)	0.01			-	-
Waist circumference (cm)	1.04 (0.97, 1.11)	0.27			1.07 (1.03, 1.12)	<0.01	-	-	1.07 (1.02, 1.11)	<0.01
Current + Past smoking (yes)	0.97 (0.34, 2.73)	0.95			1.57 (0.20, 12.12)	0.66				
HT (yes)	2.12 (0.67, 6.72)	0.20			0.71 (0.31, 1.64)	0.42				
Glucose intolerance (yes)	2.28 (0.80, 6.47)	0.12			2.72 (1.09, 6.81)	0.03	2.48 (1.00, 6.16)	0.05		
Dyslipidemia (yes)	5.16 (1.72, 15.44)	<0.01	5.69 (1.81, 17.87)	<0.01	2.93 (1.08, 7.89)	0.03	2.57 (0.95, 6.98)	0.06	2.67 (0.98, 7.23)	0.05
CKD (yes)	1.75 (0.53, 5.73)	0.35			0.84 (0.22, 3.18)	0.80				
hs-CRP (10 times)	1.44 (0.54, 3.83)	0.46			2.68 (1.19, 6.03)	0.02	2.42 (1.05, 5.60)	0.04		
CA-IMT (mm)										
0.4–1.1 (low)	1 (Referent)		1 (Referent)		1 (Referent)					
1.2–1.6 (moderate)	8.63 (0.98, 75.91)	0.05	2.43 (0.93, 73.93)	0.06	2.43 (1.00, 5.92)	0.05				
1.7+ (high)	16.98 (2.14, 134.57)	<0.01	18.09 (2.27, 144.40)	<0.01	0.69 (0.15, 3.26)	0.64				

Abbreviations: BMI: body mass index, HT: hypertension, CKD: chronic kidney disease, hs-CRP: high sensitive C-reactive protein, CA-IMT: carotid artery intima-media thickness

*Stepwise model 1: excluding waist circumference **Stepwise model 2: excluding BMI

intolerance ($p=0.01$) and dyslipidemia ($p=0.02$), and hs-CRP values ($p<0.01$) were significantly higher for female PAD patients.

To separate the risk factors of PAD from confounding factors, we used age-adjusted and stepwise multivariate-adjusted logistic regression analysis (Table 3). In age-adjusted logistic regression analysis, dyslipidemia (OR 5.16, 95% CI 1.72–15.44) was positively associated with the PAD of males. BMI (OR 1.15, 95% CI 1.03–1.28), WC (OR 1.07, 95% CI 1.03–

1.12), glucose intolerance (OR 2.72, 95% CI 1.09–6.81), dyslipidemia (OR 2.93, 95% CI 1.08–7.89), and hs-CRP (OR 2.68, 95% CI 1.19–6.03) were positively associated with PAD in females. Compared with the normal CA-IMT (low) group, abnormal CA-IMT (moderate) (OR 8.63, 95% CI 0.98–75.91) and abnormal CA-IMT (high) (OR 16.98, 95% CI 2.14–134.57) were positively associated with PAD in males. Abnormal CA-IMT (moderate) (OR 2.43, 95% CI 1.00–5.92) was positively associated with PAD in females.

Fig. 1.

Receiver operating characteristic curves of PAD from the selected models (Table 3) for 900 male (Fig. 1-a) and 1,052 female (Fig. 1-b) participants. Areas under the receiver operating characteristic curve were 0.91 (95% CI, 0.89–0.93) for males and 0.75 (95% CI, 0.73–0.77) for females.

In multivariate-adjusted logistic regression analysis, the stepwise model was selected in two ways for each sex. Because BMI and WC were strongly associated with each other, they were used in separate models as candidate variables. For males, multivariate-adjusted logistic regression analysis results (model 1,2) of age (OR 6.07, 95% CI 2.61–14.12), dyslipidemia (OR 5.69, 95% CI 1.81–17.87), and abnormal CA-IMT (high) (OR 18.09, 95% CI 2.27–144.40) were positively associated with PAD (Table 3). This result was the same when using BMI or WC in the stepwise model. For females, multivariate-adjusted logistic regression analysis results (model 1) of age (OR 1.76, 95% CI 1.10–2.81), glucose intolerance (OR 2.48, 95% CI 1.00–6.16), and hs-CRP (OR 2.42, 95% CI 1.05–5.60), and multivariate-adjusted logistic regression analysis results (model 2) of age (OR 1.71, 95% CI 1.08–2.73), WC (OR 1.07, 95% CI 1.02–1.11), and dyslipidemia (OR 2.67, 95% CI 0.98–7.23) were positively associated with PAD (Table 3).

In order to investigate the validity of the PAD odds ratios, we further calculated the ROC curves and AUC for each sex (Fig. 1). In the application of ROC curves and AUC, data from the stepwise multivariate-adjusted logistic regression analysis were used for each sex. As explanatory variables for males, age, dyslipidemia and CA-IMT were used. Age, dyslipidemia, and

WC were used as explanatory variable for females. The AUC (95% CI) was 0.91 (0.89–0.93) for males (Fig. 1-a) and 0.75 (0.73–0.77) for females (Fig. 1-b).

Discussion

In this study, the total prevalence of PAD was 1.71% ($n=41$) of all participants. The prevalence of PAD in Japanese studies^{12–14}) has tended to be lower (1.7–4.3%) than in studies from other countries (3.6–19.1%)^{5, 7–11}). This is in accordance with the fact that myocardial infarction is found less frequently in Japan than in other countries and indicates that atherosclerosis is less prevalent in Japan. Smoking has been reported to be one of the most important risk factors for PAD and atherosclerosis¹¹), however, our current smoking percentage (11.5%) was lower than that of other studies (15.1–35.8%)^{7–11}), which may have influenced the low prevalence of PAD found in this study.

Age and dyslipidemia were associated with most of the previously reported conventional risk factors for PAD-related factors^{5, 8–10}); however, few studies have reported WC as an independent risk factor for PAD^{23, 24}). A previous study reported a relationship between abdominal adiposity and PAD^{23, 24}). WC may be associ-

ated with advanced vascular damage, leading to more generalized atherosclerosis. Several factors may explain the increased prevalence of PAD. First, abdominal adiposity has been associated with significant metabolic abnormalities, including HT, dyslipidemia, glucose intolerance, and insulin resistance^{25, 26}. Second, abdominal adiposity acts as an endocrine organ by secreting several hormones and cytokines^{27, 28}. These adipocytokines are directly or indirectly involved in the process of atherosclerosis. In this study, WC was related to PAD in females, but not in males.

In order to accurately determine the independent factors related to PAD in females, we compared model 1 and model 2. In the first trial, age and dyslipidemia were extracted in both model 1 and model 2, but in the second WC, glucose intolerance, and hs-CRP were selected in both models. A previous study showed that high WC is an obesity indicator related to the association with glucose intolerance²⁵. Some studies have reported that hs-CRP is an independent risk factor for glucose intolerance, and is used as a component of metabolic syndrome²⁹. For all of these reasons, we considered high WC accompanied by hs-CRP and glucose intolerance to be a marker of PAD. Finally, we confirmed age, dyslipidemia, and WC to be independent factors related to PAD in females.

To demonstrate the relationship between PAD and WC, we further analyzed female WC. In the current Japanese metabolic syndrome criteria, WC is defined as 85 cm for males and 90 cm for females³⁰; however, this criteria is not based on evidence derived from prospective studies, whereas the Hisayama study suggested that the optimal cutoff point for WC is 90 cm for males and 80 cm for females³⁰. For this reason, we compared the cutoff value of the Hisayama criteria with Japanese metabolic syndrome criteria, using model 1 (categorized WC) in females. The odds ratio (95% CI) of Hisayama criteria was 2.31 (0.97–5.51) and its *p* value was 0.06; Japanese metabolic syndrome criteria were 3.83 (1.63–9.00) and *p* < 0.01 (not shown in **Table 3**). These results suggest that increased WC has more influence on PAD in females. WC may be a more important marker of PAD and lifestyle-related diseases in females than males.

The Edinburgh Artery Study¹⁷ reported a relationship between CA-IMT and PAD for both sexes. Cui *et al.*¹⁴ reported that low ABI (<0.9) was strongly correlated to the internal CA-IMT of elderly male Japanese (sensitivity 65%, specificity 98% for low ABI to detect CA-IMT >1.5 mm). These results suggested that CA-IMT measurement at health examinations is useful as an indicator of PAD. Our results were mostly consistent with these reports, except for gender

differences. We found that age and dyslipidemia are risk factors for PAD and are related to the development of carotid atherosclerosis. Further consideration of carotid atherosclerosis, inflammatory markers and time-dependent change is needed. This study had a cross-sectional design, which means that we can only make assumptions about possible etiologic relationships; therefore, further investigation will be necessary to classify gender differences and the relationship between PAD and CA-IMT.

The area under the ROC curve (AUC) provides a measure of the model's ability to discriminate those who experience the outcome of interest versus those who do not. It is generally accepted, as a general rule, that $AUC \geq 0.9$ is considered as outstanding discrimination, and $AUC \geq 0.7 - < 0.8$ is considered as acceptable discrimination. The observed AUC of 0.91 in male shows that the male PAD status can be predicted with confidence to some extent by the selected model, and AUC of 0.75 in females suggests that the selected model satisfactorily discriminated the PAD status of females in these residents.

There are some limitations to the present study. First, there may have been some selection bias: the subjects may have been aware of the impact of body weight, smoking, blood pressure, glucose and lipid levels on their health because they had received annual examinations at the health examination center. The prevalence of asymptomatic PAD was high; thus, a larger population-based study will be necessary to clarify the reasons for the high prevalence. Second, in cross-sectional studies it is often difficult to determine the time order of events; therefore, a prospective study should be undertaken to confirm the relationship between PAD and the conventional risk factors for PAD in these residents.

We confirmed that the prevalence of PAD in Japanese was lower than that of similar studies in other countries. The risk factors of PAD in the present study were age and dyslipidemia for both sexes, carotid atherosclerosis for males and abdominal adiposity for females. It is of interest that some of the markers of PAD differed between the sexes.

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