Coronary Plaque Regression and Lifestyle Modification in Patients Treated With Pravastatin

– Assessment Mainly by Daily Aerobic Exercise and an Increase in the Serum Level of High-Density Lipoprotein Cholesterol –

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Background: The purpose of this study was to explore the effect of lifestyle modification, mainly daily aerobic exercise, on coronary atherosclerosis in patients with coronary artery disease (CAD).

Methods and Results: A 6-month prospective observational study was conducted with 84 CAD patients receiving pravastatin treatment in order to evaluate the relationship between lifestyle modification, in particular aerobic exercise, and plaque volume as assessed by intravascular ultrasound (IVUS). Lifestyle during the study period was assessed by the lifestyle modification score. A significant decrease in plaque volume by 12.9% was observed after 6 months of pravastatin therapy ($P < 0.0001$ vs baseline). The change in plaque volume correlated with the change in the serum level of high-density lipoprotein cholesterol (HDL-C) ($r = -0.549$, $P < 0.0001$), non-HDL-C ($r = 0.248$, $P = 0.03$), low-density lipoprotein cholesterol/HDL-C ($r = 0.505$, $P < 0.0001$), apolipoprotein (apo) A-1 ($r = -0.335$, $P = 0.007$) and apoB/apoA-1 ($r = 0.335$, $P = 0.007$), and lifestyle modification score ($r = -0.616$, $P < 0.0001$). There was a clear positive correlation between a change in the serum HDL-C level and lifestyle modification score. Multivariate regression analysis revealed that the increase in serum HDL-C level and lifestyle modification score were independent predictors of coronary plaque regression.

Conclusions: An appropriate combination of statin therapy and lifestyle modification, in particular, physical activity, may result in coronary plaque regression. This combined treatment strategy, inducing an increase of the serum HDL-C, may contribute to coronary plaque regression. (*Circ J* 2010; **74**: 954–961)

Key Words: Atherosclerosis; Coronary artery disease; Lifestyle; Lipids; Statins

Several clinical trials have shown that lifestyle modifications can slow the progression of coronary atherosclerosis, and thereby reduce the incidence of cardiovascular events.^{1–3} Furthermore, epidemiological studies combined with studies providing biological plausibility have provided conclusive evidence that physical activity reduces the incidence of coronary artery disease (CAD). Thus, physical activity, but in particular, daily aerobic exercise, is recommended as a key lifestyle factor for the prevention and treatment of CAD.^{4,5}

However, little is known about how lifestyle modifications, particularly increased physical activity, might influence coronary atherosclerosis regression in patients with CAD on

treatment with a statin. The aim of this prospective observational study was to explore the association between lifestyle modification (daily aerobic exercise) and delay in the progression of coronary atherosclerosis, as assessed by changes in coronary plaque volume, in CAD patients on treatment with a statin (pravastatin).

Methods

This study was conducted as a prospective, single-center, observational study. CAD patients who had undergone percutaneous coronary intervention (PCI) following intravascular ultrasound (IVUS) examination between July 2006,

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and December 2008 were enrolled in the study. Coronary plaque volume was assessed by volumetric analysis using 3-dimensional (3D) IVUS at baseline and after 6 months' intervention. Immediately after the first IVUS examination, pravastatin therapy was initiated at the starting dose of 10 or 20mg in patients with serum levels of low-density lipoprotein cholesterol (LDL-C) <140mg/dl and ≥140mg/dl, respectively. Subsequently, the dose of pravastatin was adjusted to maintain the serum LDL-C level at <100mg/dl throughout the course of study.

Subjects were asked to attend a 1-h lecture on lifestyle modification delivered by physicians using the same teaching materials. All the patients received dietary counseling and advice on lifestyle modification, including smoking cessation, weight management (subjects with a body mass index (BMI) >25 were instructed to lose weight based on a BMI goal, with 22 set as the target BMI), cultivation of the exercise habit (minimum 30–60min of physical activity, such as walking, cycling or other aerobic activity, preferably daily, or at least 3 or 4 times weekly), supplemented by an increase in daily lifestyle activities.⁵

Assessment of Lifestyle Modification

To evaluate lifestyle modification, in particular, the frequency of daily aerobic exercise, during the 6-month study period after the first IVUS examination, the lifestyle modification score was calculated using a questionnaire. The scoring for the subscale of exercise habit in this questionnaire was as follows: mean frequency of aerobic exercise per week (6=6 times or more; 5=5 times; 4=4 times; 3=3 times; 2=2 times; 1=once). The total lifestyle modification score was calculated by adding the scores for the following lifestyle factors: (1) weight management (0=not within desirable BMI range; 1=within desirable BMI range) and (2) smoking history (1=no history of smoking in the previous 12 months or smoking cessation within the previous 6 months; 0=failed to quit smoking within the previous 6 months).

Study Population

A total of 152 patients were screened, and 102 patients were finally enrolled; all of the enrolled patients had acceptable baseline IVUS findings and were on treatment with pravastatin. Of the 18 patients who were withdrawn from the study, 8 developed adverse events (myalgia in 2 and liver dysfunction in 2) and 10 were excluded because the final IVUS examination results could not be obtained. Finally, a total of 84 patients who had IVUS examinations at both baseline and after 6 months of treatment available for evaluation were included for the analysis.

Subject inclusion in the study required demonstration of at least 1 obstruction with more than 25% narrowing of the angiographic luminal diameter in the PCI-treated coronary vessel. The exclusion criteria were acute myocardial infarction within 3 weeks after of the symptom, narrowing of the left main coronary artery (luminal diameter ≥50%), left ventricular ejection fraction <40%, hepatic or renal dysfunction (creatinine ≥1.5mg/dl, alanine aminotransferase and aspartate aminotransferase ≥twice the upper limits of normal), inflammatory diseases, known malignant disease, or history of use of any lipid-lowering drugs. The study was approved by the institutional ethics committee.

IVUS Study

After PCI, the IVUS examinations were carried out using a CVIS system (Atlantis SR Plus 40MHz; Boston Scientific,

Maple Grove, MN, USA). Prior to the IVUS examination, arterial blood pressure was measured and isosorbide dinitrate (1–2mg) was administered directly into the coronary artery. A guidewire was then inserted as far as possible into the PCI-treated artery, followed by insertion of the IVUS catheter. The location of the transducer was checked fluoroscopically, and images taken inside the coronary artery at the rate of 0.5mm/s with a motorized pullback device were recorded on S-VHS tape.

The plaque area was defined as the difference between the cross-sectional vessel area (the area lined by the tunica media and inner layers) and the cross-sectional lumen area (the area lined by the innermost layer of the tunica intima). The "online" mode was selected and the inter-frame distance of the IVUS was set at 0.1mm. Images from the S-VHS videotape were then fed in. Subsequently, the 3D images obtained at baseline and those obtained after 6 months' intervention were displayed in parallel on a computer screen, in the "offline" mode, to determine the sites of measurement. Using a Netra 3D IVUS system (ScImage, Los Altos, CA, USA), the cross-sectional vessel, luminal and plaque areas were measured. These 3 areas were separately totaled to yield the respective volumes. The sites of measurement with IVUS were selected from side branch to side branch of the coronary artery. To minimize the influence of PCI, only lesions at least 10mm away from the PCI site were selected for the measurements.⁶

The primary efficacy parameter of the percent plaque volume was calculated using the following equation: $\Delta \text{plaque volume} = (\text{plaque volume at 6 months} - \text{baseline plaque volume}) / \text{baseline plaque volume} \times 100$. Two independent investigators who were unaware of the patients' clinical data were responsible for measuring all the vessel parameters. An analysis of the intraobserver and interobserver variability of the measurements showed high reproducibility ($r=0.94-0.97$; $r=0.92-0.96$, respectively).⁶

Measurement of Laboratory Parameters

Serum fasting blood samples were collected in the morning before the angiographic examinations. The serum levels of total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured enzymatically in an automatic analyzer (Hitachi 7080, Tokyo, Japan), with the requisite reagents procured from Wako Pure Chemical Industries (Osaka, Japan). The serum non-HDL-C level was calculated as serum TC–serum HDL-C. Serum apolipoprotein (apo) and Lp(a) levels were determined by turbidimetric latex agglutination assays.

Statistical Analysis

Data were expressed as mean ± standard deviation for continuous variables and as percentages for discrete variables. A paired t-test was used to compare the changes in the variables from the baseline to the examination conducted 6 months later. Because the data for the serum TG level and vessel parameters did not show a normal distribution, they are expressed as medians (25th and 75th percentiles), and Wilcoxon's signed rank test was used to compare the differences in TG level and the vessel parameters between the baseline and the examination conducted 6 months later. Spearman's rank correlation was used to describe the association between the lifestyle modification scores and the changes in the serum lipid levels.

Univariate and multivariate regression analyses were performed to identify independent predictors of the regression

Table 1. Patients' Characteristics

	N=84
M/F, n (%)	71 (84)/13 (16)
Age, years	63±10
Risk factors, n (%)	
Hypertension	58 (69)
Diabetes mellitus	23 (27)
Smoking history (never/current/quit)	15 (18)/54 (64)/15 (18)
Body mass index (kg/m ²)	24±3
Diseased vessels, n (%)	
SVD/DVD/TVD	48 (57)/31 (37)/5 (6)
Target plaque location, n (%)	
LAD/LCX/RCA	43 (51)/9 (11)/32 (38)
Analysed segment, n (%)	
Proximal to the intervention site	54 (64)
Distal to the intervention site	30 (36)
Coronary artery intervention, n (%)	
Balloon angioplasty/stent	17 (20)/67 (80)
Concomitant medication, n (%)	
Aspirin	84 (100)
ACEI	23 (27)
Angiotensin II receptor blockers	18 (22)
Calcium-channel blockers	34 (41)
β-blockers	33 (39)
Nitrates	29 (35)
LVEF (%)	60±14

SVD, single vessel disease; DVD, double vessel disease; TVD, triple vessel disease; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; ACEI, angiotensin-converting enzyme inhibitor; LVEF, left ventricular ejection fraction.

of coronary atherosclerosis. Of the independent variables, age, sex, presence/absence of hypertension, presence/absence of diabetes mellitus, smoking status of the patient, concomitant medications, the serum levels of lipids and apolipoproteins at the baseline and 6 months later, the percent changes in these parameters after 6 months' treatment, and lifestyle modification score were treated. All variables related to the change in coronary plaque volume with $P<0.05$ in a univariate regression analysis were entered into the multivariate model. A P -value <0.05 was considered to be statistically significant. All statistical analyses were performed with the

SPSS software (SPSS Inc, Chicago, IL, USA) for Windows (version 12.0.1).

Results

No serious adverse reactions to pravastatin or other drugs were observed in any of the patients, and no coronary events occurred during the study period. Mean pravastatin dose was 12.5 ± 3.2 mg/day. The patient characteristics are shown in **Table 1**.

Effects of Lifestyle Modification

The frequency of daily exercise of the patients was as follows: 0 times a week, 6 patients (7.1%); once a week, 5 patients (6.0%); twice a week, 9 patients (10.7%); 3 times a week, 10 patients (11.9%); 4 times a week, 34 patients (40.5%); 5 times a week, 9 patients (10.7%); 6 times a week or more, 11 patients (13.1%). There were 54 patients (64%) who were smokers before the start of the study, and 49 of them succeeded in quitting smoking during the study period. Overall, the patients showed a change in the BMI from 23.8 ± 3.0 kg/m² to 23.7 ± 3.0 kg/m², although the difference was not significant ($P=0.38$); on the other hand, patients with a BMI of 25 kg/m² or higher showed a change from 26.7 ± 1.9 kg/m² to 24.8 ± 2.0 kg/m², which represented a significant decrease ($P<0.05$). The lifestyle modification scores were as follows: 0, 3 patients (3.6%); 1, 7 patients (8.3%); 2, 8 patients (9.5%); 3, 9 patients (10.7%); 4, 13 patients (15.5%); 5, 14 patients (16.7%); 6, 13 patients (15.5%); 7, 6 patients (7.1%); 8, 11 patients (13.1%).

Laboratory Profiles

Significant decreases in the serum levels of TC, LDL-C and non-HDL-C by $-7.3\pm18.4\%$, $-11.3\pm26.9\%$, and $-12.1\pm22.2\%$, respectively, occurred (all $P<0.0001$ vs baseline value, respectively) in the study subjects during the study period. The serum HDL-C level was significantly increased by 4.81 ± 11.2 mg/dl ($13.8\pm28.4\%$, $P<0.001$ vs baseline value) after 6 months of treatment. The serum LDL-C:HDL-C ratio was also significantly decreased by $-17.7\pm29.9\%$ during the treatment period ($P<0.0001$ vs baseline value). There were no significant changes in the serum levels of TG. The serum level of apoA-1 was significantly increased by $14.0\pm18.3\%$ ($P<0.0001$ vs baseline value), while the serum levels of Lp(a) and apoB and the apoB/apoA-1 ratio were significantly decreased by -21.4 ($-42.5/3.6$), $-6.4\pm20.1\%$, and $-14.6\pm19.3\%$ ($P=0.001$, 0.001 , and <0.0001 vs baseline value,

Table 2. Changes in Laboratory Profiles

Parameters	Baseline	6 months	Δ	P value compared with baseline
TC (mg/dl)	204±39	185±29	-7.3±18.4	<0.0001
LDL-C (mg/dl)	130±38	103±26	-11.3±26.9	<0.0001
HDL-C (mg/dl)	47±11	53±13	13.8±28.4	<0.001
TG (mg/dl)*	124 (90/194)	118 (86/176)	-7.1 (-30/29)	0.493
Non-HDL-C (mg/dl)	164±36	131±24	-12.1±22.2	<0.0001
LDL-C/HDL-C	2.86±0.88	2.09±0.81	17.7±29.9	<0.0001
Lp(a) (mg/dl)*	13.0 (8.3/26.8)	12.0 (6.0/24.0)	-21.4 (-42.5/3.6)	0.001
ApoA-1 (mg/dl)	122±18	135±20	14.0±18.3	<0.0001
ApoB (mg/dl)	96±18	88±15	-6.4±20.1	0.001
ApoB/apoA-1	0.81±0.19	0.67±0.15	-14.6±19.3	<0.0001

*Data expressed as medians (25th and 75th percentiles), and Wilcoxon's signed rank test was used.

Δ, percent change from baseline; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; Lp(a), lipoprotein (a); apo, apolipoprotein.

Figure 1. Relationship between the lifestyle modification score and changes in the serum lipid levels. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Figure 2. Changes in the vessel parameters. Horizontal lines represent 75th, median, and 25th percentiles values. The circles represent individual data out of the 75th–25th percentile range.

respectively) (Table 2).

As shown in Figure 1, the lifestyle modification score correlated with the changes in the serum HDL-C level, but not with the changes in the serum levels of LDL-C, TG and non-HDL-C.

Volumetric Analyses of the IVUS Parameters

The average lesion length was 6.35 ± 3.58 mm. The plaque

volume was significantly reduced by $12.6 \pm 20.2\%$, from 38.5 mm^3 ($22.7\text{--}66.3 \text{ mm}^3$) at baseline to 33.5 mm^3 ($19.8\text{--}58.2 \text{ mm}^3$) at the 6-month follow-up examination (vs baseline value, $P < 0.0001$). The percent plaque volume was also significantly reduced from $44.9 \pm 12.3\%$ at baseline to $38.8 \pm 12.3\%$ at the 6-month follow-up examination ($P < 0.0001$). The lumen volume was significantly increased by $9.9 \pm 22.3\%$, from 43.6 mm^3 ($27.3\text{--}68.8 \text{ mm}^3$) at baseline to 50.2 mm^3

Table 3. Univariate Regression Analysis to Determine the Predictors of Coronary Plaque Regression

	Baseline		6 months		Δ	
	r	P value	r	P value	r	P value
Age	-0.04	0.77				
Sex	0.08	0.50				
Diabetes mellitus	0.01	0.92				
Hypertension	-0.06	0.60				
Smoking	-0.03	0.83				
ACEI	0.10	0.41				
Angiotensin II receptor blocker	0.07	0.57				
Calcium-channel blocker	-0.08	0.50				
TC	-0.07	0.55	-0.03	0.82	0.01	0.99
LDL-C	-0.02	0.89	0.08	0.45	0.02	0.90
HDL-C	0.13	0.26	-0.37	0.001	-0.55	<0.0001
Log TG	-0.02	0.87	0.12	0.31	0.07	0.69
Non-HDL-C	-0.11	0.34	0.14	0.22	0.10	0.40
LDL-C/HDL-C	-0.01	0.40	0.38	0.001	0.43	<0.0001
Log Lp(a)	-0.19	0.14	-0.03	0.83	-0.17	0.56
ApoA-1	0.02	0.90	-0.35	<0.01	-0.36	<0.01
ApoB	-0.07	0.60	0.018	0.88	0.11	0.40
ApoB/apoA-1	-0.06	0.62	0.245	0.03	0.22	0.07
Lifestyle modification score	-0.62	<0.0001				

Abbreviations see in Tables 1,2.

Table 4. Multivariate Regression Analyses to Determine the Predictors of Coronary Plaque Regression

Parameter	β (SE)	95%CI	P value
Model 1			
6m HDL-C	0.05 (0.003)	-0.01/0.01	0.82
6m LDL-C/HDL-C	0.09 (0.05)	-0.08/0.12	0.66
6m apoA-1	-0.14 (0.002)	-0.01/0.003	0.50
6m apoB/apoA-1	-0.02 (0.22)	-0.48/0.42	0.89
Δ HDL-C	-0.35 (0.10)	-0.44/0.03	0.02
Δ LDL-C/HDL-C	0.22 (0.10)	-0.04/0.35	0.11
Δ apoA-1	-0.10 (0.14)	-0.39/0.18	0.47
Model 2			
6m HDL-C	0.05 (0.003)	-0.01/0.01	0.81
6m LDL-C/HDL-C	0.05 (0.05)	-0.08/0.11	0.81
6m apoA-1	0.05 (0.002)	-0.004/0.004	0.82
6m apoB/apoA-1	0.02 (0.22)	-0.41/0.46	0.90
Lifestyle modification score	-0.48 (0.01)	-0.07/-0.02	0.002
Δ LDL-C/HDL-C	0.17 (0.09)	-0.07/0.31	0.20
Δ apoA-1	-0.09 (0.13)	-0.37/0.17	0.47

SE, standard error; CI, confidence interval. Other abbreviations see in Table 2.

In model 1: Lifestyle modification score was excluded from the independent variables because of multicollinearity with Δ HDL-C; Multiple R, 0.63; $P<0.0001$; F, 5.31.

In model 2: Δ HDL-C was excluded from the independent variables because of multicollinearity with the lifestyle modification score; Multiple R, 0.67; $P<0.0001$; F, 6.41.

(31.9–73.32 mm³) at the 6-month follow-up examination (vs baseline value, $P=0.005$). The change in the total vessel volume from 88.5 mm³ (53.9–134.6 mm³) at baseline to 89.7 mm³ (56.6–118.0 mm³) at the 6-month follow-up examination was not statistically significant (vs baseline value, $P=0.29$) (Figure 2). The baseline percentage plaque volume did not correlate with the change in plaque volume ($r=0.035$, $P=0.79$), indicating that the baseline percentage plaque volume does not affect the degree of regression of atherosclerosis.

Univariate and Multivariate Regression Analyses for Identifying the Predictors of Coronary Plaque Regression

Based on the determination of their significance in the univariate regression analysis (Table 3), 8 variables were entered into a multivariate regression analysis model. As shown in Table 4, 2 multivariate regression analyses models were used, because both the lifestyle modification score and Δ HDL-C showed multicollinearity. The results of the multivariate regression analysis demonstrated that the Δ HDL-C was an independent predictor of the change in coronary plaque volume (Model 1). Furthermore, after replacing Δ HDL-C,

which strongly correlated with the lifestyle modification score, multivariate analysis identified the lifestyle modification score as an independent predictor of attenuation of coronary plaque progression (Model 2). Thus, lifestyle modification, in particular, daily aerobic exercise and an increase in the serum HDL-C level remained significantly associated with coronary plaque regression in pravastatin-treated patients with CAD.

Discussion

Although numerous factors have been reported to attenuate the progression of atherosclerosis, actual regression achieved by an increase in the serum HDL-C level induced by a combination of statin treatment and lifestyle modification, mainly daily aerobic exercise, may provide new insight into the prevention of progression of coronary atherosclerosis in patients with CAD.

In recent years, aggressive lipid-lowering by intensive statin therapy to obtain target LDL-C levels of 60–70 mg/dl^{7,8} has been shown to delay progression or even induce regression of coronary atherosclerosis. Such a therapeutic effect suggests a close relationship between a decrease in the serum LDL-C level and suppression of coronary plaque formation. The observed absence of a correlation between changes in the serum LDL-C level and changes in coronary plaque volume in our study may be explained by the low baseline LDL-C level and low rate of decrease of the serum LDL-C in our subjects. In the Japanese studies, however, the dosage of statins has exceeded the maximal approved dose.⁹ Therefore, pursuing alternative methods of suppressing coronary plaque progression are extremely important for the optimal care of patients with CAD. Even with modest LDL-C lowering to maintain the serum LDL-C level at only 100 mg/dl, we demonstrated a reduction in coronary plaque volume can be achieved by an elevation of the serum HDL-C level.

Both basic science studies and clinical investigations support the existence of an inverse relationship between serum HDL-C level and the rate of progression of atherosclerosis.¹⁰ It is of importance to note, however, that increasing the serum HDL-C level by pharmacological therapies, such as hormone replacement therapy and fibrates, has not consistently yielded clinical benefit in either angiographic or event trials.^{11–15} Accordingly, in recent years pharmacological interventions designed to elevate the serum HDL-C level by the administration of cholesteryl ester transfer protein inhibitors or reconstituted HDL-C have been tested for their effects in suppressing coronary plaque progression as assessed by IVUS. Although producing marked elevation of the serum HDL-C level, as expected, the aforementioned interventions failed to suppress coronary plaque progression.^{16,17}

It has also been considered that besides increasing the serum HDL-C level and decreasing the serum LDL-C level, statins may also exert numerous pleiotropic effects that might contribute to their antiatherosclerotic action, such as anti-inflammatory effects, antithrombotic effects, and attenuating endothelial dysfunction.¹⁸ The failure of agents that substantially increase the serum HDL-C level to attenuate the progression of atherosclerosis might suggest that the functions of HDL are a more appropriate target than the serum level itself.¹⁹

Based on the suggestion of involvement of an elevation in the serum HDL-C level in the effects of statins of suppressing coronary plaque progression, the effects of statins on the serum level of HDL-C have become a focus of research

interest. In a pooled analysis of 4 trials of statins, individuals with a $\geq 7.5\%$ increase in serum HDL-C levels showed statistically significant regression of coronary atherosclerosis, independent of the serum LDL-C level.²⁰ In a post hoc analysis in the “Treating to New Targets” study,²¹ the serum HDL-C levels were inversely related to the risk of cardiovascular events during statin treatment, even among patients with serum LDL-C levels < 70 mg/dl. Thus, changes in the serum HDL-C level appear to be a predictor of atherosclerotic cardiovascular risk, independent of the serum LDL-C level. These observations may strongly support our present results.

There is an important therapeutic lifestyle modification that can be instituted to raise the serum levels of HDL-C. Aerobic exercise has been reported to elevate the serum HDL-C level by 5–10%, with the increase related to the frequency and intensity of exercise.²² The mechanism by which exercise increases the serum HDL-C level is not yet fully understood, but the effect has been attributed to an elevation in the levels of lipoprotein lipase.²³ In general, the effect of statins in raising the serum HDL-C level is known to be modest (5–15%).²⁴ All of the above-described research observations indicate that reasonable elevations of the serum HDL-C level may be obtained by the addition of aggressive lifestyle interventions to statin therapy.

Despite the dramatic reductions in the cardiovascular risk with LDL-C lowering therapy, the residual cardiovascular risk still remains significant.²⁴ Therefore, intensive lifestyle interventions to raise the serum HDL-C level may serve as an additional strategy for addressing the residual cardiovascular risk in CAD patients with already elevated serum HDL-C and lowered serum LDL-C levels achieved with statin therapy. Evidently, the addition of intensive lifestyle modification to statin therapy for suppressing coronary plaque development not only has a synergistic effect in improving lipid metabolism, but also other antiarteriosclerotic effects.²⁵ Some reports have shown that aggressive lifestyle modification, including therapeutic exercise, may have beneficial effects independent of the effects on lipid metabolism in suppressing coronary arteriosclerosis.^{1,2,5,26}

Study Limitations

Because the effects of lifestyle modification are multifactorial (including, besides improvement of the serum lipid profile, improvement of serum insulin resistance, improvement of glucose tolerance, antihypertensive effect, etc) and the study sample size was limited, we cannot specify the interaction between coronary atherosclerotic regression and singular lifestyle factors. Furthermore, it is unknown which characteristic(s) of exercise (duration, intensity and frequency) may be involved in the elevation of the serum HDL-C level or coronary plaque regression. The frequency of daily aerobic exercise recorded in the study was based on the results of self-reported questionnaires. For strict evaluation of aerobic exercise, however, objective indicators (heart rate, METs, $\dot{V}O_{2\max}$ evaluation etc) may be required. Finally, from a viewpoint of lifestyle improvement, no evaluation of alcohol intake was performed in this study, despite its effect on increasing the serum level of HDL-C, because excessive intake of alcohol may possibly disturb lifestyle.

Clinical Implications

Because a significant reduction in risk of CAD might be achieved by a small improvement in the lipid profile of Japanese patients,⁹ the response of coronary atherosclerosis

to statin treatment in Japanese and Western subjects might differ markedly. There seems to be an urgent need to gather evidence regarding the effects of statins on the regression of coronary atherosclerosis in Japanese patients who are highly sensitive to statins.^{6,27-34}

An interventional study of statin therapy and lifestyle modification, in particular, vigorous physical activity conducted with the objective of inhibiting coronary atherosclerosis progression, may be necessary to verify the results of this study.

Conclusions

The results of the present study suggest that a combination of moderate lipid-lowering therapy and increased physical activity may play an important role in coronary plaque regression. Both components of the combined treatment strategy inducing an increase in the serum HDL-C level may contribute to the regression of coronary atherosclerosis.

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