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Development of Coronary Atherosclerosis in Asymptomatic Heterozygous Patients With Familial Hypercholesterolemia

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Abstract

To determine whether coronary atherosclerosis develops with age in asymptomatic patients with familial hypercholesterolemia (FH) and whether long-term cholesterol-lowering therapy is effective for primary prevention of coronary artery disease (CAD) in such patients, 13 patients with heterozygous FH (10 men, 3 women, aged 34 to 66 years) were examined by coronary angiography, and followed up for 5.8 ±3.4 years. The extent of coronary atherosclerosis was expressed as the coronary score (*CS*) by scoring (0 to 5) points in each of 15 American Heart Association segments.

The mean *CS* was 2.4 times higher in men than in women (11.5±7.9 vs 4.7±4.2) although the mean age was lower in the former than in the latter (51.2±8.4 vs 57.7±0.6 years). In men, *CS* correlated significantly with age ($CS=0.682\times age-24.4$; $r=0.800$, $p<0.01$). All patients except one had received cholesterol-lowering agents throughout the follow-up period. The untreated patient developed CAD 7 years later. One treated patient also developed CAD, but within 6 months of enrollment in this study. The other 11 treated patients did not develop CAD. Reexamination by coronary angiography in two of these patients revealed no significant progression after 6-year treatment. Coronary atherosclerosis develops with age in asymptomatic FH patients and long-term cholesterol-lowering therapy may be effective for primary prevention of CAD in such patients.

Key Words
Cholesterol (familial hypercholesterolemia), Coronary artery disease, Ischemia (silent), Angiography (coronary), Drug administration

INTRODUCTION

Familial hypercholesterolemia (FH) is a common hereditary disorder among patients with coronary artery disease (CAD)[1,2]. Familial hypercholesterolemia is characterized by hypercholesterolemia, tendon xanthoma, and premature CAD[2,3]. Most patients with heterozygous FH develop CAD by age 60 years in men, and by age 70 years in women[4]. Some patients with heterozygous FH do not develop CAD, and survive to over 80 years in spite of their high plasma cholesterol levels[2]. It is not clear whether coronary atherosclerosis develops with age in asymptomatic patients with FH.

Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are available for the management of hypercholesterolemia, so plasma cholesterol levels can be reduced to the normal range even in patients with FH[5]. Cholesterol-lowering therapy has reduced the CAD risk in non-FH patients in several epidemiological studies[6–10]. However, it is still not clear whether long-term cholesterol-lowering therapy is effective for the primary prevention of CAD in asymptomatic FH patients.

To address these questions, we examined 13 asymptomatic patients with heterozygous FH using

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Selected abbreviations and acronyms

ATT=Achilles tendon thickness
CAD=coronary artery disease
CS=coronary score
FH=familial hypercholesterolemia
HDL-C=high-density lipoprotein cholesterol
HMG-CoA=hydroxymethylglutaryl coenzyme A
LAD=left anterior descending artery
LDL=low-density lipoprotein
RCA=right coronary artery
TC=total cholesterol
TG=triglyceride

coronary angiography, and followed their clinical courses for 5.8±3.4 years. Our data indicate that coronary atherosclerosis develops with age in male asymptomatic FH patients, and that long-term cholesterol-lowering therapy may be effective for primary prevention of CAD in such patients.

MATERIALS AND METHODS

Subjects

Thirteen patients with heterozygous FH (10 men and 3 women, aged 34 to 66 years, mean 53.8±8.0 years) were enrolled in this study. Participants had diagnoses of heterozygous FH according to the criteria of Mabuchi *et al.*[4] All patients were carefully interviewed by two cardiologists independently. None had any symptoms of angina pectoris or myocardial infarction. We obtained written informed consent from each patient before coronary angiography, agreeing to angiography in spite of the absence of symptoms of CAD because they had either marked hypercholesterolemia, or prevalence of CAD in their family.

Measurement of serum lipid levels

Blood samples were obtained after overnight fasting for the measurement of serum lipid levels. Total cholesterol (TC), and triglyceride (TG) levels were measured by enzymatic methods, and high-density lipoprotein-cholesterol (HDL-C) by the polyanion method. Cholesterol-lowering drugs were prescribed after the initial determination of lipoprotein profiles.

Determination of Achilles tendon xanthoma

Achilles tendon xanthoma was determined based on the method of Blankenhorn *et al.*[11] Achilles tendon thickness (ATT) was measured on X-ray films. Thickened tendons (not less than 9 mm) were considered as the presence of Achilles tendon xanthomas[3,4].

Evaluation of coronary atherosclerosis

Coronary atherosclerosis was evaluated when patients were enrolled in this study. Coronary angiography was performed according to the method of Judkins[12]. The luminal narrowing was assessed in 15 American Heart Association (AHA) segments in all patients by two cardiologists independently. No conflicting results were obtained in any patient. The following scores were assigned to each stenosis (0% : 0 point, 1 to 25% : 1 point, 26 to 50% : 2 points, 51 to 75% : 3 points, 76 to 99% : 4 points, 100% : 5 points), and the sum of the points in affected segments was defined as the coronary score (*CS*) representing the extent of coronary atherosclerosis[3]. We examined the correlation between *CS* and such parameters as TC, TG, HDL-C, ATT, and age.

Follow-up study

We followed the clinical courses of all patients for 5.8±3.4 years (1 to 15 years) from the initial evaluation by coronary angiography. All patients except one had taken cholesterol-lowering drugs throughout the follow-up period. The diagnosis of myocardial infarction was based on medical records including electrocardiograms, echocardiograms, and coronary angiography. Angina pectoris was ruled out by the treadmill exercise electrocardiogram test. In four out of 13 patients, we repeated coronary angiography more than once from 1- to 7-year intervals.

Statistical analysis

All values are presented as mean±standard deviation. Statistical analysis used Student's *t*-test and Welch's test. A p value of less than 0.05 was considered to be significant.

RESULTS

Sex difference in coronary score

To determine whether there is a sex difference in the extent of coronary atherosclerosis, we compared mean *CS* between men and women. In both groups, the mean TC levels were over 300 mg/dl. There were no significant differences in TC and TG levels

between men and women. In women, the mean HDL-C levels were lower and the mean ATT was thinner (**Table 1**; both $p<0.1$). The mean *CS* was 2.4 times higher in men than in women (**Fig. 1**) even though the mean age was lower by 6.5 years in men than in women (**Table 1**). To prevent any effect of gender difference on the results, we analyzed men and women separately in the comparisons described below.

Table 1 Lipid levels and Achilles tendon thickness in heterozygous patients with familial hypercholesterolemia

	Age (yr)	TC (mg/dl)	TG (mg/dl)	HDL-C (mg/dl)	ATT (mm)
Men ($n=10$)	51.2 (8.4)	304.4 (50.4)	175.5 (46.8)	35.6 (10.2)	12.2 (5.2)
Women ($n=3$)	57.7 (0.6)	329.3 (39.0)	116.7 (66.7)	33.3 (4.9)	11.0 (2.3)
p value	<0.15	NS	NS	<0.1	<0.1

Data are presented as means and (standard deviation).

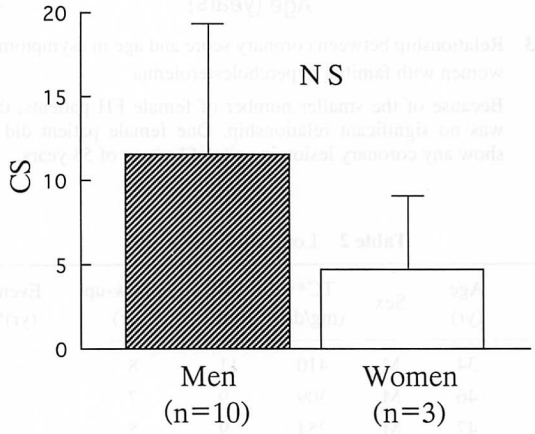

Fig. 1 Sex and coronary score in heterozygous patients with familial hypercholesterolemia

Coronary score in men was markedly higher than in women although the mean age was lower in the former.

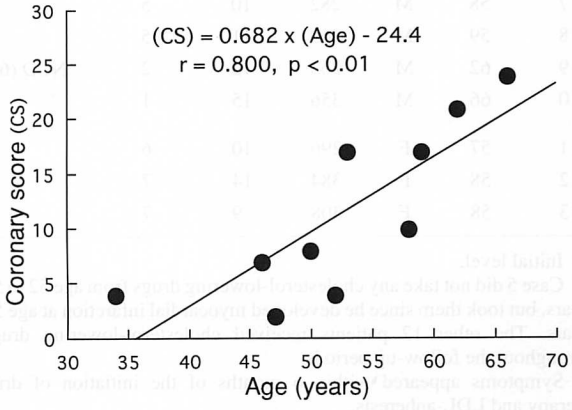

Fig. 2 Relationship between coronary score and age in asymptomatic men with familial hypercholesterolemia

There was a significant positive correlation between *CS* and age in males with FH.

Relationship between coronary score and age

To clarify the factors promoting the development of coronary atherosclerosis in asymptomatic FH patients, we examined the correlation between *CS* and parameters such as age, TC, TG, HDL-C, and ATT.

In men, we found that *CS* was correlated significantly with age ($CS=0.682\times age-24.4$; $r=0.800$, $p<0.01$; **Fig. 2**). No other parameter was correlated significantly with *CS*. The regression equation crossed the X-axis at 35.8 years. Two out of 10 patients showed total occlusion of coronary arteries. Both patients had marked networks of collaterals. Probably, this is the reason they did not have any chest pain or discomfort.

In women, we could not find any significant correlation between *CS* and parameters probably due to the smaller number of patients. *CS* in women has a lower trend compared with that in men of the same age. To our surprise, a 58-year-old woman showed normal coronary arteries (**Fig. 3**).

Follow-up study

To assess the effect of cholesterol-lowering therapy on the development of CAD, we followed the clinical courses for 5.8 ± 3.4 years after the initial coronary angiography. The features and follow-up periods are shown in **Table 2**. All patients except one (case 5) received cholesterol-lowering drugs from the beginning of the observations.

Eleven of the 12 treated patients did not develop CAD during the follow-up period (**Table 2**). Two of these 11 patients (both male) agreed to repeat coronary angiography although they were absolutely free of symptoms. Their total cholesterol levels were reduced from 410 to 260 mg/dl in case 1, and from 309 to 217 mg/dl in case 2. In case 1, there was no change in the coronary arteries for the first 2 years. Four years later (6 years from the first angiography), the third angiography was performed. We found slight progression in the proximal lesion of the right coronary artery (RCA). The luminal reduction had increased from 13% to 36%. In case 2, we found no changes in both coronary arteries after 6-year treatment (**Fig. 4**). Case 9 died of non-cardiac causes at age 64 years. The cause of death was hepatic failure. Autopsy confirmed the

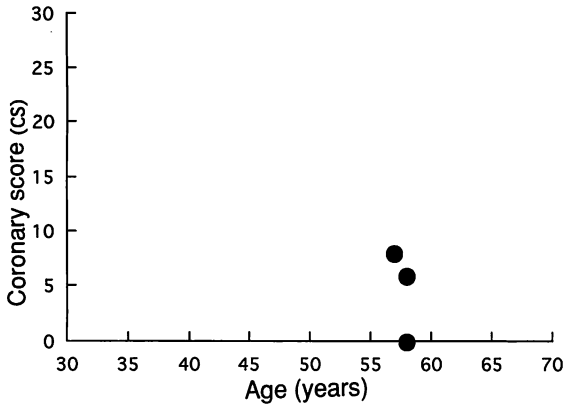

Fig. 3 Relationship between coronary score and age in asymptomatic women with familial hypercholesterolemia

Because of the smaller number of female FH patients, there was no significant relationship. One female patient did not show any coronary lesion in spite of her age of 58 years.

Table 2 Long-term follow-up

Case No	Age (yr)	Sex	TC*1 (mg/dl)	ATT (mm)	Follow-up (yr)	Events (yr)*4
1	34	M	410	11	8	
2	46	M	309	9	7	
3	47	M	254	9	5	
4	50	M	273	10	6	
5	52	M	267	11	15*2	AMI (59) AP (60)
6	53	M	361	13	2	AP (54)*3
7	58	M	282	10	5	
8	59	M	269	11	5	
9	62	M	263	12	2	NCD (64)
10	66	M	356	15	1	
11	57	F	296	10	6	
12	58	F	384	14	7	
13	58	F	308	9	7	

*1 Initial level.
*2 Case 5 did not take any cholesterol-lowering drugs from age 52 to 59 years, but took them since he developed myocardial infarction at age 59 years. The other 12 patients received cholesterol-lowering drugs throughout the follow-up periods.
*3 Symptoms appeared within 6 months of the initiation of drug therapy and LDL-apheresis.
*4 Age at which cardiac event occurred.
AP=angina pectoris; AMI=acute myocardial infarction; NCD=non-cardiac death.

clinical diagnosis. No evidence for acute myocardial infarction was found (**Table 2**).

On the other hand, one untreated patient (case 5) and one treated patient (case 6) suffered nonfatal cardiac events in their fourth decade (**Table 2**). It should be noted that the event in the treated patient (case 6) occurred within 6 months of the first angiography.

In case 5, there were only mild irregularities of both coronary arteries at age 52 years. He did not take any cholesterol-lowering drug after the first angiography, and developed acute myocardial infarction at age 59 years. The second angiography revealed total occlusion of the proximal portion of the RCA (segment 1). In addition, a new lesion (25% stenosis) appeared in the proximal portion of the left anterior descending artery (LAD; segment 6). Under the medication, we could not detect ischemia by stress myocardial scintigraphy at discharge. Thereafter, the TC level was reduced to less than 200 mg/dl at the outpatient clinic. One year later, however, he developed angina pectoris. The third angiography showed rapid progression of the LAD lesions to 90% stenosis. As a result, *CS* increased from 4 (age 52 years) to 14 (age 59 years), and then to 17 (age 60 years; **Fig. 4**). Finally, he underwent aortocoronary bypass graft surgery at our institute.

In case 6, we found total occlusion of the posterolateral branch of the RCA at the first angiography. Both coronary arteries were diffusely irregular. The coronary score ($CS=18$) was rather high for his age (53 years; **Fig. 4**). In the proximal portion of the LAD (segment 6), there were two irregular lesions (less than 50% narrowing in diameter). His cholesterol level was difficult to reduce with medication alone. We used low-density lipoprotein (LDL) apheresis as well as intensive combined drug regimens. Thereafter, the TC level was controlled well (about 200 mg/dl before apheresis, and 100 mg/dl after apheresis). Within 6 months of the first angiography, he started to suffer from severe chest pain on effort. Second angiography at age 55 years revealed total occlusion of the LAD lesion (segment 6). The coronary score increased rapidly from 18 to 21 (**Fig. 4**). The distal portion of the LAD was irrigated by a collateral network. There was no evidence for myocardial infarction. We performed percutaneous transluminal coronary angioplasty, and placed the stent at the dilated site for long-term patency.

DISCUSSION

Our data indicate that coronary atherosclerosis develops with age in asymptomatic FH patients. Coronary score, which represents the extent of coronary atherosclerosis, was correlated significantly

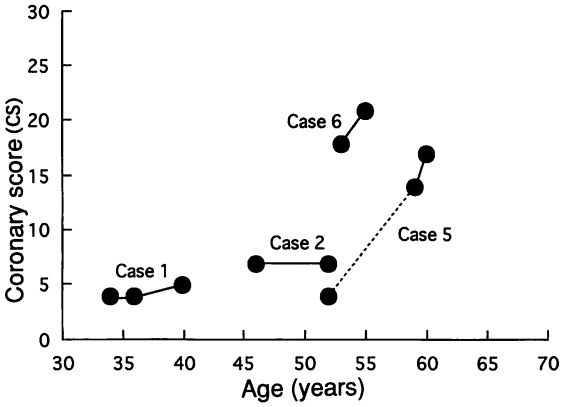

Fig. 4 Changes in coronary score during follow-up periods

Four of 13 patients underwent repeat coronary angiography. Cases 1 and 2 had been free from symptoms of CAD, while Cases 5 and 6 developed CAD during the follow-up periods. The dotted line represents the period when the patient did not receive cholesterol-lowering therapy.

with age in male patients (**Fig. 2**). In FH patients, age reflects the duration of hypercholesterolemia because the high cholesterol levels have been sustained from childhood[13] due to the genetic defect of LDL clearance. The promoting factors for coronary atherosclerosis should be not only high cholesterol levels but also the duration of hypercholesterolemia. The cholesterol levels are over 300 mg/d*l* in most patients with heterozygous FH, and do not differ widely among different families. It is reasonable, therefore, that age is the only parameter that was correlated significantly with the extent of coronary atherosclerosis. Stone *et al.*[14] examined the frequency of CAD in more than 1,000 individuals from 116 FH families. They compared the cumulative probability of CAD in affected patients with that in unaffected family members. They found that the cumulative probabilities rise linearly with age in FH patients in both sexes. This result suggests that coronary atherosclerosis itself also develops linearly with the age. Mabuchi *et al.*[4] examined coronary atherosclerosis angiographically in 105 male and 56 female heterozygous FH patients. In this study, some patients had already developed CAD. They showed a significant positive correlation between coronary score index (which corresponds to *CS* in our study) and age in both groups. This observation agrees with our results.

Our data also indicate that long-term cholesterol-lowering therapy is effective for primary prevention of CAD in asymptomatic FH patients. All patients except case 5 started cholesterol-lowering therapy when they had coronary angiography at enrollment in this study (**Table 2**). No patients who had received medication for more than 6 months developed CAD. In two of them, coronary angiography revealed little change after 6-year treatment (**Table 2, Fig. 4**; cases 1 and 2).

On the other hand, two patients developed CAD during the follow-up period (**Table 2**; cases 5 and 6). Case 5 had not received cholesterol-lowering agents for the first 7 years. The increase in *CS* is almost parallel to the regression equation (**Fig. 2**). After the second angiography, we started drug therapy but failed to prevent progression of coronary atherosclerosis. In case 6, CAD developed within 6 months in spite of the intensive cholesterol-lowering therapy (drug therapy plus LDL-apheresis). These findings suggest that it may take some time for the cholesterol-lowering therapy to have an effect on the prevention of CAD in asymptomatic FH patients.

Several randomized controlled trials demonstrate the convincing effect of cholesterol-lowering therapy on the primary[6–8] and secondary prevention[9,10] of CAD. In the Lipid Research Clinics Coronary Primary Prevention Trial[6,7], 3,806 persons without CAD were enrolled and followed for 7.4 years. The trial showed that treatment with cholestyramine decreases the incidence of major coronary events significantly compared with the control group. The Helsinki Heart Study[8], another primary prevention trial, also showed a significant reduction in myocardial infarction in the group treated with gemfibrozil. In the secondary prevention study, simvastatin was proved to improve the prognosis of patients with CAD[9]. A total of 4,444 hypercholesterolemic patients with CAD were examined, finding that the relative risk of total death in the treated group was significantly lower (0.70; $p<$ 0.0003). Similar results were obtained using another HMG-CoA reductase inhibitor, pravastatin[10]. In these studies, the reduction in CAD events was almost proportional to that in cholesterol levels[6–10]. In other words, the extent of the reduction in CAD risk depends on not which drugs are used but how low the cholesterol levels are maintained.

Recent advances of computer-based quantitative angiography now allow accurate evaluation of luminal changes in coronary arteries. Kane *et al.*[15] examined 72 patients with heterozygous FH to test whether reducing cholesterol levels by diet and

combined drug therapy can induce regression of coronary atherosclerosis. They showed that the mean change in percentage area stenosis was +0.80 in the control group (progression) but −1.53 (regression) in the treated group ($p<0.39$). In the St. Thomas' Atherosclerosis Regression Study (STARS)[16], 90 hypercholesterolemic men were randomized into three groups : receiving usual diet, dietary intervention, and diet plus cholestyramine. The mean absolute width of the coronary segments decreased by 0.201 mm (progression) in the usual diet group, increased by 0.003 mm (regression) in the dietary intervention group, and increased by 0.103 mm (regression) in the diet plus cholestyramine group ($p<0.05$). The luminal change in coronary arteries was significantly correlated with the mean LDL cholesterol levels during the trials. The extent of the regression is relatively small[15,16], while the decrease in cardiac events is relatively large[6–10]. This discrepancy may be explained by the stabilization of atherosclerotic plaques induced by cholesterol-lowering therapy.

Emerging evidence suggests that the rupture of atherosclerotic plaques may be important in the development of CAD and that cholesterol-lowering therapy may stabilize such plaques[17]. Pathologically, the growing plaques are rich in lipid and macrophages. These lipid-rich plaques are likely to rupture, resulting in intramural hemorrhage and intraluminal thrombosis. Clinical symptoms manifest only after the percentage area stenosis reaches about 85%[18]. Reduction of plasma cholesterol levels probably induces a decrease in the lipid contents of the plaques. The "lipid-poor plaques" are stable and resistant to rupture although the luminal narrowing remains. Such stabilization of atherosclerotic plaques is the main reason for the preventive effect of cholesterol-lowering therapy on CAD. In the near future, new technologies such as intravascular ultrasonography[19] may elucidate the precise mechanism by which cholesterol-lowering therapy reduces the CAD risk.

In summary, we examined 13 asymptomatic patients by coronary angiography, and followed their clinical courses for 5.8 years. We showed that coronary atherosclerosis develops with age in asymptomatic FH patients and that long-term cholesterol-lowering therapy may be efficient in primary prevention of CAD in such patients. More studies are needed to confirm the life-long effect of cholesterol-lowering therapy on the primary prevention of CAD in FH patients.

要　約

無症状の家族性高コレステロール血症ヘテロ接合体における冠動脈病変進展についての検討

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無症状の家族性高コレステロール血症ヘテロ接合体において，冠動脈硬化が年齢とともに進行するのか，長期間のコレステロール低下療法が冠動脈疾患発症の一次予防に有効であるのかを検討した．

対象は 13 例の無症状の家族性高コレステロール血症ヘテロ接合体 (男 10 例，女 3 例，年齢 34–66 歳) である．全例に冠動脈造影を行い，その後，平均 5.8±3.4 年の経過観察を行った．造影所見の狭窄度に応じ AHA 分類の 15 分画に点数 (0–5) を与え，その総和を冠動脈指数 (*CS*) として冠動脈硬化の指標に用いた．

平均年齢は男性が若かったにもかかわらず (51.2±8.4 vs 57.7±0.6 歳)，冠動脈指数の平均は男性が女性の 2.4 倍高かった (11.5±7.9 vs 4.7±4.2)．男性患者では指数と年齢が有意な正相関を示した ($CS=0.682\times$年齢-24.4; $r=0.800, p<0.01$)．13 例中 12 例は全経過観察期間中コレステロール低下剤を内服した．治療を受けなかった 1 例は 7 年後に冠動脈疾患を発症した．治療を受けた 12 例中 1 例にも冠動脈疾患は発症したが，治療開始後 6 ヵ月以内に起きたものであった．他の治療を受けた 11 例には冠動脈疾患は発症しなかった．この 11 例中 2 例で冠動脈造影を再検したが，6 年間に有意な進行は認められなかった．

無症状の家族性高コレステロール血症ヘテロ接合体においても冠動脈硬化は年齢とともに進行する．長期間のコレステロール低下療法が冠動脈疾患発症の一次予防に有効であることが示唆された．

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