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Atorvastatin lowers plasma low-density lipoprotein cholesterol and C-reactive protein in Japanese type 2 diabetic patients

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Abstract

We investigated the meaning and the worth of lowering low-density lipoprotein cholesterol (LDL-C) to less than 100 mg/dL in Japanese type 2 diabetic patients using atorvastatin. As a multicenter open-labeled study, 84 type 2 diabetic Japanese patients with hypercholesterolemia were enrolled between September 2003 and April 2004. Subjects received 16 weeks of treatment with atorvastatin. High-sensitive C-reactive protein (hs-CRP), plasminogen activator inhibitor 1, monocyte chemotactic protein 1, interleukin 6, urine albumin-creatinine ratio, hemoglobin A_{1c}, total cholesterol, and LDL-C were measured at baseline and after 8 and 16 weeks of treatment. According to the Adult Treatment Panel III of the National Cholesterol Education Program, we divided the subjects into responders (final LDL-C <100 mg/dL) and nonresponders (final LDL-C ≥ 100 mg/dL). After 16 weeks of atorvastatin treatment, as well as a reduction of total cholesterol and LDL-C, a significant reduction of hs-CRP was observed. Plasminogen activator inhibitor 1, monocyte chemotactic protein 1, and interleukin 6 were not changed. After stratification, hs-CRP declined only in responders. We concluded that atorvastatin not only improved hypercholesterolemia, but also reduced CRP even in Japanese diabetic patients. The results of this stratified study suggest that achievement of the Adult Treatment Panel III treatment goal of LDL-C might assure a reduction of inflammation, which is associated with cardiovascular events.

1. Introduction

Although cancer is the main cause of death in Japan, cardiovascular disease is the main cause of death in European countries and the United States. The importance of this disease is increasing in Japan [1]. Especially in Japanese diabetic patients, vascular disease has been the most frequent cause of death from the 1970s, and coronary heart disease increased about 2-fold from the 1970s to the 1990s [2]. Low-density lipoprotein cholesterol (LDL-C) is a well-known risk factor for cardiovascular disease, and the importance of control of LDL-C is emphasized in the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP-ATPIII) [3]. The effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) to reduce cardiovascular events, through and/or beyond their effect on LDL-C, has been proved in several studies such as the 4S [4], WOSCOPS [5], CARE [6], LIPID [7], and AFCAPS/TexCAPS [8], and the effect of statins to lower high-sensitive C-reactive protein (hs-CRP) has also been reported [9-12]. Regarding this point, Ridker et al [13-15] suggested the importance of hs-CRP as a risk factor for cardiovascular disease, and there is argument as to whether hs-CPR is more important than LDL-C [16]. However, it was reported that a statin did not have a significant effect on hs-CRP in diabetic patients [17], and this lack of hs-CRP reduction might be a reason for the difficulty in preventing vascular events in diabetic patients. In fact, in several studies, antiplatelet or statin treatment did

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not show a statistically significant effect on atherosclerotic disease in diabetic patients [18-20]. Interestingly, atorvastatin, which did not reduce nonfatal myocardial infarction or fatal coronary heart disease in diabetic patients in ASCOT-LLA [20], was efficacious in reducing the risk of first cardiovascular disease events in CARDS [21]. Although the reason for the difference between ASCOT-LLA and CARDS is unknown, differences in the achieved level of LDL-C and the reduction of hs-CRP might be possible explanations.

Although the goal of LDL-C is less than 100 mg/dL in diabetic patients in the United States [3,22] and the Japan Atherosclerosis Society (JAS) Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases [23] recognize the goal of LDL-C as less than 120 mg/dL in diabetic patients, there has been no report about the achieved level of LDL-C and reduction of hs-CRP in Japanese diabetic patients.

Of course, the purpose of cholesterol treatment is to prevent vascular events and death, but medication that lowers hs-CRP as well as LDL-C must be better than treatment that does not affect hs-CRP. Therefore, in this study, we investigated the effect of atorvastatin to reduce hs-CRP, especially in subjects whose achieved LDL-C is less than 100 mg/dL in Japanese type 2 diabetic patients.

2. Research design and methods

2.1. Patient selection

The group of patients consisted of 84 type 2 diabetic patients (men 43, women 41; age, 63.3 ± 8.8 years) with hyperlipidemia from 6 institutions who were registered between September 2003 and April 2004 (Table 1). At registration, patients older than 75 years, those with a history of cerebral infarction or cardiovascular disease, with hemoglobin A_{1c} (HbA_{1c}) greater than 10.0%, or with severe renal or hepatic dysfunction were excluded.

At registration, atorvastatin was started at 5 or 10 mg and, according to the recommendations of the JAS Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases [23], the dosage was adjusted to achieve LDL-C of less than 120 mg/dL.

During the study period, there was no change in medication for diabetes mellitus or hypertension treatment.

Table 1
Characteristics of study population

Characteristic	Enrolled	Analyzed	Responders	Nonresponders
n	84	77	44	33
Sex (male/female)	43/41	38/39	18/16	20/13
Age (y)	63.3 ± 8.8	62.8 ± 9.0	62.5 ± 9.2	63.2 ± 8.8
HbA_{1c} (%)	7.0 ± 1.0	7.0 ± 1.0	7.0 ± 1.0	7.1 ± 0.9
BMI (kg/m^2)	23.9 ± 3.5	23.9 ± 3.5	23.2 ± 3.3	24.9 ± 3.5
SBP (mm Hg)	135.5 ± 18.0	135.1 ± 18.5	136.5 ± 17.0	133.2 ± 20.4
DBP (mm Hg)	76.7 ± 11.1	76.8 ± 11.1	77.5 ± 10.9	75.8 ± 11.5

Values are mean ± SD. BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

2.2. Patient stratification

The subjects were stratified into responders who achieved an LDL-C level of less than 100 mg/dL, which is recommended in the NCEP-ATPIII [3], and nonresponders whose LDL-C was 100 mg/dL or more.

2.3. Blood collection

Blood and urine collection was performed at the start and after 8 and 16 weeks of atorvastatin administration. Body mass index, blood pressure, serum total cholesterol (TC), LDL-C, triglyceride (TG), free fatty acids (FFAs), glucose, HbA_{1c}, 1,5-AG, aspartate aminotransferase, alanine aminotransferase, hs-CRP (N Latex CRP II, Dade Behring Marburg GmbH, Marburg, Germany), plasminogen activator inhibitor 1 (PAI-1) (Imulyse PAI-1, Biopool International, Umea, Sweden), monocyte chemotactic protein 1 (MCP-1) (Quantikine Human MCP-1 Immunoassay, R&D Systems, Minneapolis, Minn), interleukin 6 (IL-6) (QuantiGlo Human IL-6 Immunoassay, R&D Systems), and urine albumin-creatinine ratio (ACR) were measured at the start and after 8 and 16 weeks of treatment.

2.4. Statistical analysis

Data are presented as mean ± SD. All variables showed a normal distribution. Analysis was performed by repeated measures analysis of variance (ANOVA), and $P < .05$ was considered significant. StatView software (version 5.01; SAS Institute, Cary, NC) was used for statistical analysis. To rule out subjects with any other disease such as common cold, we excluded data with an outlying value of CRP. An outlying value was defined as a value $x >$ upper quartile + 1.5 times (upper quartile − lower quartile).

3. Results

3.1. Clinical profile

The clinical profile of the patients is shown in Table 1. Because of loss to follow-up and outlying values, we excluded 7 patients and analyzed 77.

3.2. Lipid profile

A significant reduction in TC and LDL-C by administration of atorvastatin was observed, and the improvement in lipid profile was seen from 8 weeks after the start of treatment. There were 60 cases (77.9%) that satisfied the JAS guidelines of a goal of LDL-C less than 120 mg/dL, and 44 (57.1%) satisfied the NCEP-ATPIII goal of LDL-C less than 100 mg/dL. Triglyceride tended to decline, but this change was not statistically significant ($P = .06$), and FFA did not change at all (Table 2).

Table 2
Lipid profile, diabetic control, and blood pressure at baseline and at 8 and 16 weeks after start of treatment

	Baseline	8 wk	16 wk
BMI (kg/m^2)			
Total	23.9 ± 3.5	24.0 ± 3.6	23.7 ± 3.4
Res	23.2 ± 3.3	23.2 ± 3.4	23.3 ± 3.4
Non	24.9 ± 3.5	25.0 ± 3.7	24.5 ± 3.3
SBP (mm Hg)			
Total	135.1 ± 18.5	134.8 ± 16.3	132.4 ± 18.6
Res	136.5 ± 17.0	136.0 ± 13.6	134.5 ± 18.7
Non	133.2 ± 20.4	133.2 ± 19.5	129.1 ± 18.2
DBP (mm Hg)			
Total	76.8 ± 11.1	75.8 ± 10.8	75.2 ± 11.1
Res	77.5 ± 10.9	76.6 ± 10.2	76.6 ± 10.7
Non	75.8 ± 11.5	74.7 ± 11.7	73.1 ± 11.4
LDL-C (mg/dL)			
Total**	148.5 ± 28.3	94.5 ± 24.8	94.7 ± 26.2
Res**	142.0 ± 24.7	80.5 ± 16.8	77.0 ± 12.9
Non**	157.2 ± 30.7	114.0 ± 20.8	118.2 ± 20.2
TC (mg/dL)			
Total**	237.8 ± 34.4	175.4 ± 32.5	172.8 ± 30.7
Res**	231.9 ± 32.4	158.9 ± 23.2	156.0 ± 23.6
Non**	245.7 ± 35.9	198.0 ± 30.0	197.4 ± 22.2
TG (mg/dL)			
Total	142.8 ± 69.0	122.3 ± 60.9	117.9 ± 79.1
Res*	138.0 ± 69.5	103.0 ± 45.5	102.6 ± 83.2
Non	148.9 ± 69.0	145.2 ± 71.1	141.0 ± 66.3
FFA (mEq/L)			
Total	0.49 ± 0.21	0.46 ± 0.21	0.48 ± 0.22
Res	0.44 ± 0.19	0.46 ± 0.20	0.50 ± 0.19
Non	0.54 ± 0.22	0.46 ± 0.22	0.45 ± 0.25
PG (mg/dL)			
Total	163.9 ± 57.3	164.5 ± 55.2	163.8 ± 45.2
Res	161.8 ± 61.4	167.3 ± 60.1	154.9 ± 44.6
Non	166.6 ± 52.3	161.6 ± 47.7	179.5 ± 43.4
HbA_{1c} (%)			
Total	7.0 ± 1.0	7.3 ± 1.0	7.4 ± 1.2
Res	7.0 ± 1.0	7.3 ± 1.2	7.4 ± 1.3
Non	7.1 ± 0.9	7.3 ± 0.8	7.3 ± 1.0
1,5-AG (μg/mL)			
Total	8.8 ± 6.7	8.1 ± 6.5	8.3 ± 6.1
Res	10.0 ± 7.8	9.3 ± 7.5	9.6 ± 6.6
Non	7.2 ± 5.3	6.5 ± 5.0	6.5 ± 5.4
PAI-1 (ng/mL)			
Total	23.8 ± 10.6	25.3 ± 11.4	23.8 ± 10.9
Res	23.0 ± 7.9	23.1 ± 10.0	22.8 ± 11.3
Non	24.9 ± 13.4	28.2 ± 12.8	25.1 ± 10.6
MCP-1 (pg/dL)			
Total	164.0 ± 44.5	180.1 ± 63.2	161.3 ± 48.2
Res	156.4 ± 38.1	165.3 ± 62.6	151.8 ± 40.1
Non	174.2 ± 51.9	199.8 ± 64.1	173.9 ± 57.2
IL-6 (pg/mL)			
Total	0.87 ± 0.51	0.89 ± 0.45	0.85 ± 0.53
Res	0.87 ± 0.57	0.83 ± 0.44	0.77 ± 0.54
Non	0.86 ± 0.43	0.97 ± 0.47	0.96 ± 0.51
ACR (mg/g Cr)			
Total	100.1 ± 173.3	107.0 ± 186.5	105.2 ± 217.0
Res	100.1 ± 168.3	95.4 ± 162.5	93.6 ± 197.1
Non	100.1 ± 179.7	122.4 ± 214.3	120.7 ± 241.0

Data are mean ± SD. Total indicates analyzed subjects (N = 77); Res, responders (n = 44); Non, nonresponders (n = 33); PG, prostaglandin.

* $P < .05$, repeated measures ANOVA.

** $P < .0001$, repeated measures ANOVA.

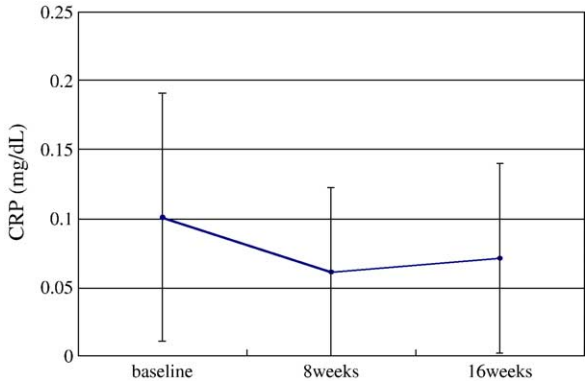

Fig. 1. Change in CRP level (mean + SD) in 77 Japanese diabetic subjects ($P < .05$).

3.3. Blood pressure, glycemic control, and liver enzymes

No change in blood pressure was observed during the study period. Only 31 cases (40.3%) satisfied a blood pressure of less than 130/80 mm Hg as recommended in guidelines such as JNC-7 [24] and ESH [25]. Regarding glycemic control, prostaglandin, HbA_{1c}, and 1,5-AG did not show a significant change during the study period. No change was found in liver enzymes and renal function during the study period.

3.4. Inflammatory and endothelial function markers

No change in PAI-1, MCP-1, and IL-6, which are inflammatory markers, was seen in this study, and no change in ACR, a marker of vascular endothelial dysfunction, was observed. However, hs-CRP decreased significantly during the study period (Fig. 1) ($P < .05$).

The level and fall of hs-CRP did not correlate with the level and fall of LDL-C. In addition, hs-CRP at the start of atorvastatin treatment did not affect the change of LDL-C during the study period, and LDL-C at the start did not affect the change of hs-CRP during the whole study period. Fig. 2 shows that hs-CRP tended to fall when LDL-C was less than 100 to 110 mg/dL.

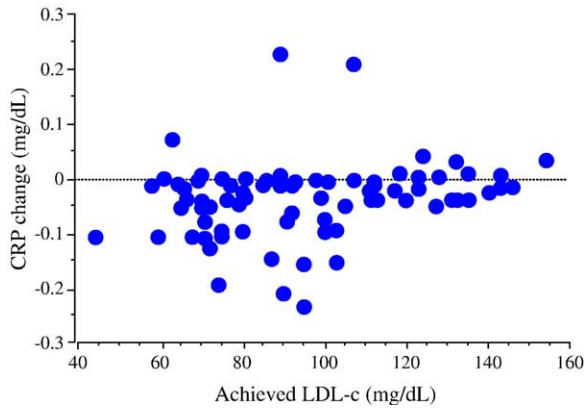

Fig. 2. Relation between change in hs-CRP and achieved LDL-C level. There appears to be a threshold LDL-C for a decrease in hs-CRP.

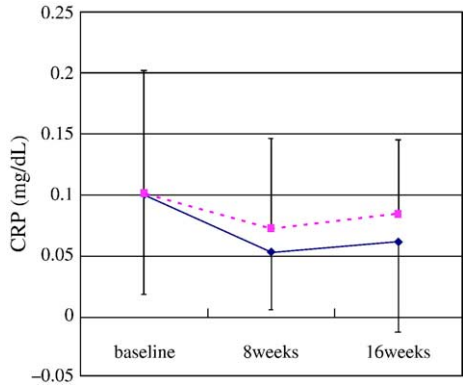

Fig. 3. Change in CRP, stratified by LDL-C response. Only responders showed a statistically significant decrease (P = .02). Solid line indicates responders; dotted line, nonresponders.

3.5. Stratification according to achieved LDL-C level

We then stratified the patients into responders (16-week LDL-C < 100 mg/dL) and nonresponders (LDL-C > 100 mg/dL). Statistical analysis showed a significant fall of hs-CRP only in responders (n = 44, P = .02) (Fig. 3), and TG showed a statistically significant reduction only in responders (P < .05) (Table 2). Although it was not statistically significant, the mean levels of IL-6 and ACR in responders decreased during the study period.

4. Discussion

The results of this study showed 3 important findings. One is that a relatively low dose of atorvastatin of 5 to 10 mg could significantly decrease the LDL-C level in Japanese type 2 diabetic patients. A high proportion of cases (77.9%, 60/77) achieved the treatment goal for LDL-C of the JAS guidelines [23], and 57.1% (44/77) of cases achieved the treatment objective for LDL-C of ATPIII [3]. These data are consistent with the effect of atorvastatin in a previous report [26,27].

The second important finding is that atorvastatin significantly lowered hs-CRP in Japanese type 2 diabetic patients. The level of hs-CRP in our study was lower than that in Westerners [12,16], equivalent to that in Japanese Americans [28], and slightly higher than that in healthy Japanese subjects [29]. Although we cannot conclude whether the low level of hs-CRP in Japanese might be associated with the low mortality from cardiovascular disease in Japan, certainly Japanese Americans have higher mortality from cardiovascular disease than Japanese [30]. Therefore, our data suggest that atorvastatin would be a useful medication for the prevention of cardiovascular disease in Japanese type 2 diabetic patients. The discrepancy between hs-CRP and other inflammatory markers could suggest that hs-CRP or pentraxin might be specific markers of atherosclerosis.

The third important finding is that a reduction of hs-CRP was observed only in patients who satisfied the treatment goal of NCEP-ATPIII. A significant fall in hs-CRP was not seen in cases whose LDL-C did not become less than 100 mg/dL even if LDL-C reached less than 120 mg/dL, which is recommended in the JAS guidelines. Kent and Taylor [31] reported a change in hs-CRP by atorvastatin or pravastatin administration for hyperlipidemia. According to their report, hs-CRP fell to 0.23 or 0.22 in the group with LDL-C of less than 70 or 70 to 99 mg/dL, but CRP was higher (0.38 or 0.41) in the group with LDL-C of 100 to 129 or greater than 130. These data and our results suggest there is a threshold value of LDL-C for a reduction of hs-CRP.

Danesh et al [16] recognized hs-CRP as a moderate predictor of cardiovascular disease, whereas Ridker et al [15] suggested that hs-CRP was a more important predictor of coronary disease than LDL-C. Thus, hs-CRP is at least an important predictor of cardiovascular disease. Therefore, it is suggested that the treatment goal of LDL-C should be less than 100 mg/dL in Japanese diabetic patients because a significant fall in hs-CRP was observed only in the group with posttreatment LDL-C of less than 100 mg/dL in our study.

The JAS guidelines [23] recommended a treatment goal of LDL-C of 120 mg/dL in diabetic patients based on the Hisayama study [32] (data published in Japanese by Y Kiyohara). However, because the Hisayama study showed that a LDL-C level of 160 mg/dL or more is a risk factor for cardiovascular disease in nondiabetic persons, the subjects in the Hisayama study were different from the general Japanese population, for whom the recommended LDL-C level is less than 140 mg/dL in the JAS guidelines. In addition, although the J-LIT study showed that Japanese hyperlipidemic patients with or without diabetes have cardiovascular risk when LDL-C is 120 mg/dL or more [33], the J-LIT secondary prevention study [34] and Japan Diabetes Complications Study revealed that the relative risk when LDL-C was controlled to less than 100 mg/dL was lower than the risk at an LDL-C level of less than 120 mg/dL [35]. Haffner et al [36] reported that the incidence of new coronary artery disease onset in diabetic patients was the same as the incidence of coronary artery disease recurrence. These data and our observations suggest that the goal of LDL-C treatment should be less than 100 mg/dL even in Japanese diabetic patients.

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