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Original Article

Statins Reduce Extensive Aortic Atheromas in Patients with Abdominal Aortic Aneurysms

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Objective: **Statins have been used widely to reduce dyslipidemia and recently have been reported to have pleiotropic effects such as plaque reduction and stabilization. This study retrospectively evaluated the regression of extensive thoracic atheromas ("shaggy aorta") in abdominal aortic aneurysm (AAA) patients who underwent contrast-enhanced computed tomography (CECT) before and after statin administration.**

Materials and Methods: **CECT was used to examine thoracic aortas of 29 patients (statin group; n = 22, non-statin group; n = 7) with extensive atheromas from the ostium of the left subclavian artery to that of the more proximal renal artery. Extensive thoracic atheroma was defined by: (1) thickness >5 mm, (2) involved circumference of thoracic aorta >50%, and (3) length >30 mm. The areas of atheroma (cm^2) were measured before and after administration of statins, and the atheroma reduction ratio (ARR) was evaluated.**

Results: **The area of atheroma decreased after administration of statins, and the ARR was significant (P <0.01). The ARR increased with all cases in non-statin group. No complications associated with extensive atheroma were observed during the follow-up period.**

Conclusion: **This pilot study indicates statins can reduce extensive thoracic atheromas and lower lipid concentrations.**

Keywords: statins, atheroma, abdominal aortic aneurysm, shaggy aorta

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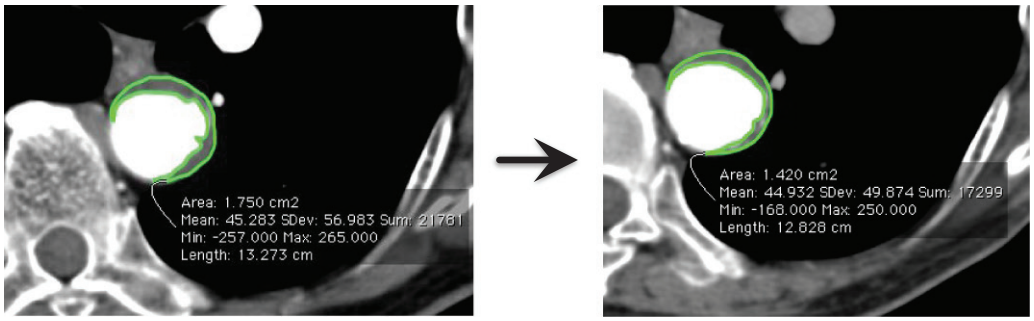
Introduction

Extensive aortic atheromas are frequently observed in patients with abdominal aortic aneurysms (AAAs) and can be located along the aorta or in an aneurysmal sac. An atheroma with an irregular and spiculated appearance is commonly called a "shaggy aorta"; however, this term has not been clearly defined.[1)] Vascular surgeons sometimes encounter adverse events after AAA repair that may be related to shower embolization.[2,3)] Therefore, surgeons have traditionally made efforts to prevent intraoperative embolization by flushing debris or by clamping the aorta at a "safer" site. Endovascular aneurysm repair (EVAR) has recently come into wide use because it results in excellent outcomes and is less stressful for the



Pre-administration *Post-administration*

Fig. 1 Computed tomographic image of an extensive atheromatous area that was measured manually before and after administration of statins.

patient. This procedure is performed in a closed space from which atheromatous debris cannot be flushed out; therefore, the shaggy aorta has recently been considered a contraindication for EVAR.[3)]

Statins have been reported to have pleiotropic effects such as regression and stabilization of plaques in the coronary artery.[4–8)] In addition, magnetic resonance imaging results (MRI) indicated regression of a thoracic aortic plaque after lipid-lowering therapy with simvastatin.[9,10)] An atheroma thrombus accompanying an abdominal aortic aneurysm is supposed to indicate coagulopathy due to an intraluminal thrombus,[11,12)] and a shaggy atheroma may be similar to the usual aortic atheromas in this regard.

In this study, we focused on the pleiotropic effects and selected AAA cases with extensive atheromas in the thoracic aorta that were not directly affected by surgical aneurysm repair; we then examined the effect of statins on atheroma regression. This is the first study to examine the effect of statin reducing the aortic "shaggy" atheroma.

Patients and Methods

Patients from 4 institutions, the University of Tokyo Hospital (Tokyo, Japan), Morinomiya Hospital (Osaka, Japan), Mitsui Memorial Hospital (Tokyo, Japan), and Tokyo Metropolitan Geriatric Hospital (Tokyo, Japan), participated in this study, and those with abdominal aortic aneurysms who underwent aneurysm repair from January 2002 to November 2011 were examined retrospectively. To evaluate the effect of statins on extensive atheromas in the thoracic aorta, we selected "shaggy aorta" patients who were treated with statins, and those who had undergone contrast-enhanced computed tomography (CECT) both before and after statin administration, with an interval of at least 2 months between starting statins and the second CECT study. As a control group, we selected "shaggy aorta" patients who were not treated with statins, who had undergone CECT. The portion of the thoracic aorta from the ostium of the left subclavian artery to that of the more proximal renal artery was examined using CECT at one of the above institutions. Extensive thoracic atheromas were defined by the following characteristics: (1) thickness >5 mm; (2) circumference of thoracic aorta involved >50%; and (3) length >30 mm. Twenty-nine patients fulfilled these criteria.

The CECT images of these 29 patients were collected at the University of Tokyo Hospital, and individual data were blinded. Three trained examiners, an author, and 2 medical students, measured the atheroma volumes to evaluate the intra-observer variation. They measured all the atheromatous area in the thoracic lesion manually with circling tool of the software (Osirix®), and therefore integrated them (**Fig. 1**). An atheroma reduction ratio (ARR) was calculated by subtracting the area (cm^2) of atheroma after statin administration from the area before statin administration and dividing the difference by the area of atheroma before statin administration.

The patients' demographic data are shown in **Table 1**. Statin treated patients (statin group) were 22, and non-statin treated patients (non-statin group) were 7. Six different statins were used: pitavastatin (n = 7), atorvastatin (n = 7), rosuvastatin (n = 4), fluvastatin (n = 2), simvastatin (n = 1), and pravastatin (n = 1). Pitavastatin, atorvastatin, and rosuvastatin are considered strong statins with high lipid-lowering effects (**Table 2**). Serum lipid concentrations were compared retrospectively; high-density lipoprotein cholesterol (HDL-C) level was measured in 8 patients, and low-density lipoprotein cholesterol (LDL-C) level in 9 patients both before and 3 months after statin administration.

Follow-up examinations had been performed from the time of administration of statins to January 2012 (771 ± 897 days). Postoperative complications were recorded on

Table 1 Characteristics of the patients

Variable, n (%)	Statin group (n = 22)	Non-statin group (n = 7)	P value
Age	78.4 ± 6.1	77.1 ± 6.3	NS
Male	22 (100)	6 (85)	NS
Aneurysmal diameter (anteroposterior) (mm)	52.3 ± 6.4	53.3 ± 4.5	NS
Comorbidities			
Advanced age (≥80)	12 (55)	4 (57)	NS
Hypertension	19 (86)	6 (85)	NS
Diabetes mellitus	4 (18)	3 (43)	NS
Ischemic heart disease	8 (36)	5 (71)	NS
Cerebrovascular disease	5 (23)	0 (0)	NS
Chronic kidney disease (≥CKD3)	2 (10)	0 (0)	NS
Respiratory disease	4 (18)	1 (14)	NS
Operation			
Endovascular aneurysm repair	16 (73)	1 (14)	<0.01
Open aneurysm repair	5 (23)	5 (72)	0.02
Not performed	1 (4)	1 (14)	NS

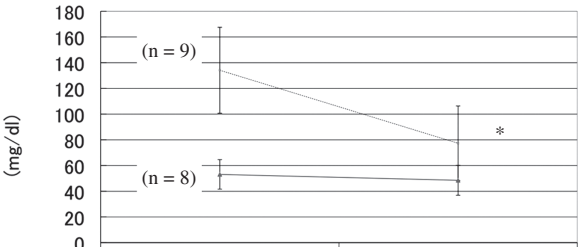
CKD: Chronic kidney disease; NS: Not significant

Table 2 The kind of statin and ARR in each cases

Case	Statin	Dosage	Pre-prescription (cm^2)	Post-prescription (cm^2)	ARR (%)	Period (months)
Strong Statins						
1	Pitavastatin	4 mg	28.2 ± 11.4	24.6 ± 9.1	–11.8 ± 4.7	6
2	Pitavastatin	4 mg	75.7 ± 4.0	67.0 ± 2.9	–11.4 ± 5.9	2
3	Pitavastatin	2 mg	25.5 ± 7.8	23.9 ± 6.6	–6.2 ± 2.3	7
4	Pitavastatin	2 mg	130.2 ± 17.1	126.8 ± 20.9	–2.9 ± 3.7	7
5	Pitavastatin	4 mg	56.2 ± 4.1	53.2 ± 7.5	–5.5 ± 7.7	3
6	Pitavastatin	4 mg	57 ± 6.4	49.1 ± 1.9	–12.9 ± 12.3	2
7	Pitavastatin	4 mg	87.2 ± 5.1	85.9 ± 4.4	–1.4 ± 3.7	4
8	Atorvastatin	5 mg	44.9 ± 9.2	44.1 ± 9.8	–1.8 ± 6.5	6
9	Atorvastatin	5 mg	20.9 ± 5.7	19.5 ± 6.3	–7.3 ± 4.5	6
10	Atorvastatin	5 mg	28.9 ± 6.3	27.9 ± 4.6	–2.4 ± 7.0	3
11	Atorvastatin	10 mg	17.2 ± 2.6	14.7 ± 2.5	–15.0 ± 4.2	2
12	Atorvastatin	10 mg	69.3 ± 4.9	65.7 ± 5.0	–5.2 ± 4.0	6
13	Atorvastatin	10 mg	24.2 ± 3.9	21.5 ± 4.3	–11.6 ± 3.9	8
14	Atorvastatin	10 mg	34.2 ± 11.9	34.3 ± 13.1	–0.4 ± 3.8	7
15	Rosuvastatin	5 mg	188.9 ± 20.8	150.6 ± 18.6	–20.3 ± 2.9	7
16	Rosuvastatin	2.5 mg	31.1 ± 6.5	30.8 ± 4.9	0 ± 10.7	7
17	Rosuvastatin	2.5 mg	37.5 ± 11.9	36.0 ± 12.1	–4.2 ± 3.9	6
18	Rosuvastatin	2.5 mg	26.4 ± 6.3	27.0 ± 7.6	1.2 ± 4.3	6
Mild Statins						
19	Fluvastatin	20 mg	20.7 ± 12.4	16.6 ± 10.1	–20.2 ± 1.0	2
20	Fluvastatin	30 mg	11.3 ± 0.9	10.6 ± 2.2	–6.6 ± 12.5	8
21	Simvastatin	5 mg	55.8 ± 25.6	57.3 ± 30.8	0.6 ± 7.8	7
22	Pravastatin	10 mg	28.7 ± 6.5	25.4 ± 5.4	–11.5 ± 1.9	10

Period is the interval between contrast-enhanced computed tomography scans; scans were performed before and after the administration of statins. ARR: Atheroma reduction ratio

the basis of modified versions of previously published classifications and grades of embolization-related complications.[3,13] Differences in the data pre- and post-administration of statins were analyzed using paired Student's *t*-test. In statin group, the association between the ARR and the changes in the serum lipid levels of LDL-C and HDL-C at each points of evaluating by CECT before and after administration of statins was analyzed by Pearson correlation coefficient. The values are reported as the mean ± standard deviation (SD). The level of significance was set at $P < 0.05$. This study was performed according to the ethical policies of our institution.



	Pre-administration	Post-administration (3 months)
HDL-C	53.1	48.5
LDL-C	134.1	77.3

(* p <0.01)

Fig. 2 LDL-C significantly decreased 3 months after the administration of statins. HDL: high-density-lipoprotein cholesterol; LDL-C: low-density-lipoprotein cholesterol.

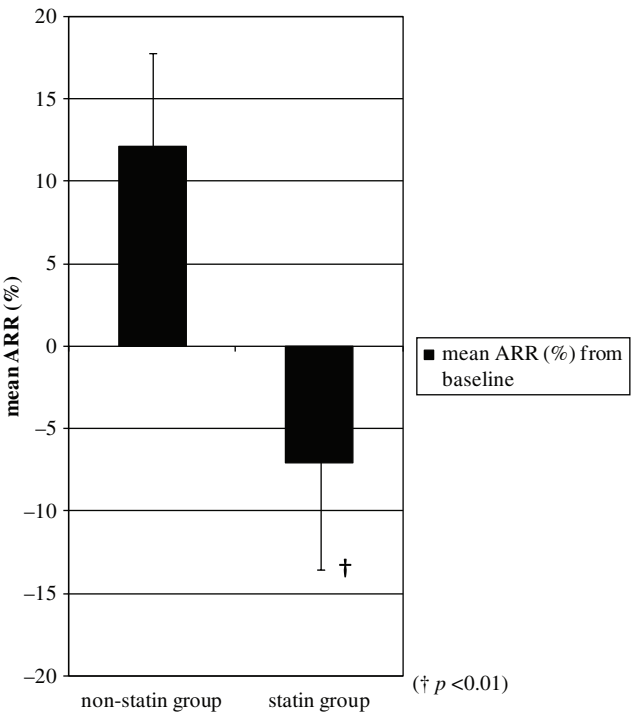


Fig. 3 A significant decrease in mean atheroma reduction ratio (ARR) (%) was observed after the administration of statins in statin group. In non-statin group, atheroma area increased with all cases and the ARR significantly increased.

Results

The expected lipid-lowering effect of statins was observed; the LDL-C level decreased from 134.1 ± 33.5 mg/dL to 77.3 ± 29.0 mg/dL (P <0.01; **Fig. 2**). The change in HDL-C level, from 53.1 ± 11.5 mg/dL to 48.5 ± 11.6 mg/dL, was not statistically significant (P = 0.37).

The atheroma area pre- and post-administration of statins and the ARR are shown in **Table 2** as the averages of the measurements made by the 3 examiners; the duration of statin treatment before the second evaluation by CECT is also shown (5.6 ± 2.3 months). The mean ARR of this statin group was –7.1% ± 6.4% (**Fig. 3**), representing a significant decrease (P <0.01). Eight patients showed a significant reduction of ARR values >10%. Among these, strong statins had been administered in 6 cases. The ARR after administration of a mild statin was significant in only 1 case (Case 19); the patient in that case had refused to undergo aneurysm repair. In statin group, the ARR didn't correlate with the changes in the serum levels of LDL-C and HDL-C (**Fig. 4**). On the other hand, in non-statin group, the atheroma area increased with all cases at the second evaluation by CECT and the mean ARR was +12.1% ± 5.7%, representing a significant increase (**Fig. 3**). The average period until the second CECT is 12.4 ± 8.4 months. No complication, including peripheral embolization, was detected during the follow-up period.

Discussion

Both open surgery and EVAR for shaggy aorta sometimes result in shower embolization, which can cause strokes, bowel ischemia, deterioration of renal function, lower limb ischemia, and more. High rates of embolic events in patients with aortic atheroma plaques have been sporadically reported.[9,10,14–17] In most of these reports, the plaque had been evaluated by transesophageal echocardiography (TEE) or magnetic resonance imaging (MRI). In the present study, we measured plaque in shaggy aortas using CECT, because this technique is noninvasive and is available in almost all hospitals; therefore, follow-up in AAA patients is convenient.

Few studies have reported an adverse effect of shaggy aorta on the outcome of open AAA repair; however, recent reports on EVAR for AAA found that shower embolization, an adverse event, correlated with atheroma of the aortic wall.[2,3] In this endovascular era, we have sought a neoadjuvant therapy for EVAR, and recent reports have revealed that preoperative statins are beneficial in patients undergoing aortic aneurysm repair without reference to the relationship between the operative maneuvers and atheromatous shower.[18]

It had been considered that the beneficial effects of statins are mainly due to cholesterol reduction. But some reports have revealed another mechanisms independent

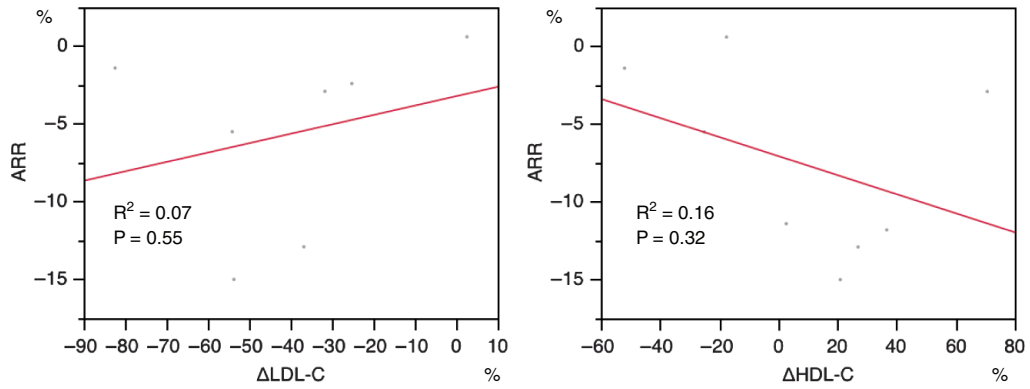


Fig. 4 ΔLDL-C in 7 patients and ΔHDL-C in 8 patients did not correlate with the ARR. Δ, percent change from baseline.

of LDL-C reduction. In our study, statins decreased the LDL-C level but the percent change of LDL-C and HDL-C level didn't correlate with ARR. This data was supported by the COSMOS study in Japan that revealed that there was no significant relationship between the percent change of coronary atheroma volume and the HDL-C or the LDL-C/HDL-C ratio.[19] From these data, statins have supposed to have pleiotropic effects, and some mechanisms such as plaque stabilization, anti-inflammatory action, improvement of endothelial function were hypothesized.[8,20] However, the exact mechanism of atheroma reduction has not been unveiled.

No complications associated with extensive atheroma were detected during the follow-up period. Statins have been speculated to lead to plaque stabilization by decreasing smooth muscle cell migration and proliferation and modifying endothelial function.[21] This plaque stabilization, independent of the cholesterol-lowering effect of statins, may possibly lead to an inhibition of the shower embolization that is associated with extensive atheromas.[21,22]

MRI results of some reports have indicated that statins reduce the volume of aortic atheromas.[8,9,23] MRI can show components of atherosclerotic plaque such as thrombus-rich lesions, lipid-rich lesions, and calcified plaque that makes it possible to find vulnerable plaque.[24,25] However, identifying each type of lesion by CECT is difficult. Our study used CECT to evaluate the atheromas because the AAA patients in whom surgery was indicated had usually undergone CECT during the preoperative evaluation; we therefore had easy access to the imaging data. Corti and other authors have established MRI-based methods of measuring the lumen area, vessel-wall thickness, and total vascular area.[8,9] They also performed morphological analysis and plaque characterization. We did not attempt to distinguish the plaque constituents. We measured plaque by the shape of the identified luminal protrusion. The aortic outer surface is difficult to detect in both MRI and CECT images; therefore, the atheromatous area must be measured manually. We measured the atheromatous area in those CECT slices that showed conspicuous and extensive atheroma, in order to limit the range of error among the examiners.

Our results showed a tendency toward atheroma reduction within a short period; in the fastest case of significant reduction, the reduction was observed within 2 months. Carotid artery plaques have been previously reported to show reduction within 3 months.[26] We speculate that the pleiotropic effect may appear in parallel with the lipid-lowering effect, which has been shown previously and in our study to be apparent within 3 months. According to this hypothesis, strong statins may have greater effects on atheromas; however, we were unable to detect the significant difference between strong and mild statins in our small series.

One reason we selected AAA patients for our study was to confirm the direct effect of statins on extensive atheromas accompanying AAAs large enough to warrant surgery. Inflammation during atherosclerosis has been considered to promote the formation, progression, and rupture of atherosclerotic plaques. Therefore, we think that inflammation may provide clinical utility and can be used as a target therapy.[27] Statins have been often considered to exert pleiotropic effects on atherosclerotic plaques via anti-inflammatory action.[8] There has especially been a focus on high-sensitivity C-reactive protein (hsCRP), an inflammatory biomarker, as a independent predictor of vascular events.[28,29] This anti-inflammatory effect of statins should be considered in the present study, but our retrospective examination had less data regarding factors involved in the inflammatory process, such as hsCRP.

Most patients recruited to this study had undergone surgical treatment, and surgical intervention may possibly affect vascular wall inflammation. In this study, the operative site both for open surgery and for EVAR was mainly the infrarenal abdominal aorta, but the measured atheromatous area was from the ostium of the left subclavian artery to that of the renal artery; in other words, the suprarenal area. Therefore, we thought that the surgical procedures would probably not directly affect vascular wall inflammation and atheroma in the measured area.

The limitation of this study is the small number of enrolled patients for sufficient evaluation of atheroma reduction, and the patient numbers of HDL-C and LDL-C measurements are even smaller. So, the significance is unclear for the conclusions regarding the association between the ARR and the changes in LDL-C and HDL-C. The ability of our study to evaluate patient outcomes after aneurysm repair under hostile aortic conditions was limited by the short follow-up period and the small number of patients.

Conclusion

This pilot study revealed a beneficial pleiotropic effect of statins; we observed atheroma reduction without postoperative complications, which suggests that a future randomized prospective study should be performed for evaluating outcomes after aneurysm repair. We have demonstrated that statin administration can reduce extensive aortic atheromas that accompany large AAAs.

Disclosure Statement

There are no conflicts of interest.

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