The Assessment of Carotid Atherosclerotic Plaque among Young Patients with Familial Hypercholesterolemia

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Abstract:

Objective Few data exist regarding when atherosclerotic changes occur among patients with familial hypercholesterolemia (FH). Carotid ultrasonography is a non-invasive method of evaluating this issue. The present study (1) compared the clinical utilities of carotid intima-media thickness (cIMT) and carotid plaque score (cPS) and (2) estimated the onset and progression of carotid atherosclerosis among patients with heterozygous FH (HeFH).

Methods We retrospectively analyzed 511 patients under 30 years old who underwent carotid ultrasonography at our hospital from 2006 to 2019. We classified them into the HeFH group (n=78, 21.4±5.9 years old) and non-FH group (n=433, 23.4±6.0 years old) based on the clinical diagnosis and compared their cIMT and cPS values. In addition, we estimated the onset and progression of carotid atherosclerosis among young HeFH patients.

Results There was no significant difference in the cIMT between the HeFH and non-FH groups (0.44 mm vs. 0.42 mm, p=0.25). In contrast, the cPS was significantly higher in the HeFH group than in the non-FH group (1.11 vs. 0.26, p=0.002). The regression equation for cPS of HeFH group was Y=-2.05+0.15X (r=0.37, p<0.001).

Conclusion An assessment based on the cPS rather than the cIMT appears to be better to capture the progress of carotid atherosclerosis among young HeFH patients. Carotid atherosclerosis may start to develop at 14 years old in patients with HeFH.

Key words: familial hypercholesterolemia, lipoprotein, carotid plaque

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Introduction

Familial hypercholesterolemia (FH) is characterized by an elevated low-density lipoprotein (LDL)-cholesterol level, tendon xanthomas, and premature atherosclerosis (1, 2). There are two major forms of this disease: heterozygous FH (HeFH) and homozygous FH (HoFH) (3). The prevalence of HeFH has now been estimated to be around 1 in 300 among the general populations, making it one of the most common Mendelian diseases (4).

It is important to note that the major complication of atherosclerosis is preventable when diagnosed and treated very early. In fact, we and others have shown that early intervention for patients with HeFH appears to lead to a good prognosis (5-8). However, few data exist regarding when to start treating patients to prevent the development of atherosclerosis. To this end, we previously showed that coronary plaque may start to develop at around 23 years old in men and 34 years old in women, and that carotid plaque may start to develop at around 17 years old in men and 26 years old in women among patients with HeFH (9, 10). However, these cut-offs were estimated based on data obtained from adults, not younger patients. We also showed that the carotid plaque score (cPS) was a more useful marker than the carotid intima-media thickness (cIMT) for risk stratification of HeFH as well as non-FH among adults, as the cPS can reflect the overall carotid artery plaque burden (10, 11).
Accordingly, in the present study, we (1) compared the clinical utilities of cIMT and cPS and (2) estimated the onset and progression of carotid atherosclerosis among young HeFH patients (≤30 years old).

Figure 1. Study flow chart.

Materials and Methods

Study population

A total of 525 subjects ≤30 years old who underwent carotid ultrasound from April 2006 to March 2019 at Kanazawa University Hospital were retrospectively investigated. We excluded three patients with HoFH, nine with aortitis, and two with other types of vasculitis. Ultimately, 511 patients were included in this study (Fig. 1). Among them, we identified 78 with HeFH and 433 with non-FH who were typically suffering from other metabolic disorders, such as diabetes and obesity.

Our review of the baseline information included the medical history, physical examination findings, and blood test results. Most study subjects were inpatients who had been referred to the hospital, enabling the assessment of fasting blood samples.

Ethical considerations

This study was approved by the Ethics Committee of Kanazawa University (2019-263). All procedures were in accordance with the ethical standards of the institutional and national committees on human experimentation and complied with the 1975 Declaration of Helsinki, as revised in 2008.

Biochemical analyses

Biochemical analyses were performed using blood samples after overnight fasting. Serum levels of LDL-cholesterol, triglycerides, and high-density lipoprotein (HDL)-cholesterol were determined enzymatically using standard automated instrumentation in Kanazawa University Hospital. Serum lipid levels were obtained before the introduction of lipid-lowering therapies.

Clinical evaluations

The diagnosis of FH was determined according to the clinical criteria determined by the Japan Atherosclerosis Society 2017 for adults and pediatrics (12, 13). We defined hypertension as a systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or the use of antihypertensive medications. We defined diabetes using the clinical criteria determined by the Japan Diabetes Society (14).

Carotid ultrasound analyses

The parameters for carotid ultrasound were obtained using Apio carotid ultrasonography (Toshiba Medical Systems, Tokyo, Japan) with a standard 7.5-MHz transducer. Images were obtained by trained sonographers fully blinded to the clinical data. We determined the cIMT as described previously (15). In brief, the cIMT was determined as the average of three points of thickness in both common carotid arteries (CCA; three independent cIMT determinations were measured in the walls at the site of greatest thickness of each CCA, and these measurements were averaged and expressed as the mean cIMT). The cPS was determined as the sum of the max thickness of plaque (mm) thickening >1.1 mm per segment (S1-S4) on both sides [S1, region of the internal carotid artery (ICA) <15 mm distal to its bifurcation from the CCA; S2, region of the ICA and CCA <15 mm proximal to the bifurcation; S3, region of the CCA >15 mm and <30 mm proximal to the bifurcation; S4, region of the CCA >30 mm proximal to the bifurcation below the flow divider]. Carotid ultrasound data were obtained in the untreated state in all patients with FH, while some of the images in non-FH patients (8 of 433) were obtained after the introduction of lipid-lowering therapies.

Genetic analyses

Determinations of genetic backgrounds for the FH gene were performed by a specific panel-sequencing approach developed in-house. In brief, the LDL receptor, apolipoprotein B (APOB), and proprotein convertase subtilisin/kexin type 9 (PCSK9) were sequenced using a next-generation sequencer. The pathogenicity of the genetic variants was determined based on the American College of Medical Genetics and Genomics (ACMG) guideline (16, 17).

Statistical analyses

Continuous variables with a normal distribution were expressed as the mean±standard deviation (SD). Categorical variables were expressed as the number and percentage. Fisher’s exact or chi-square test was used where applicable. For values with a non-normal distribution, the median and interquartile range (IQR) were described. Mann-Whitney U tests were used to compare the cPS and cIMT between the FH and non-FH group. Linear regression models were used to evaluate the correlation between the age and cPS value among patients with HeFH. All statistical analyses were conducted using the R statistical software program. All p values <0.05 were considered to be statistically significant.
Table. Baseline Characteristics of Study Subjects.

| Characteristic                       | All (n=511) | HeFH (n=78) | Non-FH (n=433) | p value |
|--------------------------------------|-------------|-------------|----------------|---------|
| Age (years)                          | 23.1±6.0    | 21.4±5.9    | 23.4±6.0       | 0.006   |
| Men (%)                              | 274 (54)    | 40 (51)     | 234 (54)       | 0.744   |
| Obesity (body mass index ≥25 kg/m², %) | 113 (22)    | 3 (4)       | 109 (25)       | <0.001  |
| Hypertension (%)                     | 67 (13)     | 1 (1)       | 66 (15)        | 0.001   |
| Diabetes (%)                         | 87 (17)     | 1 (1)       | 86 (20)        | <0.001  |
| Dyslipidemia (%)                     | 172 (34)    | 78 (100)    | 94 (22)        | <0.001  |
| Total cholesterol (mg/dL)            | 213±76      | 329±73      | 190±51         | <0.001  |
| LDL-cholesterol (mg/dL)              | 139±74      | 257±68      | 113±44         | <0.001  |
| HDL-cholesterol (mg/dL)              | 52±17       | 57±15       | 51±17          | 0.013   |
| Triglycerides (mg/dL)                | 125 [64-147] | 89 [56-115] | 137 [68-157]   | 0.001   |
| Lipid-lowering therapy (%)           | 42 (8)      | 24 (30)     | 18 (4)         | <0.001  |
| Duration of lipid-lowering therapies (years) | 1.6 [1.0-2.4] | 1.5 [0.9-2.5] | 1.6 [1.0-2.4] | 0.32     |

FH: Familial hypercholesterolemia

Results

Characteristics of study subjects

The clinical characteristics of the study subjects are shown in Table. The mean age was 23.1 years old. There were significant differences between the HeFH and non-FH group in the age, obesity, hypertension, diabetes, dyslipidemia, serum lipid levels, and usage of lipid-lowering therapies (Table). We noted no significant difference in the gender proportions between the groups in the present study. Of note, the differences between these two groups, especially concerning the relatively high proportion of hypertension and diabetes in the non-FH group, were probably derived from the fact that these patients exhibited risk factors for atherosclerosis at relatively young ages, motivating them to undergo carotid ultrasound proactively. In contrast, almost no young HeFH patients exhibited such a risk, so they only underwent carotid ultrasound because they had been diagnosed with HeFH.

The comparison of cPS and cIMT between the HeFH and non-FH groups

First, we compared the median of “mean cIMT” between HeFH and non-FH. We found that there was no significant difference between these two groups (0.44 mm vs. 0.42 mm, p=0.122, Fig. 2A). However, the median cPS in the HeFH group was significantly larger than that in the non-FH group (1.11 vs. 0.26, p<0.001, Fig. 2B).

Development of cPS among FH patients

Finally, we evaluated the correlation coefficient between age and cPS in the HeFH group (Fig. 3). The regression equation was Y=-2.05+0.147X (r=0.37, p<0.001) in patients with HeFH. These results suggest that carotid atherosclerosis starts to develop on average at 14 years old in patients with HeFH.

Discussion

In this study, we (1) compared the clinical utilities of cIMT and cPS and (2) estimated the onset and progression of carotid atherosclerosis among patients with HeFH. We found that the assessment based on the cPS, rather than the cIMT, appears to be better for accurately capturing the progress of carotid atherosclerosis among young HeFH patients, and carotid atherosclerosis may start to develop as early as 14 years old in patients with HeFH.

Carotid plaque assessed with carotid ultrasound has proven a useful tool as a surrogate marker of systemic atherosclerosis (18). The burden of carotid plaque was shown to be significantly associated with the severity of systemic atherosclerosis (19). In fact, there are several parameters that can be obtained using carotid ultrasound, such as cIMT and cPS. Both of these parameters reflect the burden of carotid plaque. However, several studies, including our own, have suggested that cPS, which reflects the plaque burden throughout the carotid artery, may be a better surrogate marker than cIMT (11, 15, 20). In the present study, we extended these findings to young patients with FH (≤30 years old).

Identification and early intervention for patients with HeFH have been shown to be associated with a markedly better prognosis than delayed intervention (5-8). The current clinical guidelines suggest starting treatment at 10 years old (13). However, relatively few HeFH patients in their teens are currently being treated at our daily clinic for several reasons, including a lack of data on when their atherosclerosis actually started to develop. In fact, only 24 (30%) patients with FH in the present study were being treated, indicating that the administration of lipid-lowering therapies to younger generations is still uncommon, even for patients with FH in a real-world setting.

There are several strategies for assessing atherosclerosis in such patients, including coronary computed tomography and carotid ultrasound. Coronary computed tomography has
been useful not only for assessing coronary atherosclerosis itself but also for further risk stratification (21, 22). In contrast, carotid ultrasound can assess carotid atherosclerosis and is also useful for less-invasive risk stratification. At present, carotid ultrasound may be recommended over coronary computed tomography for young patients with HeFH, especially those in their teens (23). In the present study, we found that carotid plaque started to develop around 14 years old among HeFH patients. In addition, we know well that it is quite difficult to stem the progression of atherosclerotic plaque, even with aggressive LDL-lowering therapies (24). Accordingly, we need to keep in mind that LDL-lowering therapy for patients with FH should be started no later than the teen years. Furthermore, cPS may be better surrogate marker than cIMT for assessing atherosclerosis in these patients.

**Study limitations**

Several limitations associated with the present study warrant mention. First, it was a retrospective, cross-sectional, observational analysis. Second, this study investigated patients who underwent carotid ultrasound for any reason, which may have resulted in some bias. In Kanazawa University Hospital, most patients who underwent any type of surgery with any risk factors for systemic atherosclerosis, such as obesity, hypertension, diabetes, or dyslipidemia underwent a routine assessment of carotid ultrasound. This may have diluted the referred bias. Third, we were unable to assess the development of carotid atherosclerosis divided by gender because of our small sample size. However, the gender-based differences should be much smaller in this population than among older populations. Fourth, some of the patients were receiving lipid-lowering therapies at carotid ultrasound, which may have affected our results. However, the duration of lipid-lowering therapy administration was only a few years. In addition, the proportion of patients under lipid-lowering therapies was quite small. Therefore, the potential bias to our results was likely negligible.

In conclusion, making an assessment based on cPS appears to be better than one based on cIMT for capturing the progress of carotid atherosclerosis among young HeFH patients. Carotid atherosclerosis may start to develop at 14

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**Figure 2.** The comparison between the HeFH and non-FH groups. Purple indicates HeFH. Red indicates non-FH. (A) cIMT. (B) cPS.

**Figure 3.** The correlation between age and cPS among HeFH patients. The X-axis represents age. The Y-axis represents cPS.
years old in patients with HeFH.

Our study was approved by the Institutional Review Boards of Kanazawa University (2019-263). All patients provided their written informed consent before participating in the study.

The authors state that they have no Conflict of Interest (COI).

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