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Difference in the Risk Factors for Coronary, Renal and Other Peripheral Arteriosclerosis in Heterozygous Familial Hypercholesterolemia

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Background The aim of the present study was to clarify the risk factors of several types of arteriosclerosis lesions in Japanese individuals with heterozygous familial hypercholesterolemia (FH): renal arteriosclerosis (RAS), abdominal aortic sclerosis (AOS), iliac arteriosclerosis (IAS) and coronary artery disease (CAD).
Methods and Results Coronary angiography (CAG) and abdominal aortic angiography (AAA) were performed in 117 consecutive heterozygous FH subjects (79 men, 38 women; age 22–76). RAS (stenotic lesion or aneurysm) was observed in 39 cases (33%), predominantly in the proximal portion (74%) and both sides equally (right/left = 27/23). Most cases of RAS (64%) presented with <25% stenosis. The differences in the contributing risk factors for the progression and development of RAS, AOS, IAS and CAD in FH were then analyzed. Multiple logistic regression analyses showed independent risk factors for formation of atherosclerosis in each artery were: age alone for RAS; age and plasma low-density lipoprotein cholesterol (LDL-C) for AOS; age, LDL-C and high-density lipoprotein cholesterol (HDL-C) for IAS; and HDL-C and diabetes mellitus for CAD.
Conclusion In Japanese subjects with heterozygous FH, there are distinct risk factors for the development and progression of atherosclerosis in the renal, iliac, abdominal aorta, and coronary arteries. (*Circ J* 2004; **68:** 623–627)

Key Words: Abdominal aortic sclerosis; Coronary artery disease; Familial hypercholesterolemia; Iliac arteriosclerosis; Renal arteriosclerosis

Atherosclerotic lesions in an individual do not progress at a same rate[1] despite the systemic atherosclerosis risk factors affecting all arteries uniformly. The severity and extent of lesions differ throughout the body[2] and although the topographic distribution of atherosclerotic lesions in rabbits fed a low-level cholesterol diet has been shown[3] no studies of humans have been conducted to date.

Familial hypercholesterolemia (FH) is characterized by accelerated atherosclerotic lesions, and because the prevalence of heterozygous FH is not rare (1 in 500 in general population)[4–6] it provides a good opportunity to examine the variance in the development of peripheral arteriosclerosis.

Of the peripheral arteriosclerotic diseases, the clinical significance of renal arteriosclerosis (RAS) has been underestimated despite its clinical importance in progressing to renovascular hypertension (RVHT) and nephrosclerosis. Therefore, we investigated the distribution of the atherosclerotic lesions in heterozygous FH, including RAS, abdominal aortic sclerosis (AOS) and iliac arteriosclerosis (IAS) and coronary artery disease (CAD), by performing coronary and abdominal aortic angiography (AAA) and then analyzing in detail the possible contributing factors.

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Methods

Subjects

Subjects were 117 consecutive heterozygous FH patients who underwent coronary angiography (CAG) in 4 hospitals (Kanazawa University Hospital, Kanazawa Cardiovascular Hospital, Fukui Cardiovascular Hospital, Komatsu Municipal Hospital) from April 1994 to March 1997 (These 4 hospitals are in the Hokuriku district (north central) of Japan, where approximately 3% of the Japanese population resides). The diagnosis of FH was based on the criteria we previously reported[6] The subjects consisted of 79 men and 38 women aged 22–76 years (mean, 53 years). None had undergone any angioplastic or vascular surgeries, such as coronary artery bypass graft (CABG) surgery, percutaneous transluminal coronary angioplasty (PTCA), stenting or percutaneous transluminal angioplasty (PTA), or lipid-lowering therapies before this study. Smokers and habitual alcohol consumers were identified by the information obtained in a patient questionnaire. Subjects who smoked at least 10 cigarettes per day were classified as current smokers. Subjects who habitually consumed more than 1 unit of alcohol (633 ml of beer or 180 ml of wine or 180 ml of sake or 70 ml of hard liquor) every week were classified as current drinkers. Measurement of Achilles tendon thickness was based on the method we previously described[7]

Table 1 Clinical Characteristics of the Heterozygous Familial Hypercholesterolemia Patients With and Without Renal Arteriosclerosis (RAS)

	Total subjects	RAS (+)	RAS (−)	p value
n	117	39 (33%)	78 (67%)	
Age (years)	53±11	59±9	50±11	<0.0001*
Gender				
Men	79 (66%)	23 (59%)	56 (72%)	NS
Women	38 (34%)	16 (41%)	22 (28%)	NS
Total cholesterol (mg/dl)	307±68	295±56	312±73	NS
Triglycerides (mg/dl)	146±81	151±81	142±82	NS
HDL cholesterol (mg/dl)	40±12	41±10	40±14	NS
LDL cholesterol (mg/dl)	238±73	223±56	246±80	NS
Achilles tendon thickness (mm)	13±3	13±3	13±4	NS
Hypertension	36 (31%)	15 (38%)	21 (27%)	NS
Diabetes mellitus	23 (20%)	9 (23%)	14 (18%)	NS
Cigarette smoking	57 (49%)	15 (38%)	42 (54%)	NS
Alcohol drinking	45 (38%)	10 (26%)	35 (45%)	NS
Coronary angiographic findings				
Coronary artery disease (CAD)	70 (60%)	27 (69%)	43 (55%)	NS
With organic stenosis	59 (50%)	22 (56%)	37 (47%)	NS
1 vessel disease	21 (18%)	6 (15%)	15 (19%)	
2 vessel disease	19 (16%)	7 (18%)	12 (15%)	
3 vessel disease	19 (16%)	9 (23%)	10 (13%)	
No. of ≥75% stenosis	1.0±1.1	1.2±1.3	0.9±1.1	NS
Abdominal aortic sclerosis (AOS)	80 (68%)	35 (90%)	45 (58%)	0.0010*
Iliac arteriosclerosis (IAS)	66 (56%)	29 (74%)	37 (47%)	0.0148*

All continuous values are represented by mean±SD (mg/dl). p value in hypertension, diabetes mellitus, cigarette smoking and alcohol drinking was χ^2 p value. LDL-cholesterol was calculated by Friedewald formula. Organic stenosis was defined as ≥75% stenosis in a coronary artery.

Table 2 Prevalence of Angiographically Determined Arteriosclerotic Lesions in the FH Subjects

	Total	Men	Women
Renal arteriosclerosis (RAS)	39 (33%)	23 (29%)	16 (42%)
Bilateral	11 (9%)	7 (9%)	4 (11%)
Abdominal aortic sclerosis (AOS)	80 (68%)	53 (67%)	27 (71%)
Abdominal aortic aneurysm	17 (15%)	13 (16%)	4 (11%)
Iliac arteriosclerosis (IAS)	66 (56%)	45 (57%)	21 (55%)

FH, Familial hypercholesterolemia.

Hypertensive and diabetic patients were identified by their clinical history. Hypertension (HT) was defined as present if either antihypertensive treatment had been instituted or blood pressure was >140 mmHg systolic or 90 mmHg diastolic or both. The definition of diabetes mellitus (DM) was the 1985 World Health Organization Criteria[8]

This study was approved by the ethical committee of each hospital and informed consent was obtained from each participant.

Angiography

All of the study subjects underwent selective CAG according to the Judkins technique[9] recorded on 35-mm films. The degree of coronary atherosclerosis was determined in 15 coronary artery segments according to the definition of the Ad Hoc Committee on Grading of CAD of the American Heart Association[10] We referred to Abram's Angiography: Vascular and Interventional Radiology (Publisher: Lippincott Williams & Wilkins Publishers; 3rd edition (February 1983)) to read all of the results of the angiography. An arteriosclerotic lesion was defined as greater than 5% stenosis or an aneurysm and Organic stenosis was defined as greater than or equal to 75% stenosis. All of the patients also underwent AAA (nonselective cineangiography recorded on 35-mm films or digital subtraction angiography (DSA) recorded on X-ray film), which imaged all of both renal arteries. The degree of RAS was evaluated in a process similar to CAD evaluation. The location of RAS was defined as proximal, middle and distal according to the distance from the bifurcation of the renal artery. The grading of stenosis was based on the consensus of 2 cardiologists who were unaware of the patients' clinical profiles.

Analysis of Serum Lipids

Fasting venous blood was collected into an EDTA-containing tube. Plasma total cholesterol (TC) and triglyceride (TG) concentrations were determined by enzymatic methods. Plasma high-density lipoprotein cholesterol (HDL-C) concentration was measured after precipitation of apolipoprotein B-containing lipoproteins with dextran sulfate and magnesium chloride. Low density lipoprotein (LDL)-cholesterol was calculated by the Friedewald formula.

Statistics

Parametric values were expressed as mean±standard deviation (SD). Statistical significance was inferred at a value of $p<0.05$. Gender, cigarette smoking status, alcohol drinking status, DM and HT were analyzed as binary variables. Difference between patients with or without RAS were assessed with Student's t-test for continuous variables and Pearson's chi-squared test for frequencies with 95% confidence intervals (CI). The risk factors for RAS, AOS

Table 3 Angiographic Findings of Renal Arteriosclerosis in Heterozygous Familial Hypercholesterolemia Patients

	Total	Men	Women
Site			
Right	*27 (54%)*	*13*	*14*
Left	*23 (46%)*	*16*	*7*
Location			
Proximal	*37 (74%)*	*22*	*15*
Middle	*12 (24%)*	*6*	*6*
Distal	*1 (2%) : aneurysm*	*1*	*0*
Morphology			
Aneurysm	*1 (2%)*	*1*	*0*
Stenosis			
≥90%	*1 (2%) : renovascular hypertension (RVHT)*	*0*	*1*
≥75%	*3 (6%)*	*1*	*2*
≥25%	*13 (26%)*	*7*	*6*
<25%	*32 (64%)*	*20*	*12*

Table 4 Multiple Logistic Regression Analyses of Factors Affecting the Existence of Atherosclerotic Lesions

	Dependent variables							
	RAS		AOS		IAS		CAD	
	OR	p value	OR	p value	OR	p value	OR	p value
Independent variables								
Age	*4.889*	*0.0270**	*13.571*	*0.0002**	*12.326*	*0.0004**	*0.948*	*0.3303*
Gender	*0.046*	*0.8307*	*0.020*	*0.8880*	*0.522*	*0.4700*	*0.852*	*0.3560*
LDL-cholesterol	*0.215*	*0.6427*	*7.528*	*0.0061**	*4.315*	*0.0378**	*0.401*	*0.5266*
HDL-cholesterol	*0.055*	*0.8139*	*1.175*	*0.2784*	*2.413*	*0.1203*	*5.450*	*0.0196**
Triglycerides	*0.483*	*0.4872*	*0.086*	*0.7692*	*1.514*	*0.2185*	*0.073*	*0.7874*
Cigarette smoking	*0.040*	*0.8421*	*1.869*	*0.1716*	*2.373*	*0.1235*	*0.054*	*0.8159*
Alcohol drinking	*0.639*	*0.4240*	*0.524*	*0.4690*	*2.362*	*0.1243*	*1.646*	*0.1996*
Diabetes mellitus	*0.154*	*0.6945*	*0.029*	*0.8650*	*0.508*	*0.4761*	*3.949*	*0.0469**
Hypertension	*0.149*	*0.6996*	*0.282*	*0.5952*	*2.305*	*0.1290*	*0.591*	*0.4419*

Gender, smoking, alcohol, hypertension and diabetes mellitus were expressed in dichotomy data using dummy variables (0 and 1). Cigarette smoking and alcohol drinking were classified by current states. LDL-cholesterol, triglyceride and HDL-cholesterol were expressed as numerical data. AOS, abdominal aortic stenosis; CAD, coronary artery disease; IAS, iliac artery stenosis; RAS, renal artery stenosis.

IAS and CAD were assessed by multivariate logistic regression analyses. Association strength is presented as an odds ratio (OR) with 95% CI. Statistical data analyses were performed using the statistical package StatView 5.0 for Macintosh (Abacus Concepts, Berkeley, CA, USA).

Results

Characteristics of the Subjects

The clinical characteristics of heterozygous FH patients with or without RAS are shown in Table 1. Lipid and lipoprotein profiles of the study subjects were similar to those in a previous report on Japanese FH.[11] Among the 117 study subjects, 70 (60%) had CAD and 56 (48%) had organic stenosis. RAS was observed in 39 patients (33%), AOS in 80 patients (68%), and IAS in 66 patients (56%) (Tables 1,2). Subjects with RAS were significantly older than those without (Table 1). In a total of 50 lesions, RAS was observed predominantly in the proximal portion (74%) and in both sides equally (right 54%; left 46%). The angiographical characteristics of RAS were as follows: aneurysm (2%), ≥75% stenosis (8%), 25–74% stenosis (26%) and <25% stenosis (64%). Renovascular HT (RVHT) was observed in only 1 case (Table 3).

Association of Several Metabolic Parameters With the Development of Atherosclerosis

Multiple logistic regression analyses were conducted with RAS, AOS, IAS or CAD as dependent variables, and age, gender, LDL-C, TG, HDL-C, cigarette smoking, alcohol drinking and the presence of DM and HT as independent variables (Table 4). RAS was not independent related to those parameters except for age. AOS had a positive relation with age and LDL-C, IAS with age, LDL-C and HDL-C, and CAD with HDL-C and the presence of DM.

Next, we investigated the association of the prevalence of each sclerotic lesion in the renal artery, aorta and iliac artery to the severity of CAD according to CAD grade (Table 5). RAS did not have a significant association with the severity of CAD in all subjects and men (Table 5). In women, however, individuals with 3 vessel disease (VD) of the coronary artery had a higher incidence of RAS than did those without 3VD, although the study sample size was small (Table 5).

Discussion

The main findings of the present study are: (1) 39 of 117 (33%) heterozygous FH subjects had RAS; (2) RAS in FH is characterized by mild stenosis; and (3) the risk factors for the progression of atherosclerosis in FH are distinct for RAS, AOS, IAS and CAD.

This is the first study to analyze in detail the development of RAS in FH subjects. RVHT, which is considered to be a typical end-stage presentation of RAS, was found in

Table 5 Prevalence of Arteriosclerotic Lesions in Each Region Categorized by Number of Affected Vessels

	3VD	2VD	1VD	0VD	Total
All subjects					
Total	19	19	21	58	117
RA (+)	9	7	6	17	39
RA (–)	10	12	15	41	78
%RA	47.4	36.8	28.6	29.3	
Ao (+)	19	14	15	32	80
Ao (–)	0	5	6	26	37
%Ao	100*	73.7	71.4	55.2	
IA (+)	18	13	11	24	66
IA (–)	1	6	10	34	51
%IA	94.7*	68.4	52.4	41.4	
Men					
Total	14	17	18	30	79
RA (+)	5	6	4	8	23
RA (–)	9	11	14	22	56
%RA	35.7	35.3	22.2	26.7	
Ao (+)	14	12	12	16	54
Ao (–)	0	5	6	14	25
%Ao	100*	70.6	66.7	53.3	
IA (+)	13	11	9	13	46
IA (–)	1	6	9	17	33
%IA	92.9*	64.7	50.0	43.3	
Women					
Total	5	2	3	28	38
RA (+)	4	1	2	9	16
RA (–)	1	1	1	19	22
%RA	80*	50	66.7	32.1	
Ao (+)	5	2	3	16	26
Ao (–)	0	0	0	12	12
%Ao	100	100	100	57.1	
IA (+)	5	2	2	11	20
IA (–)	0	0	1	17	18
%IA	100*	100	66.7	39.3	

*Statistical significance was evaluated by comparison with 0VD, *p<0.05.*
RA (+), Ao (+) and IA (+), positive for atherosclerotic lesions of the renal, aortic and iliac arteries, respectively.
*%RA (+) was calculated by 100*RA (+)/RA (+) + RA (–); similarly for %Ao (+) and %IA (+).*
VD, vessel disease.

only 1 case (0.9%) and the prevalent lesion characteristic of RAS was mild to moderate stenosis. In view of the fact that RVHT is very rare and routine renal artery evaluation for FH subjects is not performed, we consider that RAS in FH may have been overlooked in the majority of cases. Clinical characteristics, except for age, were found to be similar between FH individuals with and without RAS. Although peripheral arteriosclerosis, in general, is known to be associated with plasma TG concentrations,[12] in this study RAS was not associated with elevated TG concentrations. Also, RAS had a weaker relationship to LDL-C and CAD than did AOS and IAS. In view of the high prevalence of CAD[13,14] and AOS[15] in FH, our finding of the renal arteries having a lower prevalence of atherosclerosis suggests that these particular arteries somehow possess a resistance to the progression of atherosclerosis.

Given that there is compelling evidence showing the effectiveness of long-term treatment with lipid-lowering agents on CAD,[16–19] it is hard to explain why serum LDL-C concentrations were not associated with the existence of CAD (Table 4). In the J-LIT study, a long -term clinical study of more than 50,000 Japanese hyperlipidemic subjects, it has been demonstrated that the elevation of LDL-C, particularly >160 mg/dl for primary prevention and >140 mg/dl for the secondary prevention, was associated with a higher incidence of CAD.[20,21] We presume the result shown in Table 4 is related to the fact that all of the study subjects had FH, which already has a markedly high serum LDL-C concentration. In addition to CAD, lipid-lowering therapy is also effective for the prevention of events related to peripheral vascular atherosclerosis![18,19]

The metabolic parameter other than LDL-C and TG that could be associated with peripheral atherosclerosis is HDL-C. In our study, CAD had a significant relationship with serum HDL-C concentration by multiple logistic regression analyses, suggesting that it is an independent determinant of the progression of atherosclerosis in the coronary artery (Table 4).

Although it is known that diabetic patients often have diffuse CAD and arteriosclerosis obliterans (ASO), in this study, CAD, not IAS, had a significant relationship with the existence of DM (Table 4). We presume this is partly because in the present study DM would predominantly affect the atherosclerotic progression in the coronary arteries rather than the iliac arteries as the study subjects were relatively young in age. This notion is supported by our finding that age had a positive relationship with RAS, AOS and IAS, but not with CAD. Because CAD has been observed in FH individuals who are younger than CAD patients in the general population, age seemed to have little, if any, impact on the progression of CAD in our study subjects.

Even in each individual, atherosclerotic plaques do not develop at an equal rate and are not evenly distributed throughout the vasculature. Contributing factors to atherosclerosis progression are reported to be regional disturbances of blood flow, which can then result in rheological differences;[22,23] or alterations in proteoglycan structure! It is reported that over-expressed proteoglycan accelerates lipoprotein retention and therefore atherosclerosis.[24] Other contributing factors to the development of atherosclerosis are lipoprotein (a) (Lp(a))[25,26] and homocysteine.[27] Indeed, we previously reported that a mutation of the common methylenetetrahydrofolate reductase gene is associated with elevated concentrations of plasma homocysteine, leading to the early onset of CAD in FH.[28] Lp(a), which is known to be a highly atherogenic lipoprotein having a protein moiety apoB100 disulfide, binds to proteoglycans.[29] Degradation of endothelial heparan sulfate proteoglycan by homocysteine is considered to cause a loss of ability to protect the endothelial cell surface from oxidative stress.[30] Previous studies have shown that differences in expression of the proteoglycan of the arterial wall affects the subendothelial retention of atherogenic lipoproteins, including remnant particles.[24] Besides the risk factors already mentioned, a recent study by Taira et al has shown that a positive family history for CAD and the existence of midband lipoprotein in the plasma are potential risk factors for carotid atherosclerosis in FH.[31]

One of the limitations of our present work is that all of the atherosclerotic lesions were judged visually, which lead to very early stenotic lesions of less than 5% to be overlooked.

In conclusion, we have angiographically demonstrated the regional differences in atherosclerosis progression in the renal arteries, coronary arteries, iliac arteries and abdominal aorta of heterozygous FH subjects, and found that the contributing factors to the development and progression of atherosclerosis are distinct for each of these regions.

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