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Decrease in oxidized high-density lipoprotein is associated with slowed progression of coronary artery calcification: Subanalysis of a prospective multicenter study

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HIGHLIGHTS

- This study evaluated the role of oxidized HDL in the development of coronary artery calcification.
- The decrease in oxidized HDL after statin treatment was associated with attenuation of CAC progression.
- The findings in this study indicate that oxidized HDL may serve as a target for preventing atherosclerosis.

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ABSTRACT

Background and aims: Oxidized high-density lipoprotein (oxHDL) is characterized by reduced anti-inflammatory properties compared with HDL. However, the role of oxHDL in the pathogenesis of coronary artery calcification (CAC), a marker of subclinical atherosclerosis, remains unclear. We prospectively investigated the association between the change in oxHDL and progression of CAC in a substudy of a multicenter study.

Methods: In the principal study, patients with a CAC score of 1–999 were treated with pitavastatin with/without eicosapentaenoic acid. Measurement of CAC with multidetector-row computed tomography and a blood test were performed at baseline and at the 1-year follow-up. In the principal study, the increase in CAC did not differ among treatment groups. In this substudy, patients were divided into two groups: CAC progression (change in Agatston score of > 0) and no CAC progression.

Results: In total, 140 patients were analyzed. The oxHDL level significantly decreased from 167 (132–246) at baseline to 122 (103–149) after treatment (median [25th–75th percentile], U/ml) ($p < 0.001$). The annual change in CAC was significantly positively associated with changes in oxHDL ($r = 0.17$, $p = 0.04$), triglycerides ($r = 0.17$, $p = 0.04$), and high-sensitivity C-reactive protein ($r = 0.22$, $p = 0.01$) but was not associated with changes in low-density lipoprotein cholesterol or HDL-cholesterol. Multiple logistic analysis demonstrated that the decrease in oxHDL per 10 U/ml was independently associated with CAC progression (odds ratio, 0.95; 95% confidence interval, 0.90–0.99; $p = 0.04$).

Conclusions: The decrease in oxHDL is associated with the attenuation of CAC progression, suggesting that oxHDL is a potential target for atherosclerosis prevention.

1. Introduction

Coronary artery calcification (CAC), as quantified by computed tomography (CT), is closely correlated with overall atherosclerotic plaque formation and predicts incident cardiovascular disease (CVD) [1,2]. In addition, serial assessment of CAC has been used to monitor the progression of atherosclerosis and assess the effectiveness of medical therapies aimed at reducing cardiac risk [3]. We recently reported the

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results of a prospective multicenter study that examined the effects of intensive and standard pitavastatin treatment with or without eicosapentaenoic acid on the annual progression of CAC [4]. The principal study found that the progression of CAC in each patient group was not affected by the allocated treatments. Thus, determination of the factors involved in CAC progression is of great clinical interest.

As a residual cardiovascular risk factor, high-density lipoprotein cholesterol (HDL-C) is of great interest in lipid management. A lower HDL-C level is an independent risk factor for CVD [5]. However, previous clinical trials have shown that cholesteryl ester transfer protein inhibitors or high-dose niacin significantly increased HDL-C levels but failed to reduce cardiovascular events [6–8]. HDL can undergo a variety of modifications, including oxidation, making it dysfunctional and even proatherogenic [9]. Emerging evidence shows that the HDL-C efflux capacity is inversely associated with the prevalence of obstructive coronary artery disease [10] and the incidence of cardiovascular events [11]. The main component of HDL, apolipoprotein A-I (apoA-I), is very easily oxidized, resulting in selective inhibition of ABCA1-dependent cholesterol efflux from macrophages. We have developed an enzyme-linked immunosorbent assay system for measuring oxidized HDL (oxHDL) [12]. This assay showed that oxHDL is increased in diabetic patients [12] and is predictive of CVD outcomes in patients undergoing hemodialysis for chronic renal failure [13,14]. However, the association between CAC progression and oxHDL remains unknown.

In this subanalysis, we investigated the association between changes in the oxHDL level and the annual progression of CAC in patients with hypercholesterolemia who were undergoing statin therapy.

2. Materials and methods

2.1. Ethics

The principal study was a prospective, open-label, multicenter trial conducted from May 2010 to August 2011. That study was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and other hospitals. Written informed consent was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study is registered at the UMIN Clinical Trials Registry (UMIN000003171; Effect of pitavastatin and EPA on coronary artery calcification detected by computed tomography: PEACH study) (EPA, eicosapentaenoic acid).

2.2. Study protocol

The study design is shown in Supplemental Fig. 1. The principal study protocol has been described previously [4]. Patients were enrolled after eligibility evaluation, which included baseline multidetector row CT (MDCT) image acquisition, in each institution. Eligible participants were > 20-year-old patients with an Agatston score of 1–999, hypercholesterolemia, and no history of CVD. After taking pitavastatin at 2 mg/day for 2 months to check for tolerance, all participants were randomly allocated to the PIT2, PIT4, or PIT2 + EPA group (PIT2, pitavastatin at 2 mg/day; PIT4, pitavastatin at 4 mg/day; PIT2 + EPA, pitavastatin at 2 mg + eicosapentaenoic acid at 1800 mg/day). Baseline blood test data were obtained immediately before starting the allocated treatment. MDCT and blood tests were performed again at the 1-year follow-up [4].

Fig. 1 is a flow diagram of the study design. In the principal study, we enrolled 217 patients at 27 centers in Japan. Among them, 157 patients were included in the primary analysis. Seventeen patients were excluded because their stored blood samples were not available for measurement of the serum oxHDL level. Finally, 140 patients were included in this secondary analysis. The primary outcome of the substudy was the association between the change in the oxHDL concentration and the annual CAC progression (Agatston score).

The patients were divided into two groups according to the annual change in the Agatston score: patients in the CAC progression group had an annual change in the Agatston score of > 0, and patients in the CAC non-progression group had an annual change in the Agatston score of ≤0. We then examined the association between the annual change in the oxHDL level and the progression of CAC.

2.3. MDCT imaging and CAC analysis

MDCT imaging was performed in a standardized fashion as previously described [4]. MDCT images were documented in a Digital Imaging and Communications in Medicine format, which was sent to the core laboratory at L&L Company (Osaka, Japan) for blinded analysis. The CAC score was determined as described by Agatston et al. [15].

2.4. Risk factors and laboratory analyses

Data on demographics, smoking status, and medication were collected for each participant. Laboratory values including the total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), triglycerides, apoA-I, serum creatinine, and high-sensitivity C-reactive protein (hsCRP) levels were determined at an independent core laboratory (SRL Corp., Tokyo, Japan). Residual serum was separated and stored at −80 °C, and the serum concentration of oxHDL was measured using an enzyme-linked immunosorbent assay (Ikagaku Corp., Kyoto, Japan) as previously described [12]. Briefly, anti-human oxidized apoA-I monoclonal antibody solution was immobilized in each well of a 96-well microplate. After the addition of samples, the microplate was incubated for 1 h at room temperature. A biotinylated anti-human apoA-I monoclonal antibody was then added as a secondary antibody. Finally, after reaction with a peroxidase-labeled avidin conjugate, optical absorbance was measured. The intra- and inter-assay coefficients of variation of the oxHDL assay were 8.2% and 10.0%, respectively. The serum paraoxonase-1 (PON1) paraoxonase activity at baseline (n = 140) was measured using a colorimetric measurement method (Rel Assay Diagnostics, Gaziantep, Turkey), as previously described [16].

2.5. Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) as appropriate. Categorical variables are presented as frequency and proportion (%). Differences between any two groups were evaluated using the chi-square test for categorical variables and Student's t-test or the Mann–Whitney *U* test for continuous variables. Associations of variables were assessed by Pearson's correlation coefficient. The independent relationship between the decrease in oxHDL and CAC progression was assessed by multivariate logistic regression analysis, adjusting for variables at baseline with a p value of < 0.15 in the univariate analysis (baseline oxHDL, LDL-C, Agatston score, and current smoking). A p value < 0.05 was considered significant. All statistical analyses were performed using SPSS 27.0 for Windows (IBM, Armonk, NY, USA).

3. Results

3.1. Baseline patient characteristics

The baseline patient characteristics are summarized in Table 1. The mean age was 67 years, and 53% of patients were men. In terms of

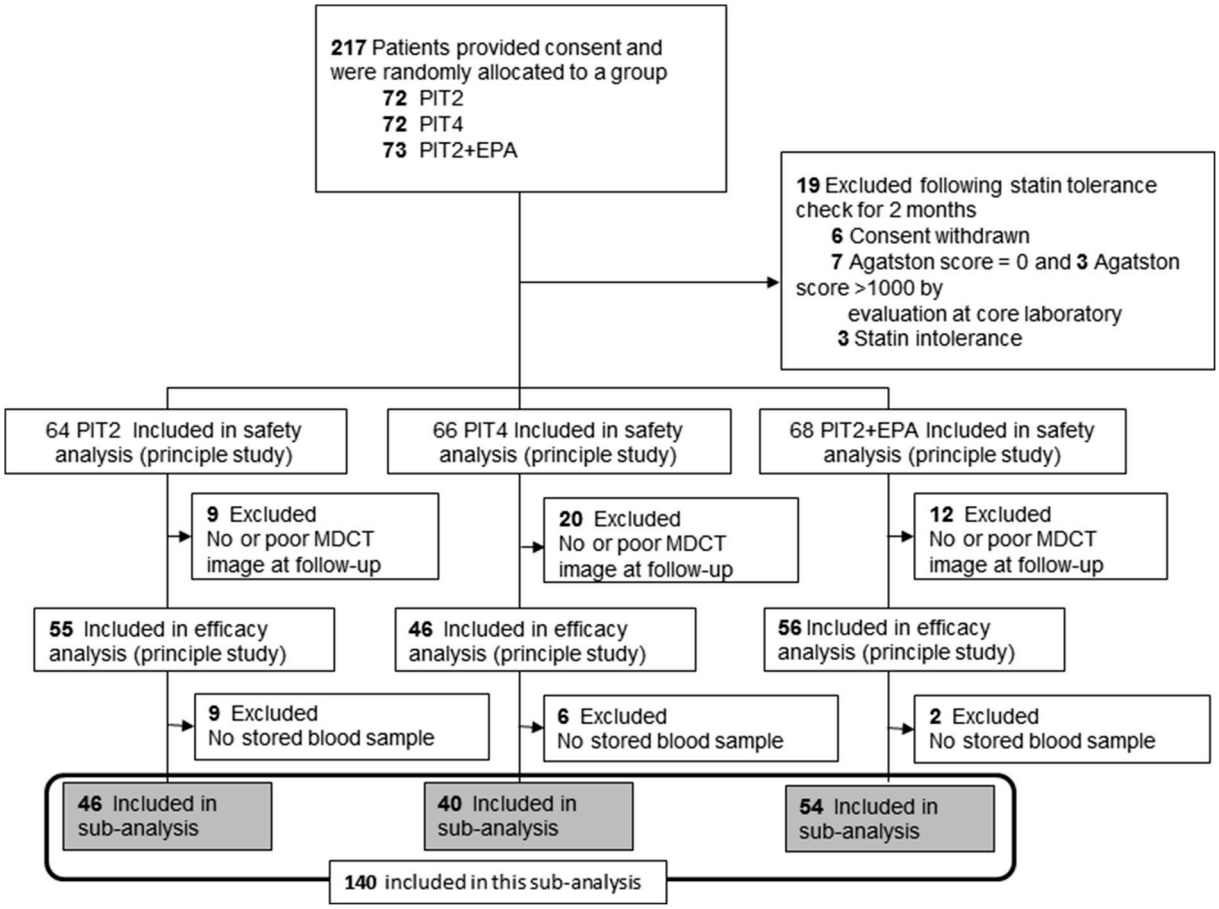

Fig. 1. Flow diagram of patients in this study.
EPA, eicosapentaenoic acid at 1800 mg/day; MDCT, multidetector row computed tomography; PIT2, pitavastatin at 2 mg/day; PIT4, pitavastatin at 4 mg/day.

comorbidities, 80% of patients had hypertension and 27% had diabetes mellitus. The median serum oxHDL concentration was 167 U/mL, and the median Agatston score was 92. The mean serum PON1 activity was 188.4 U/L.

The oxHDL levels in 30 normolipidemic healthy subjects (age, 30 ± 10 years; 60% men) were also measured (Supplemental Table 1). oxHDL levels were significantly lower in healthy subjects than in patients with hypercholesterolemia (150 [107–176] and 167 [132–246],

Table 1
Comparison of baseline characteristics between patients with and without CAC progression.

	All (n = 140)	Non-progression (n = 37)	Progression (n = 103)	*p*-value*
Age, years	67 ± 10	66 ± 9	67 ± 10	0.56
Male sex	74 (53)	20 (54)	54 (52)	0.87
Body mass index, kg/m^2	25.1 ± 4.0	25.9 ± 4.7	24.9 ± 3.8	0.18
Hypertension	111 (80)	30 (81)	81 (79)	0.61
Diabetes mellitus	38 (27)	8 (21)	30 (29)	0.42
Current smoking	20 (14)	8 (21)	12 (12)	0.13
Hemoglobin A1c, %	5.7 ± 0.7	5.7 ± 0.6	5.7 ± 0.7	0.83
Triglycerides, mg/dL	119 (89–168)	123 (92–168)	117 (85–168)	0.62
LDL-C, mg/dL	93.8 ± 24.5	101 ± 24	91 ± 24	0.03
HDL-C, mg/dL	55.6 ± 13.3	53 ± 12	56 ± 14	0.26
oxHDL, U/mL	167 (132–246)	185 (135–287)	165 (129–227)	0.10
oxHDL/apoA-I	1.15 (0.89–1.53)	1.37 (0.92–1.71)	1.11 (0.87–1.48)	0.06
Paraoxonase activity, U/L	188.4 ± 54.6	186.2 ± 56.6	189.0 ± 54.0	0.81
Serum creatinine, mg/dL	0.76 (0.67–0.89)	0.77 (0.69–0.86)	0.76 (0.64–0.90)	0.65
hsCRP, mg/L	0.53 (0.30–1.08)	0.54 (0.34–1.13)	0.53 (0.25–1.08)	0.69
Agatston score	92 (24–243)	58 (17–170)	114 (24–281)	0.02
Treatment with PIT2	46 (33)	14 (38)	32 (31)	0.45
Treatment with PIT4	40 (29)	9 (24)	31 (30)	0.51
Treatment with PIT2 + EPA	44 (31)	14 (38)	40 (39)	0.92

Data are presented as mean ± standard deviation, number (%), or median (25th–75th percentile), as appropriate.
LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; oxHDL, oxidized high-density lipoprotein; apoA-I, apolipoprotein A-I; hsCRP, high-sensitivity C-reactive protein; PIT2, pitavastatin at 2 mg/day; PIT4, pitavastatin at 4 mg/day; EPA, eicosapentaenoic acid.
*Comparison between non-progression and progression.

Table 2
Change in blood pressure, biochemical parameters, and CAC score from start of allocated treatment to 12-month follow-up.

	Overall	PIT2	PIT4	PIT2 + EPA	*p*-value
Systolic BP, mmHg	−3.4 (−6.4 to −0.5)	−1.7 (−6.7 to 3.4)	−7.2 (−12.6 to −1.7)	−2.1 (−7.0 to 2.7)	0.28
Diastolic BP, mmHg	−1.4 (−3.3 to 0.5)	0.2 (−3.0 to 3.5)	−2.7 (−6.3 to 0.8)	−1.9 (−5.0 to 1.2)	0.45
Total-cholesterol, mg/dL	−7.2 (−11.1 to −3.3)	−3.5 (−10.3 to 3.2)	−12.6 (−19.8 to −5.3)	−6.4 (−12.6 to −0.1)	0.20
LDL-C, mg/dL	−6.2 (−9.2 to −3.2)	−2.2 (−7.3 to 3.0)	−11.4 (−16.9 to −5.9)	−5.8 (−10.5 to −1.1)	0.054
HDL-C, mg/dL	−0.3 (−1.8 to 1.2)	0.4 (−2.1 to 3.0)	0.2 (−2.5 to 2.9)	−1.3 (−3.6 to 1.1)	0.57
Triglycerides, mg/dL	−8.2 (−26.7 to 10.3)	−3.7 (−36.0 to 28.5)	9.3 (−25.3 to 43.8)	−24.8 (−54.6 to 4.9)	0.32
oxHDL, U/mL	−67.3 (−84.1 to −50.4)	−53.6 (−83.1 to −24.2)	−75.4 (−107.0 to −43.8)	−72.8 (−100.0 to −45.6)	0.54
oxHDL/apoA-I	−0.44 (−0.55 to −0.33)	−0.40 (−0.58 to −0.21)	−0.49 (−0.69 to −0.29)	−0.44 (−0.62 to −0.27)	0.81
Hemoglobin A1c, %	−0.08 (−0.16 to 0.00)	−0.08 (−0.22 to 0.07)	−0.16 (−0.31 to −0.01)	−0.02 (−0.15 to 0.11)	0.38
hsCRP, mg/L	−0.23 (−0.88 to 0.42)	0.13 (−1.01 to 1.27)	−0.44 (−1.66 to 0.79)	−0.39 (−1.44 to 0.66)	0.75
CAC score, %	38.9 (22.5–55.4)	34.2 (5.4–63.1)	40.8 (9.8–71.7)	41.6 (14.9–68.2)	0.93

Data are presented as estimate (95% confidence interval).
PIT2, pitavastatin at 2 mg/day; PIT4, pitavastatin at 4 mg/day; EPA, eicosapentaenoic acid; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; oxHDL, oxidized high-density lipoprotein; apoA-I, apolipoprotein A-I; hsCRP, high-sensitivity C-reactive protein; CAC, coronary artery calcification.

respectively; median [25th–75th percentile], U/ml) ($p = 0.006$).

3.2. Association of oxHDL level with other parameters

The baseline log-transformed oxHDL level was correlated with total cholesterol (r = 0.21, $p = 0.01$), HDL-C (r = 0.33, $p < 0.01$), and log-transformed triglycerides (r = −0.21, $p = 0.01$). There were no significant correlations between the baseline oxHDL level and age, body mass index, hemoglobin A1c, LDL-C, serum creatinine, or hsCRP. The baseline PON1 paraoxonase activity was not correlated with the baseline log-transformed oxHDL (r = 0.13, $p = 0.12$) or the log-transformed oxHDL/apoA-I (r = 0.02, $p = 0.81$). The baseline log-transformed Agatston score was correlated with the oxHDL level at baseline (r = −0.17, $p = 0.04$), but the follow-up log-transformed Agatston score was not correlated with the oxHDL level at follow-up (r = −0.08, $p = 0.33$).

3.3. Change in blood pressure, biochemical parameters, and CAC score

Table 2 shows the mean annual change in oxHDL and other variables in each treatment group. In all three groups, the oxHDL level at follow-up was lower than that at baseline. Treatment with PIT4 and PIT2 + EPA slightly reduced oxHDL levels compared with PIT2 alone, but not significantly. The annual change in CAC score had a weak but significant correlation with the annual changes in oxHDL (r = 0.17, $p = 0.04$). The annual change in CAC score was also significantly correlated with triglycerides (r = 0.17, $p = 0.04$) and hsCRP (r = 0.22, $p = 0.01$), but was not significantly correlated with the annual changes in systolic blood pressure (r = −0.06, $p = 0.51$), LDL-C (r = 0.05, $p = 0.54$), HDL-C (r = 0.01, $p = 0.95$), or hemoglobin A1c (r = −0.14, $p = 0.164$).

3.4. Comparison of variables according to CAC progression

At the 1-year follow-up, 103 patients (74%) showed CAC progression. When baseline patient characteristics were compared between CAC progression and non-progression groups, the Agatston score was significantly lower in the CAC non-progression group (Table 1). Table 3 shows a comparison of the annual changes in variables between CAC progression and non-progression groups. The changes in oxHDL and oxHDL/apoA-I were significantly greater in the CAC non-progression group. No significant changes in the other variables were observed (Table 3).

3.5. Association between annual change in oxHDL and CAC progression

The univariate logistic regression analysis showed that the odds ratio (OR) per 10-U/mL annual decrease in the oxHDL level for CAC progression was statistically significant (OR: 0.96, 95% CI: 0.92–0.99, $p = 0.02$). The multivariate logistic regression analysis revealed that the annual decrease in oxHDL level was an independent determinant of CAC progression after adjusting for baseline oxHDL, LDL-C, Agatston score, and current smoking (OR: 0.95, 95% CI: 0.90–0.99, $p = 0.04$).

4. Discussion

The main finding of this study is that the decrease in oxHDL level was significantly associated with the attenuation of CAC progression in patients with hypercholesterolemia and undergoing statin therapy. To our knowledge, this is the first study to evaluate the association between change in oxHDL level and CAC progression.

CAC has been strongly established as an independent predictor of adverse events, with a significant incremental prognostic value over traditional risk stratification algorithms [1,2]. CAC progression has also been reported to be significantly associated with a higher rate of cardiovascular events [16–19]. A large observational study encompassing more than 20,000 participants demonstrated that an increase in CAC is associated with a 4- to 7-fold increase in cardiovascular events independent of baseline CAC score, cardiovascular risk factors, and demographic variables [17]. Furthermore, studies have demonstrated that progression of CAC is significantly associated with an increase in both calcified and noncalcified plaque volume, paralleling an increase in the atherosclerosis burden and cardiovascular risk [20]. Thus, an increasing CAC score is undoubtedly associated with increasing overall atherosclerosis and more cardiovascular events. This study showed that a decrease in oxHDL level was associated with attenuation of CAC progression. This finding suggests that oxHDL may be a potential target to slow the progression of atherosclerosis.

PON1 is considered to be the principal enzyme contained within HDL that is responsible for the antioxidant effect of HDL [20]. In the present study, the association between baseline PON1 activity and oxHDL concentration was evaluated to estimate the possible atheroprone mechanism of oxHDL. However, no significant association was found between them, even after adjustment of oxHDL by apoA-I. One reason for this lack of association is that the genetic polymorphism showed strong effects on PON1 activity [21]. In line with our results, Kresanov et al. [22] reported that PON1 activity was not associated with levels of oxHDL lipids in a population-based cross-sectional study

Table 3
Comparison of annual changes in variables among patients with and without CAC progression over 1 year.

	Non-progression (n = 37)	Progression (n = 103)	*p*-value
Systolic BP, mmHg	−7.3 (−12.9 to −1.7)	−2.0 (−5.4 to 1.5)	0.11
Diastolic BP, mmHg	−1.9 (−5.5 to 1.8)	−1.2 (−3.5 to 1.0)	0.77
Heart rate, bpm	−1.3 (−4.7 to 2.2)	−1.2 (−3.4 to 1.0)	0.96
Total cholesterol, mg/dL	−10.0 (−17.6 to −2.4)	−6.2 (−10.8 to −1.7)	0.40
Triglycerides, mg/dL	−8.3 (−44.4 to 27.8)	−8.1 (−29.7 to 13.5)	0.99
LDL-C, mg/dL	−9.3 (−15.1 to −3.5)	−5.1 (−8.6 to −1.6)	0.22
HDL-C, mg/dL	−0.6 (−3.4 to 2.3)	−0.2 (−1.9 to 1.5)	0.83
oxHDL, U/mL	−102 (−134 to −70)	−55 (−74 to −36)	0.015
oxHDL/apoA-1	−0.71 (−0.91 to −0.51)	−0.34 (−0.47 to −0.22)	0.003
Hemoglobin A1c, %	−0.04 (−0.21 to 0.12)	−0.09 (−0.18 to 0.00)	0.61
hsCRP, mg/L	−0.51 (−1.78 to 0.76)	−0.13 (−0.89 to 0.63)	0.62

Data are presented as estimate (95% confidence interval).
CAC, coronary artery calcification; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; oxHDL, oxidized high-density lipoprotein; apoA-I, apolipoprotein A-I; hsCRP, high-sensitivity C-reactive protein.

of 1895 Finnish adults. Furthermore, PON1 was shown to regulate HDL-mediated cholesterol efflux from macrophages [23]. However, we could not evaluate this efflux property in oxHDL in the present study. Future studies are needed to clarify the mechanistic roles of oxHDL in atherosclerosis progression.

Calcification is a common feature of atherosclerotic lesions. This study demonstrated the association between change in oxHDL and CAC progression; however, whether oxHDL is a causal factor involved in CAC progression remains unclear. HDL plays a role in regulating calcification of vascular cells [24–26]. HDL protecedt against vascular calcification by regulating the osteoblastic differentiation and osteogenic activity of vascular smooth muscle cells induced by inflammatory cytokines such as interleukin-1β [24]. Furthermore, oxidation of HDL enhanced osteogenic activity in calcifying vascular cells. HDL is considered to be susceptible to conversion from an anti-atherogenic to pro-atherogenic state. Sharma et al. [27] reported that oxHDL induces proinflammatory effects on monocytes, including an increase in their binding to aortic endothelial cells. Thus, HDL regulates vascular calcification through direct and indirect manners. However, there is a possibility that the change in oxHDL was reflected by the change in chronic inflammation or systemic oxidative stress, which regulates CAC progression. All patients in this study were treated with pitavastatin, which reportedly reduces inflammatory markers in patients with dyslipidemia. Thus, the change in the inflammatory status by pitavastatin treatment may affect CAC progression. Specific intervention to reduce oxHDL is needed in a future study to clarify the causal relationship between oxHDL and CAC progression [28].

In this study, oxHDL at follow-up decreased from baseline in all three groups without a reduction of the HDL-C level. This led to an improvement in the balance between oxHDL and HDL, which is beneficial for protection against atherosclerosis progression. A previous study involving patients with dyslipidemia showed that higher-dose statin therapy reduced oxidative stress markers more than lower-dose statin therapy [29]. Another study involving patients with coronary artery disease showed that treatment with EPA plus a statin reduced oxidative stress more than treatment with a statin alone [30]. Accordingly, statin therapy and a combination of statin + EPA therapy potentially reduce oxHDL levels independent of HDL levels, suggesting that these medications improve dysfunctional HDL. Future studies are required to identify a medical therapy that reduces oxHDL, leading to an improvement in the anti-atherosclerotic function of HDL.

This study has several limitations. First, because the study included only patients with hypercholesterolemia undergoing statin therapy, the results cannot be applied to the general population. Second, although the Agatston score is an excellent surrogate marker for the prediction of CVD, we only analyzed CAC progression as the endpoint, not actual CVD events. Therefore, we cannot conclude that there is an association between the increase in oxHDL and CVD events. Third, data on coronary CT angiography were not available in this study; thus, changes in plaque volumes and morphology could not be evaluated.

In conclusion, this study demonstrated that a reduction in the oxHDL level is significantly associated with the attenuation of CAC progression in patients with hypercholesterolemia and undergoing statin therapy. Further studies are required to identify the best method with which to improve HDL function for protection against the development of atherosclerosis.

Conflicts of interest

HI received honoraria from Kowa Pharmaceutical Co. and Mochida Pharmaceutical Co. The other authors have no conflicts of interest to disclose.

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Author contributions

K Kohno, T Miyoshi, KN, and HI were involved in the conception, design, or planning of the study. T Miki, K Kotani, SS, YK, and HI were involved in the acquisition of data. T Miki and T Miyoshi were involved in the analysis of data. K Kotani, T Miyoshi, and HI were involved in the interpretation of results. T Miki, T Miyoshi, and HI substantially contributed to drafting of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.01.032.

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