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The short-term effect of atorvastatin on carotid plaque morphology assessed by computer-assisted gray-scale densitometry: a pilot study

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Abstract

Soft, lipid-containing carotid plaques, which appear echolucent on ultrasound imaging, have been associated with increased risk of ischemic stroke. We sought to investigate the effect of short-term treatment with atorvastatin on the change of carotid plaque echodensity. We treated 40 stroke-free and statin-naïve subjects with 80 mg atorvastatin daily for 30 days. Computer assisted gray-scale densitometry (GSD) index was calculated at baseline and 30 days after treatment from the normalized plaque images. A multiple logistic regression was used to assess the effect modification of low-density lipoprotein (LDL) cholesterol on plaque stabilization after adjusting for age, sex, and smoking. The average number of carotid plaques at baseline was 2 (range: 0–5; 27 subjects with carotid plaque) and did not change 30 days following atorvastatin treatment. The mean GSD index significantly increased from 73 ± 16 (range: 1–125) at baseline to 89 ± 15 (range: 1–137) at 30 days after treatment ($P < 0.05$). The adjusted odds ratio for the positive GSD plaque index change (vs. no change or decreased gray-scale median (GSM) index) was 1.71 (95% confidence interval: 1.1–7.6, $P < 0.01$). In conclusion, we observed decreased echolucency (increased echodensity) of carotid artery plaques after short-term treatment with atorvastatin.

Keywords

Carotid arteries; Carotid ultrasound; Atherosclerotic plaque; Echolucency; Statins

Introduction

Several studies have demonstrated the beneficial effects of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors on vascular properties.¹ Recently, using the same population of this study and the same experimental protocol, we demonstrated that short-term treatment with high-dose atorvastatin was associated with improvement in the

carotid elasticity metrics.² However, little is known of the early response of plaque morphological properties to a statin.¹ Term ‘vulnerable plaque’ has been proposed for atherosclerotic plaques that are prone to the rupture and erosion and therefore precipitate an acute arterial thrombosis and embolism.³ The possibility of stabilizing the vulnerable plaques has been supported by the results from the lipid lowering trials, in which dramatic reduction of the acute coronary events and stroke was noted despite only subtle improvements in arterial luminal diameter.¹ Plaque echogenicity that corresponds to the ‘vulnerable’ plaque histology may be an important outcome of the anti-atherosclerotic treatments. Previously, it has been reported that an aggressive atorvastatin regimen (80 mg daily) had enhanced carotid plaque echogenicity in patients with moderate carotid stenosis at 12 months of follow-up.⁴ However, not only aggressive but also intensive lipid-lowering treatment among individuals with low-density lipoprotein (LDL) less than 100 mg/dl succeeded to increase carotid plaque echogenicity.⁵ We hypothesize that carotid plaque echogenicity measured by the ultra-sonographic gray-scale densitometry (GSD) index can be altered following a short-term treatment of atorvastatin. Therefore, we aimed this pilot study to assess the effect of 80 mg of atorvastatin on the GSD index change after 30-day treatment.

Subjects and Methods

This was a sub-study of an investigator initiated study (‘The short-term effect of atorvastatin on carotid artery wall elasticity: a B-mode ultrasound pilot study’)² in which 40 stroke-free and statin-naïve subjects over 45 years of age underwent high-resolution carotid ultrasound imaging (GE LOGIQ 700; Healthcare, Milwaukee, WI, USA; with 11 MHz linear-array probe)⁶ at two time points: baseline (first clinical evaluation before treatment) and 30 days after the treatment with 80 mg oral administration of atorvastatin tablets once a day according to the treatment eligibility by the National Cholesterol Education Program: Adult Treatment Panel III (NCEP ATP III).⁷ Subjects were selected from a larger group of high-risk patients undergoing carotid ultrasound scanning at the non-invasive vascular laboratory of the Department of Neurology at Columbia University, New York, USA, if they were eligible for lipid lowering treatment according to the NCEP ATP III criteria.

To be eligible, participants were required to have either: (1) coronary heart disease (CHD) or CHD-equivalent (peripheral artery disease, abdominal aortic aneurysm, symptomatic carotid artery disease, diabetes, or multiple risk factors conferring a 10-year risk for CHD >20%); (2) ≥ 2 risk factors for CHD and an LDL ≥ 130 mg/dl; or (3) <2 risk factors and an LDL ≥ 160 mg/dl. NCEP ATP III risk factors for CHD include: (1) age: men ≥ 45 years; women ≥ 55 years; (2) hypertension: blood pressure $\geq 140/90$ mmHg, or need for antihypertensive medication; (3) high-density lipoprotein <40 mg/dl; (4) cigarette smoking; and (5) family history of premature CHD: CHD in a male first-degree relative <55 years or in a female first-degree relative <65 years. Patients with carotid stenosis 60% or greater were excluded from the study due to their potential inclusion in carotid interventional trials. Other exclusion criteria were any use of fibrates or other lipid-lowering medication; hospitalization for acute coronary syndrome within the past 6 months; hepatic or renal dysfunction; connective tissue or chronic inflammatory disease; history of malignancy; any acute illness; leukocytosis (white blood cell count >10 000/cu mm); thrombocytosis (platelet count >450 K/cu mm); anemia (hematocrit <40%); corticosteroid use; pregnancy; and breastfeeding.

The blood analyses were performed according to the procedures described previously.⁸

The study was approved by the Western Institutional Review Board. Written informed consent was obtained from all participants.

Digitally recorded high-resolution ultrasound plaque images were analyzed off-line by computer-assisted post-processing image densitometry algorithm (Fig. 1) M² Ath; (IMT Inc., Paris, France). For each subject, images from 12 carotid sites (the near and the far walls of the common carotid artery, the bifurcation and the internal carotid artery on both sides of the neck) were reviewed, normalized, and the GSD index calculated at the two time points. Plaque was defined as an area of focal wall thickening 50% greater than surrounding wall thickness confirmed by marking and comparing plaque thickness with the thickness of the surrounding wall during scanning by electronic calipers.⁶ A total of 576 carotid plaque images was obtained and evaluated (27 patients with plaque $\times$ 12 carotid sites $\times$ two time points = 576). The GSD index within an individual was calculated as an average density of the reflecting gray-scale normalized image signals from each plaque.

Statistical analysis

Carotid plaque GSD index within an individual was expressed as a mean (and SD) and the inter-quartile ranges. The absolute and relative changes of the GSD index within an individual at baseline and 30 days after the initiation of treatment were compared using the paired *t*-test (one-tailed difference was considered significant at alpha of 0.05). Any increase in an individual GSD index was considered a positive change or plaque stabilization effect. A multiple logistic regression was used to assess the effect modification of LDL cholesterol (baseline and 30-day change) on plaque stabilization (GSD index) after adjusting for age, sex, and smoking.

Results

The mean subject age was 70 ± 7 years, and 55% were men; 64% were Caribbean-Hispanic, 24% were African-American, and 12% were Caucasian.

There was a significant treatment effect of atorvastatin on reduction of both total and LDL cholesterol levels compared to baseline ($P < 0.01$). LDL decreased from a mean baseline level of 144 ± 38 mg/dl to 70 ± 25 mg/dl at day 30. Laboratory parameters expressed as mean $\pm$ SD at baseline and after 30 days of atorvastatin treatment are presented in Table 1. Patients were taking different combinations of cardiovascular drugs, which were unmodified during the 30 days of treatment with atorvastatin. The average number of carotid plaques was 2 (range: 0–5; 27 subjects with carotid plaque) at baseline and did not change 30 days following treatment. The mean maximal carotid plaque thickness did not significantly change between baseline and the follow-up (1.78 mm versus 1.69 mm) (Table 1).

The mean GSD index was 73 ± 16 (range: 1–125) at baseline and 89 ± 15 (range: 1–137) at 30 days ($P < 0.05$) (Table 1). Of 24 study participants, four (17%) showed a reduction of the GSD index and 14 (60%) showed an increase of the GSD index. The adjusted odds ratio for the positive GSD plaque index change (vs. no change or decreased gray-scale median (GSM) index) was 1.71 (95% confidence interval: 1.1–7.6, $P < 0.01$). These results remained the same after adjustment for the baseline levels of LDL or LDL change from baseline. Therefore, the effect of atorvastatin on plaque stabilization was independent of the baseline levels of LDL cholesterol and LDL cholesterol reduction.

Discussion

Treatment with atorvastatin reduces the risk of cardiovascular disease, transient ischemic attack, and stroke in part through the stabilization of atherosclerotic plaque.⁹ Stabilization of carotid plaques by pharmacological intervention including atorvastatin is a promising strategy for stroke prevention. In the present study, we observed a decreased echolucency (increased echodensity) of carotid artery plaques after short-term treatment with high dose

of atorvastatin suggestive of plaque stabilization. This effect was independent of baseline LDL cholesterol levels and the degree of LDL reduction 30 days following the atorvastatin treatment. In this short-term study, we did not find a reduction of plaque size or a plaque number from baseline. Recently, in the same study population and using the same experimental design, we also demonstrated an improvement in carotid elasticity with short-term administration of high-dose atorvastatin.²

The mechanism by which atorvastatin alters the atherosclerotic plaque morphology includes reducing plaque lipid content, inflammation, and thrombotic actions as a consequence of plasma lipid-lowering effects and/or the pleiotropic mechanisms. In experimental studies, a carotid plaque stabilizing effect of atorvastatin has been demonstrated by regulating 5-lipoxygenase pathway in rabbits,¹⁰ and by modifying inflammatory pathways regulated by NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells), PPAR α (peroxisome proliferator-activated receptor alpha), and PPAR γ (peroxisome proliferator-activated receptor gamma).¹¹ The observed reduction in carotid plaque echogenicity measured by GSD index in our study was independent of LDL cholesterol levels or LDL cholesterol change after treatment, supporting the pleiotropic effect of atorvastatin on plaque stabilization.

The introduction of high-resolution B-mode scanners and the use of a quantitative computer-assisted ultrasonographic index of echogenicity such as the GSD or GSM index have greatly improved the correlation between plaque characterization, plaque histological components, and clinical features.^{12,13} Low echogenicity of the carotid plaque has been related to an increased risk of incident stroke and recurrent stroke after carotid stenting.^{14,15} In the ICAROS (Imaging in Carotid Angioplasty and Risk of Stroke), carotid plaque echolucency (GSM 25 or less) increased the risk of stroke after carotid artery stenting. In a study using three-dimensional ultrasound-derived vessel wall volume, a significant decrease in vessel wall volume was reported in 35 patients with carotid stenosis >60% after 3-month treatment with 80 mg of atorvastatin compared to placebo.¹⁶ Similar was observed using MRI T2 plaque imaging by the administration of ultrasmall super-paramagnetic iron oxide particles. A significant difference in ultrasmall superparamagnetic iron oxide particle uptake between patients treated with low dose (10 mg) versus high dose (80 mg) of atorvastatin at different follow-up time points (0, 6, and 12 weeks) was reported, indicating dose-response effects on plaque inflammation.¹⁷ The GSD index or GSM may be even more promising marker of plaque stabilization of potential clinical use because of simplicity of assessment, reliability, and ability to be measured from plaque images collected during a standard clinical B-mode ultrasonography.

Strengths of our study include quantitative, computer-assisted evaluation of carotid plaque echogenicity following a standardized and validated carotid ultrasound imaging protocol, which was optimized for sequential plaque assessments and image analyses.⁶ Potential weaknesses are a small number of participants and a lack of placebo group. Another limitation to acknowledge is the short duration of the study, which prevented from identifying any relationship with clinical outcomes.

This is a pilot study; therefore, interventions yielding reductions in carotid plaque echogenicity should be further explored for their potential impact on reducing vascular risk. Ultrasonographic plaque echogenicity index such as the GSD index may help in the vascular risk stratification in order to target individuals at increased vascular risk for intensive preventive therapies and for monitoring of the effects of anti-atherosclerotic therapies.

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Figure 1.
Carotid plaque gray-scale densitometry index calculation.

Table 1

Laboratory and clinical parameters before and 30 days after atorvastatin treatment

	Baseline	30 days after treatment	P
Body mass index (kg/m ²)	28±4.9	28±4.5	NS
Total cholesterol (mg/dl)	221±30	127±17	<0.01
LDL (mg/dl)	144±38	70±25	<0.01
HDL (mg/dl)	49±15	50±14	NS
Triglyceride (mg/dl)	134±63	127±82	NS
Fast glucose (mg/dl)	100±28	103±24	NS
SBP (mmHg)	137±17	135±15	NS
DBP (mmHg)	79±9	77±10	NS
Average number of carotid plaques	2	2	NS
Mean maximal carotid plaque thickness (mm)	1.78	1.69	NS
GSD index	73±16	89±15	<0.05

Note: LDL: low-density lipoprotein; HDL: high-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; GSD: gray-scale densitometry; NS: not significant.