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 body2 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.

**Methods**

**Subjects** 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

**Background** The aim of the present study was to clarify the risk factors of several types of arteriosclerotic 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
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. 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, 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. 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 based on the consensus of 2 cardiologists who were unaware of the patients’ clinical profiles.

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

<table>
<thead>
<tr>
<th></th>
<th>Total subjects</th>
<th>RAS (+)</th>
<th>RAS (–)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>117</td>
<td>39 (33%)</td>
<td>78 (67%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53±11</td>
<td>59±9</td>
<td>50±11</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>79 (66%)</td>
<td>23 (59%)</td>
<td>56 (72%)</td>
<td>NS</td>
</tr>
<tr>
<td>Women</td>
<td>38 (34%)</td>
<td>16 (41%)</td>
<td>22 (28%)</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>307±68</td>
<td>295±56</td>
<td>312±73</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>146±81</td>
<td>151±81</td>
<td>142±82</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>40±12</td>
<td>41±10</td>
<td>40±14</td>
<td>NS</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>238±73</td>
<td>223±56</td>
<td>246±80</td>
<td>NS</td>
</tr>
<tr>
<td>Achilles tendon thickness (mm)</td>
<td>13±3</td>
<td>13±3</td>
<td>13±4</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (31%)</td>
<td>15 (38%)</td>
<td>21 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23 (20%)</td>
<td>9 (23%)</td>
<td>14 (18%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>57 (49%)</td>
<td>15 (38%)</td>
<td>42 (54%)</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td>45 (38%)</td>
<td>10 (26%)</td>
<td>35 (45%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

All continuous values are represented by mean±SD (mg/dl). p value in hypertension, diabetes mellitus, cigarette smoking and alcohol drinking was $^{2}p$ 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

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal arteriosclerosis (RAS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>39 (33%)</td>
<td>23 (29%)</td>
<td>16 (42%)</td>
</tr>
<tr>
<td>Abdominal aortic sclerosis (AOS)</td>
<td>11 (9%)</td>
<td>7 (9%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>80 (68%)</td>
<td>53 (67%)</td>
<td>27 (77%)</td>
</tr>
<tr>
<td>Iliac arteriosclerosis (IAS)</td>
<td>17 (15%)</td>
<td>13 (16%)</td>
<td>4 (11%)</td>
</tr>
<tr>
<td></td>
<td>66 (56%)</td>
<td>45 (57%)</td>
<td>21 (55%)</td>
</tr>
</tbody>
</table>

FH, Familial hypercholesterolemia.
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. 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
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 in the renal, aortic and iliac arteries, respectively. Therefore, it is likely that differences in expression of the proteoglycan of the arterial wall affects the subendothelial retention of atherogenic lipoproteins, including remnant particles. It is known that over-expressed proteoglycan accelerates lipoprotein retention and therefore atherosclerosis. Other contributing factors to the development of atherosclerosis are lipoprotein (a), lipoprotein(a) and homocysteine. 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. Lp(a), which is known to be a highly atherogenic lipoprotein having a protein moiety apoB100 disulfide, binds to proteoglycans. 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. 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. 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.

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.
References


