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ORIGINAL PAPER

Anti-inflammatory effect of statin is continuously working throughout use: a prospective three time point ^{18}F-FDG PET/CT imaging study

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Abstract

No data exist whether statins have robust anti-inflammatory effects of atherosclerotic plaques primarily during the early treatment period or continuously throughout use. This prospective three time point ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) study of the carotid artery assessed anti-inflammatory effects of statin during the early treatment period (initiation to 3 months) and late treatment period (3 months to 1 year) and their correlation with lipid and inflammatory profile changes during a year of therapy. Nine statin-naïve stable angina patients with inflammatory carotid plaques received 20 mg/day atorvastatin after undergoing initial ^{18}F-FDG PET/CT scanning of carotid arteries and ascending thoracic aorta, and then completed serial ^{18}F-FDG PET/CT imaging at 3 and 12 months whose data were analyzed. The primary outcome was the inter-scan percent change in target-to-background ratio (ΔTBR) within the index vessel. At 3 months of atorvastatin treatment, mean serum low-density lipoprotein cholesterol (LDL-C) level decreased by 36.4% to < 70 mg/dL (p = 0.001) and mean serum high-density lipoprotein cholesterol level increased to > 40 mg/dL (p = 0.041), with both maintained with no further reduction up to 1 year (p = 0.516 and 0.715, respectively) while mean serum high sensitivity C-reactive protein level only numerically decreased (p = 0.093). The index vessel ΔTBR showed continuous plaque inflammation reduction over 1 year, by 4.4% (p = 0.015) from the initiation to 3rd months and 6.2% (p = 0.009) from 3rd months to 1 year, respectively, without correlation with lipid profile changes. The ΔTBR of the bilateral carotid arteries and ascending aorta also continuously decreased from 3 months to 1 year. Three time point ^{18}F-FDG PET/CT imaging demonstrates that statin's anti-inflammatory effect continues throughout its use up to 1 year, even though yielding stable below-target plasma LDL-C levels at 3 months.

Keywords Statin · ^{18}F-FDG PET/CT · Low-density lipoprotein cholesterol

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Abbreviations

^{18}F-FDG	F-18 fluorine fluorodeoxyglucose
HDL-C	High-density lipoprotein cholesterol
hs-CRP	High sensitivity C-reactive protein
LDL-C	Low-density lipoprotein cholesterol
MBq	Megabecquerel
MDS	Most diseased segment
MRI	Magnetic resonance imaging
PET/CT	Positron emission tomography/computed tomography
ROI	Region of interest
SUV_{max}	Maximum standardized uptake value
TBR	Target to background ratio

Introduction

The impact of statins on clinical outcome has been well established in patients with atherosclerotic cardiovascular diseases, exerted by dual mechanisms including plasma low density lipoprotein-cholesterol (LDL-C) lowering and pleiotropic anti-inflammatory effects on atherosclerotic plaques [1–5]. Interestingly, studies evaluating time-dependent LDL-C lowering effect of statin have found that it rapidly lowered plasma LDL-C level within 6 or 16 weeks of therapy, and maintained LDL-C levels thereafter up to 1 year with little need for up-titration [6, 7]. However, studies monitoring its anti-inflammatory effects on atherosclerotic plaques are limited in terms of study duration up to 3 months. A landmark imaging study of human atherosclerotic plaque inflammation using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) of carotid arteries, a noninvasive measure of atherosclerotic plaque inflammation, demonstrated that statin therapy had significant dose-dependent reductions in vascular inflammation from the initiation to 3 months after therapy [8]. However, no data exist whether statins have robust anti-inflammatory effects of atherosclerotic plaques continuously throughout use, or primarily during the earlier treatment period [9, 10].

To address this issue, we adopted this prospective three time point ^{18}F-FDG PET/CT study, assessed anti-inflammatory effects of a statin during the early treatment period (initiation to 3 months) and late treatment period (3 months to 1 year), and their correlation with lipid and inflammatory profile changes during a year of therapy.

Methods

Design and subjects

This study was a prospective, open-labeled, single-center study. Consecutive stable angina patients who underwent percutaneous coronary intervention were screened using cervical ultrasound for carotid artery atherosclerosis. Patients who had non-calcified carotid atherosclerotic plaques that were ≥ 3 mm in extent and who had not been treated with any lipid-lowering drugs (statins, fibrates, or nicotinic acid) within 4 weeks were eligible for the study.

Patients with active infectious disease, diabetes, chronic kidney disease (glomerular filtration rate, GFR < 60 mL/min/1.73 m^2), a history of cardiovascular disease (stroke, myocardial infarction) or cancer were excluded. The study protocol was approved by the Institutional Review Board of Seoul St. Mary's Hospital, Seoul, Korea. All subjects submitted written informed consents.

^{18}F-FDG PET/CT imaging

After at least 6 h of fasting and confirmation of blood sugar levels lower than 130 mg/dL, the study patients were intravenously administered 370 to 555 MBq of ^{18}F-FDG [11]. The patients were subjected to bed rest before image acquisition. Sixty minutes after FDG injection, PET/CT images were obtained using a dedicated PET/CT scanner (BiographTruepoint; Siemens Medical Solutions, Knoxville, TN). Non-contrast-enhanced CT images were first obtained from the skull base to the proximal thigh and were used for attenuation correction (40-section helical, 5 mm slice thickness). PET images were acquired at 2 min per bed with approximately five to six beds. Ninety minutes after FDG injection, delayed PET/CT images of the carotid arteries and ascending thoracic aorta were obtained. Non-contrast-enhanced CT images were obtained from the skull base to the lower margin of the neck, and PET images were then acquired at 10 min per bed with approximately two to three beds. Three months and 1 year after atorvastatin therapy, follow-up PET/CT images were obtained using the same imaging protocol.

PET/CT imaging analysis

Imaging analysis was performed on a workstation using fusion software (Syngo; Siemens Medical Solutions, Knoxville, TN). FDG uptake was measured along both carotid arteries (starting at the bifurcation and extending inferiorly) and along the ascending thoracic aorta (starting 2–3 cm above the aortic valve and continuing to the bottom of the aortic arch) at approximately 5 mm intervals in the axial direction. On each image slice, a region of interest (ROI) was chosen within the artery, and the maximum standardized uptake value (SUV_{max}) was calculated. The SUV is the decay-corrected tissue concentration of FDG that is adjusted for the injected dose and the body weight and is a widely used parameter for the quantification of FDG uptake.

We calculated the target to background ratio (TBR) by normalizing the blood pool activity by dividing the arterial SUV by the blood pool SUV estimated from either the internal jugular vein or the inferior vena cava. To evaluate the blood pool activity, at least five ROIs were identified in consecutive vein slices, and the values were averaged. For the 3 month and 1 year follow-up PET/CT images, we obtained the TBRs using the same method.

Measurement of blood metabolic, lipid, and inflammation biomarkers

Blood was collected before atorvastatin therapy, which was baseline, and at 3 months and 1 year after therapy to measure serum metabolic, lipid and inflammation biomarkers.

Fasting serum glucose, total cholesterol, triglyceride, direct LDL-C and direct high-density lipoprotein cholesterol (HDL-C) levels were measured on a Hitachi 7600 automatic chemistry analyzer (Hitachi Co., Tokyo, Japan) using reagents from Sekisui Medical (Tokyo, Japan). High sensitivity C-reactive protein (hs-CRP) levels were measured using an immunoturbidimetric assay with reagents from Wako Pure Chemical Industries (Osaka, Japan) on a Hitachi 7600 automatic chemistry analyzer.

Outcomes

The primary outcome was the percent change in arterial wall FDG uptake within the index vessel (either right carotid, left carotid, or ascending thoracic aorta) from the baseline to second and from second to third ^{18}F-FDG PET/CT scans, assessed by the change in target-to-background ratio (ΔTBR) within the index carotid artery. Index vessel was defined as the artery with a highest TBR among right and left carotid arteries, and ascending thoracic aorta.

Additionally, we conducted a separate exploratory analysis on the carotid arteries only because these vessels are responsible for atherothrombotic stroke. We referred to a carotid artery with plaque buildup detected with US before the treatment as the index vessel. In the case where both carotid arteries had plaque buildup, we chose the one with a greater TBR to serve as the index vessel.

In the PET/CT images, we obtained two variables to assess arterial FDG uptake: (1) the mean TBR, which is the average of TBR for all of the axial segments from each artery, and (2) the most diseased segment (MDS) TBR, which is the average TBR of the most diseased segment. The MDS was defined as the 1.5 cm segment comprising the three contiguous axial segments with the greatest SUV in each artery. The percent change in the TBR (ΔTBR) was calculated between the baseline and 3 month and 1 year follow-up PET/CT images.

The secondary outcomes included change from baseline in fasting blood sugar, glycated hemoglobin, lipid profiles and hs-CRP after 3 months and 1 year of statin therapy and their correlation with ΔTBR from PET/CT.

Statistical analyses

Statistical analyses were performed using SPSS (v13.0; San Diego, CA). The data are expressed as the mean ± standard error of the mean. Repeated measures analysis of variance (ANOVA) was used to assess differences in the FDG uptake and the blood parameters between baseline and 3 months and 1 year of therapy. Associations were tested using Pearson's correlation coefficient. A p-value of less than 0.05 was considered statistically significant. Adjustments for multiple comparisons were not performed because of the small sample size.

Results

Clinical characteristics

Nine statin-naïve patients who consented to undergo ^{18}F-FDG PET/CT at baseline completed serial PET/CT scans at 3 months and 1 year of follow-up. All of the patients received 20 mg/day atorvastatin from the baseline study up to 1 year (Fig. 1). The demographic of 8 patients [4 males; mean age 58 years (range 51–74)] who completed 1-year follow-up is displayed in Table 1. More than 50% of the patients had angiographically documented multi-vessel coronary artery disease, but all patients had normal systolic function of the left ventricle.

Treatment effects of atorvastatin on laboratory results

Atorvastatin 20 mg/day significantly reduced serum total cholesterol ($p = 0.003$) within 3 months of therapy but did not reduce triglycerides ($p = 0.057$, Table 2). Serum LDL-C levels markedly decreased from 101.38 ± 28.49 to 64.87 ± 12.70 mg/dL ($p = 0.003$) at 1 year of therapy; the decrease mainly occurred within the first 3 months. The first 3 months of therapy effectively reduced LDL-C to less than 70 mg/dL (59.75 ± 11.25 mg/dL), and this level was well maintained for the remaining 9 months. However, no more reductions occurred despite long-term statin use (Fig. 2a).

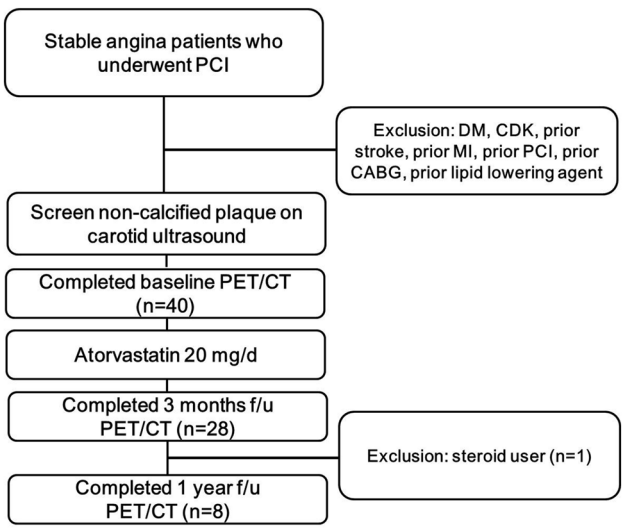

Fig. 1 Forty eligible patients were assigned to receive 20 mg of atorvastatin daily. A total of nine patients completed the serial FDG-PET/CT imaging and blood sampling

Table 1 Baseline clinical characteristics at admission

Clinical characteristics	N = 8
Age (years)	56.8 ± 8.78
Male [n (%)]	4 (50.0)
Body mass index (kg/m^2)	25.1 ± 2.1
Hypertension [n (%)]	3 (37.5)
Dyslipidemia [n (%)]	1 (12.5)
Current smoker [n (%)]	3 (37.5)
CVA [n (%)]	0 (0)
Previous MI [n (%)]	0 (0)
Multivessel CAD [n (%)]	5 (62.5)
Family history of CAD [n (%)]	1 (12.5)
LVEF %	60.66 ± 5.16
Medication at discharge after index PCI	
Aspirin [n (%)]	8 (100.0)
Clopidogrel [n (%)]	8 (100.0)
Atorvastatin [n (%)]	8 (100.0)
Beta blocker [n (%)]	6 (75.0)
ACE inhibitor or ARB [n (%)]	8 (100)
Ca-channel blocker [n (%)]	1 (12.5)
Medication at 3 months	
Aspirin [n (%)]	8 (100.0)
Clopidogrel [n (%)]	8 (100. 0)
Atorvastatin [n (%)]	8 (100.0)
Beta blocker [n (%)]	5 (62.5)
ACE inhibitor or ARB [n (%)]	8 (100)
Ca-channel blocker [n (%)]	0 (12.5)
Nitrate [n (%)]	1 (12.5)
Nicorandil [n (%)]	1 (12.5)
Medication at 1 year	
Aspirin [n (%)]	8 (100.0)
Clopidogrel [n (%)]	6 (75.0)
Atorvastatin [n (%)]	8 (100.0)
Beta blocker [n (%)]	6 (75.0)
ACE inhibitor or ARB [n (%)]	8 (100)
Nitrate [n (%)]	1 (12.5)
Nicorandil [n (%)]	2 (25.0)

The same pattern was noted for HDL-C levels. Within the first 3 months, HDL-C levels increased from 34.88 ± 6.46 to 39.75 ± 7.88 mg/dL (p = 0.050), but no additional improvement occurred during the remaining 9 months (Fig. 2b). Figure 3 shows an example of serial ^{8}F-FDG PET/CT results. At baseline, intense FDG uptake is noted at a right carotid plaque (Fig. 3a). After 3 months of statin treatment, the same plaque demonstrated less FDG uptake than at baseline (Fig. 3b). After 1 year of therapy, less plaque inflammation was observed than at 3 months (Fig. 3c).

One of the best-known serum inflammatory biomarkers, hs-CRP, demonstrated a pattern of gradual numerical decrease (1.16 ± 1.16 mg/L at baseline and 0.44 ± 0.28 mg/L and 0.41 ± 0.23 mg/L at the end of 3 months and 1 year of therapy, respectively), but no significant difference was found. No changes occurred during the statin therapy in the levels of fasting blood sugar and glycated hemoglobin.

Treatment effects on ^{18}F-FDG PET/CT image

The average TBRs of each vessel at baseline were greater than 1.6, indicating that vascular inflammation was sufficiently identifiable by ^{18}F-FDG PET/CT (Table 3). The TBRs within the index vessel were continuously reduced by 5.38% and 4.61% for the first 3 months and the last 9 months of therapy, respectively (p = 0.005 and 0.006, Fig. 4). The same patterns of decrease were also noted for TBRs within the index carotid artery (Fig. 5).

The percent change in TBRs from baseline to 3 months of statin therapy and from 3 months to 1 year were compared (Fig. 6). A 5.4% reduction of TBR during the first 3 months of therapy and an additional 4.7% reduction during the last 9 months of therapy were found when assessing the index vessels. The reduction rate of the TBR in the index vessel was 1.79% per month during the first 3 months of therapy and was slightly decreased to 0.51% per month for the next 9 months. This pattern was also demonstrated in the index carotid artery and in the MDS.

Table 2 Laboratory findings at follow-up

	Laboratory findings			p values		
	At admission	3 months	1 year	p*	p†	p‡
Glucose (mL/dL)	109.63.00 ± 61.46	107.38 ± 18.21	107.13 ± 18.66	0.284	0.951	0.656
HbA1c	5.85 ± 0.56	5.9 ± 0.97	6.05 ± 0.88	0.448	0.402	0.373
Total cholesterol (mL/dL)	185.00 ± 38.77	126.25 ± 17.76	136.62 ± 23.26	0.003	0.480	0.002
Triglyceride (mL/dL)	278.88 ± 194.95	166.50 ± 118.43	171.1 ± 95.72	0.057	0.972	0.083
LDL-C (mL/dL)	101.38 ± 28.49	59.75 ± 11.25	64.87 ± 12.7	0.001	0.516	0.003
HDL-C (mL/dL)	34.88 ± 6.46	39.75 ± 7.88	44.25 ± 5.34	0.050	0.715	0.029
hs-CRP (mg/L)	0.11 ± 0.13	0.14 ± 0.22	0.04 ± 0.23	0.093	0.339	0.339

*At admission and 3 months, †at 3 months and 1 year, ‡at admission and 1 year

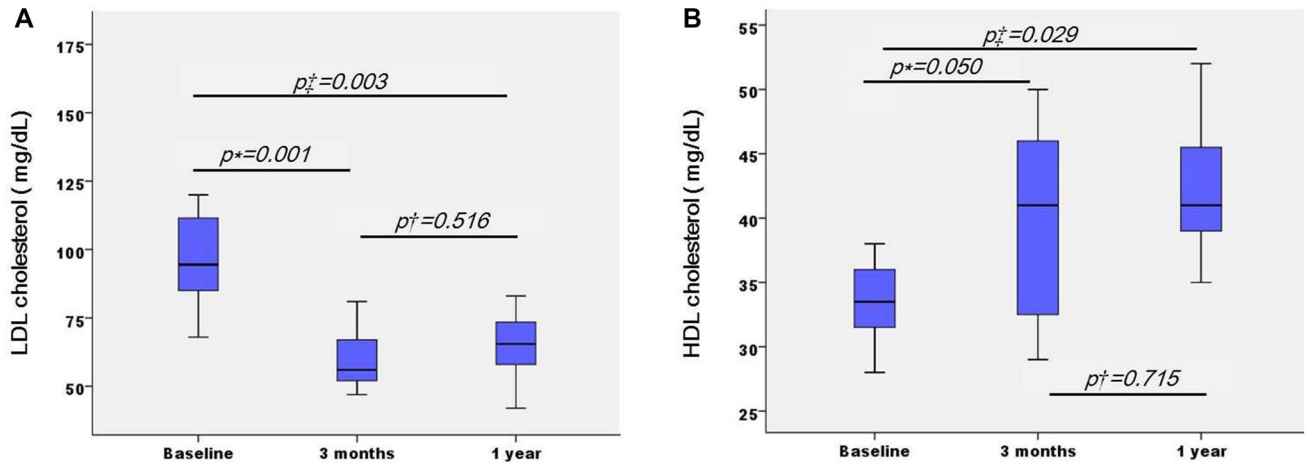

Fig. 2 **a** Serum LDL-C levels of patients (n = 9) who completed 1 year follow-up PET/CT significantly decreased after 1 year of therapy ($p < 0.001$), primarily during the first 3 months. The first 3 months of therapy effectively reduced LDL-C to less than 70 mg/dL, whereas no additional reductions occurred with long-term statin use ($p = 0.516$). **b** Within the first 3 months, HDL-C levels significantly increased ($p = 0.041$), but no additional improvement occurred during the last 9 months ($p = 0.0715$)

Comparison and correlation of the changes in laboratory results and ^{18}F-FDG PET/CT

Whereas serum LDL-C levels decreased below the target level of 70 mg/dL during the first 3 months of statin therapy and did not change during the last of 9 months, the ΔTBR identified by ^{18}F-FDG PET/CT, was continuously reduced in a time-dependent manner. The reduction rate of the TBR, according to the duration of treatment, gradually decreased over time. Additionally, HDL-C levels increased within 3 months but did not improve more during the next 9 months of therapy. hs-CRP levels failed to demonstrate a significant anti-inflammatory effect of the statin during the 1 year of treatment, although the levels were greater than 1 mg/dL at baseline.

Although a trend was observed between the changes in hs-CRP levels and the ΔTBR on the index vessel was observed ($r = 0.55$, $p = 0.19$), no significant correlation was found between the LDL-C and ΔTBR in this study ($r = 0.07$, $p = 0.85$). Likewise, no significant relationship was found between hs-CRP and LDL-C in the change from baseline ($r = 0.37$, $p = 0.40$). The TBR and the ^{18}F-FDG PET/CT value were the only measures that discriminated differences in inflammation between the treatment durations.

Discussion

Using three time point ^{18}F-FDG PET/CT imaging study, we assessed the effect of atorvastatin 20 mg daily on carotid plaque inflammation and compared these results to the lipid lowering effect over the treatment duration of 1 year. Serum LDL-C levels decreased for the first 3 months of statin therapy, but no additional significant reduction occurred over the following 9 months. Additionally, in the ^{18}F-FDG PET/CT findings, the ΔTBR continuously decreased in a time-dependent manner. This is the first study to visualize the anti-inflammatory effect of statins in serial images and compare these findings with the lipid-lowering effects during the period of 1 year.

The treatment duration resulting in complete resolution of vascular inflammation by statin remains unclear. It is yet to be investigated whether statin's anti-inflammatory action disappear when serum LDL-C reaches below 70 mg/dL or statin's plaque-cooling effect persist over a year regardless of serum LDL-C levels. Several studies have reported that statin's effects on hs-CRP levels occur within 5 weeks of treatment [12, 13]. Additionally, a magnetic resonance imaging (MRI) study found that a minimum of 12 months of treatment was required to observe a reduction in plaque size although the expected hypolipidemic effect of the statin was detected at 6 weeks [14]. Recently, Tawakol A et al. imaged carotid arteries using ^{18}F-FDG PET/CT, 4 and 12 weeks after beginning statin treatment, and a reduction in plaque activity was apparent as early as 4 weeks after treatment [8]. These onset-timing differences in anti-inflammatory effect may arise from the difference between systemic and local effects. However, a time-gap clearly exists between the lipid-lowering and anti-inflammatory effects; to achieve a sufficient anti-inflammatory effect. Thus, the onset and plateau timing of statins' anti-inflammatory effect on atherosclerotic plaques should be clearly defined.

Although statins have reduced cholesterol levels and lowered mortality rates, these drugs still allow some cardiovascular events to occur. A potential explanation for the residual burden of cardiovascular morbidity and mortality could

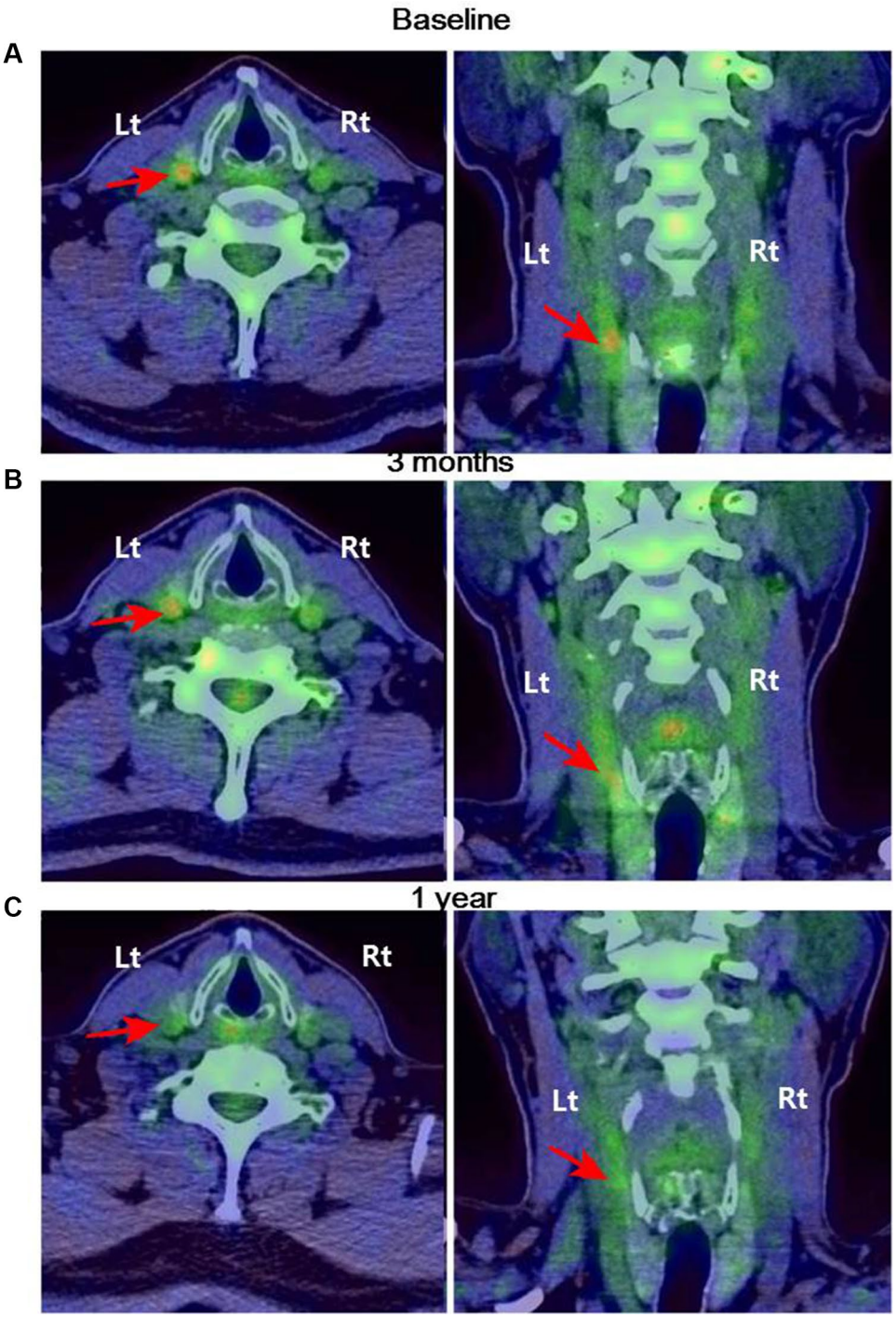

Fig. 3 **a** Plaque inflammation in the carotid artery of a patient is observed on the baseline PET/CT with high FDG uptake (arrow). **b** After 3 months of statin treatment, the same plaque demonstrated less FDG uptake (arrow) than at baseline. **c** Additionally, after 1 year of therapy, less plaque inflammation was observed (arrow) than was previously found

relate to the degree of LDL-C lowering that is achieved. However, no clinical trial evidence has clearly indicated the "lower limit" of benefit achievable by LDL-C reduction. The PROVE-IT trial supports the idea that "lower is better". In patients with acute coronary syndrome, the lower LDL-C level group yielded better clinical outcomes than patients in the less aggressively treated group [4]. In patients with stable coronary artery disease, more aggressive LDL-C lowering resulted in a greater improvement in atheroma morphology, as assessed by intravascular ultrasonography [15, 16]. However, statin's LDL lowering effects have shown fairly "flat" dose–response curves. Upon doubling the dose of a typical statin, LDL-C further decreases by approximately 6–7% indicating that the improved clinical outcomes may come not only from the LDL-C-lowering effect [17].

Statins not only possess lipid-lowering effects but also exert effects on systemic inflammatory biomarkers. However, no studies have focused on both effects in serial images

Table 3 FDG-PET/CT findings at follow-up

	TBR			Δ TBR %		‡(*p*)
	At admission	3 months	1 year	*(*p*)	†(*p*)	
TBR						
Right carotid artery	1.60 ± 0.16	1.55 ± 0.18	1.49 ± 0.18	3.12% (0.022)	3.87% (0.036)	6.87% (0.001)
Left carotid artery	1.54 ± 0.13	1.49 ± 0.15	1.42 ± 0.10	3.24% (0.008)	4.69% (0.017)	7.79% (0.001)
Ascending thoracic aorta	1.56 ± 0.20	1.51 ± 0.11	1.45 ± 0.11	3.20% (0.388)	3.97% (0.007)	7.05% (0.024)
TBR within index vessel (R-3, L-1, Ao-4)	1.67 ± 0.13	1.58 ± 0.11	1.50 ± 0.12	5.38% (0.005)	4.61% (0.006)	9.95% (0.001)
Most diseased segment TBR of index vessel	1.89 ± 0.23	1.77 ± 0.23	1.64 ± 0.18	6.34% (0.041)	7.06% (0.025)	13.1% (0.006)
TBR within index carotid artery (R-7, L-2)	1.62 ± 0.15	1.55 ± 0.17	1.49 ± 0.15	4.32% (0.001)	3.78% (0.007)	7.53% (< 0.001)
Most diseased segment TBR of index carotid artery	1.85 ± 0.27	1.79 ± 0.26	1.68 ± 0.19	3.24% (0.064)	5.79% (0.053)	8.91% (0.004)

*At admission and 3 months, †at 3 months and 1 year, ‡at admission and 1 year

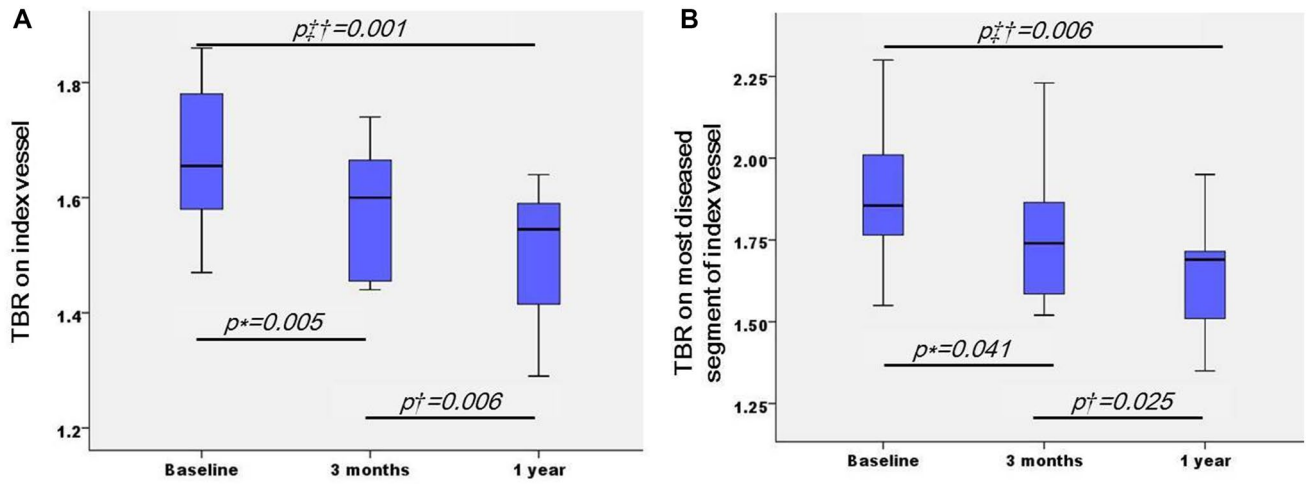

Fig. 4 **a** The TBRs of patients (n = 9) who completed 1 year follow-up PET/CT within the index vessel were continuously reduced during the first 3 months and last 9 months of therapy (p = 0.021 and 0.005, respectively). **b** The same patterns of decrease were also noted in the most diseased segment of the index vessel

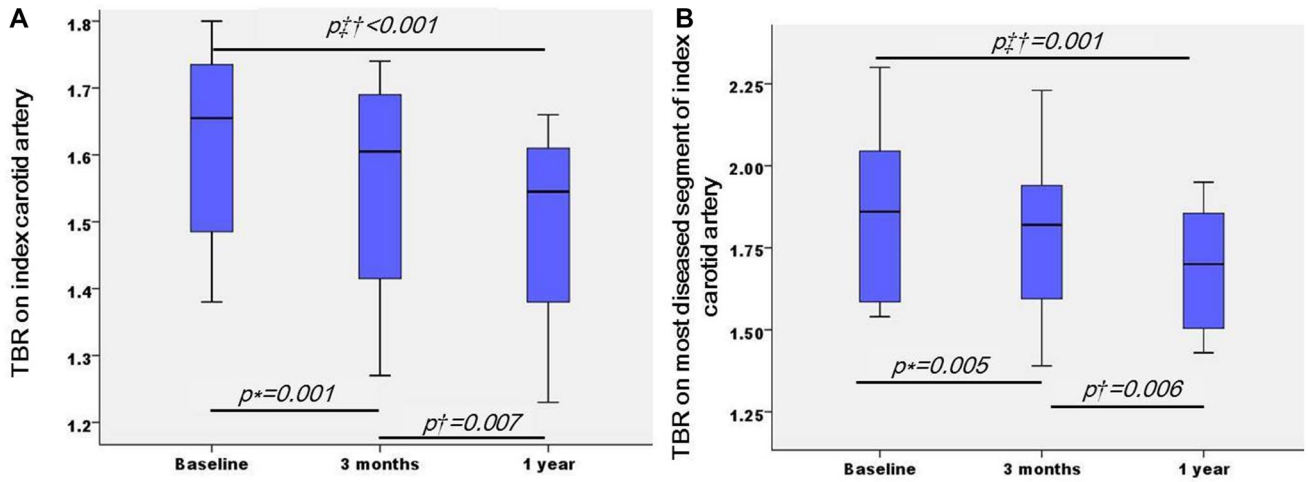

Fig. 5 **a** The TBRs of patients (n = 9) who completed 1 year follow-up PET/CT within the index carotid artery showed continuous reductions during 1 year of therapy (p = 0.015 and 0.009 during the first 3 months and the last 9 months of treatment, respectively). **b** The same patterns of decrease were also noted in the most diseased segment of the index carotid artery

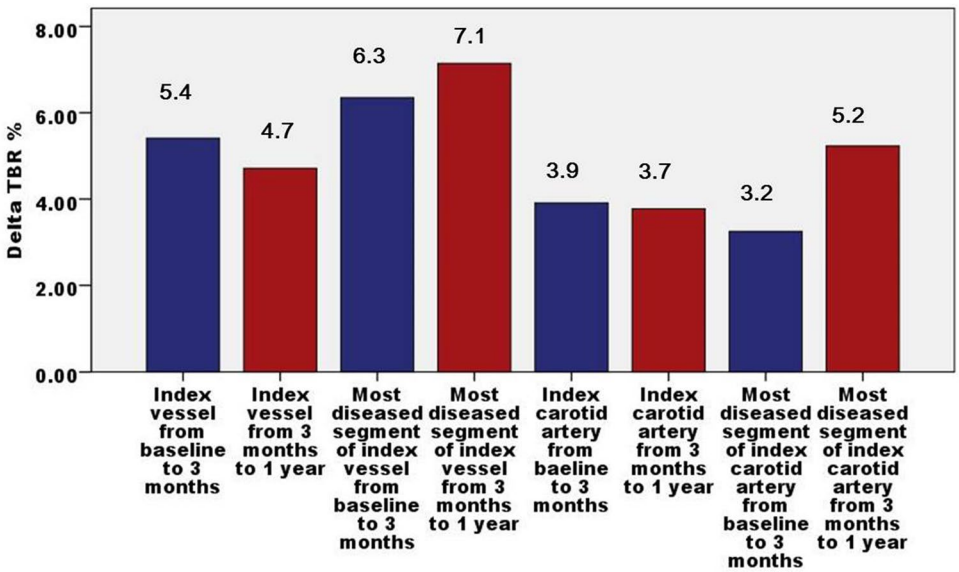

Fig. 6 Significant reductions in ΔTBRs of patients (n = 9) who completed 1 year follow-up PET/CT were observed during the last 9 months of treatment for each index. However, the reduction rates were greater for the first 3 months of treatment, at greater than 1% per month, compared with the last 9 months of treatment; the anti-inflammatory effects are apparently more effective at the beginning of statin therapy

to compare onset timing. In this context, the present study is well designed; baseline hs-CRP levels were greater than 1 mg/L, indicating the occurrence of sufficient systemic inflammatory reactions [18]. The baseline TBR of the carotid plaque was greater than 1.6, indicating sufficient local plaque inflammation [19]. Additionally, the baseline lipid profile showed a dyslipidemic status. These baseline inflammation and dyslipidemia characteristics and the sufficiently long 1-year follow-up period support the evidence that statins affect the onset timing of both effects. However, the small population number is an important limitation in this study. Three time point ^{18}F-FDG PET/CT imaging was a great barrier to patient recruitment and retention. In conclusion, with serial ^{18}F-FDG PET/CT imaging study of carotid plaques, statin treatment appeared to have a continuous anti-inflammatory effect on carotid atherosclerosis up to 1 year, even after stable plasma LDL-C levels were achieved at 3 months. This is the first study to successfully visualize that a statin further exerts anti-inflammatory actions on atherosclerotic plaques even after achieving target LDL-C below 70 mg/dL.

Perspectives

Clinical competencies

^{18}F-FDG PET/CT images can image, track and quantify the anti-inflammatory effect of a statin on carotid plaques. Contrary to expectations, statins still exert anti-inflammatory actions on carotid atherosclerosis independent of its lipid lowering effect or systematic anti-inflammatory effect up to 1 year.

Translational outlook

Considering that achieving LDL-C level below 70 mg/dL does not mean the complete resolution of plaque inflammation in culprit lesions, it appears beneficial to maintain high-intensity statin at least for the first 1 year after cardiovascular events.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interests.

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