The Early Effect of Lipid-lowering Treatment on Carotid and Femoral Intima Media Thickness (IMT)†

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Objectives: an increased intima media thickness (IMT) is an early indicator of the atherosclerotic process. We investigated the early effect of atorvastatin on the common carotid artery (CCA) and common femoral artery (CFA) IMT.

Methods: the IMT was measured in the CCA and the CFA of hyperlipidaemic patients referred with peripheral vascular disease. The measurements were performed using an automated radio frequency IMT technique pre-treatment and at 4 and 8 weeks post-treatment with 20 mg/day atorvastatin.

Results: patients (14 men; 11 women), median age 69 years (range: 48–81) had a CCA-IMT mean (SD) of 0.79 (0.21) mm pre-treatment, 0.75 (0.22) mm after 4 weeks, and 0.64 (0.15) mm after 8 weeks. The ANOVA test was significant (p = 0.024) for the CCA-IMT trend. The corresponding CFA-IMT readings were 0.83 (0.13) mm, 0.80 (0.09) mm and 0.69 (0.14) mm (p = 0.0003). After 8 weeks of treatment there was a significant reduction in total cholesterol 6.0 (0.3) to 4.3 (0.8) mmol/l, p = 0.0004 and low-density lipoprotein cholesterol 3.7 (0.2) to 2.2 (0.5), p = 0.0001. There was a significant decrease in median serum creatinine levels after 8 weeks treatment: 87 μmol/l (range 67–114) to 84 μmol/l (range: 64–112), p = 0.007.

Conclusions: cholesterol-lowering with atorvastatin 20 mg/day leads to a decrease in CCA-IMT and CFA-IMT. This difference achieved significance after 8 weeks of treatment, but a trend was visible at 4 weeks. These rapid changes in IMT may be attributable to an anti-inflammatory effect. IMT measurement may be a useful tool to rapidly assess the effect of drug treatment on the atherosclerotic process.

Key Words: Atorvastatin; Intima media thickness; Femoral; Carotid; Creatinine; Peripheral vascular disease; Urate.

Introduction

The common carotid artery intima media thickness (IMT) (CCA-IMT) can be measured accurately non-invasively.1–5 Furthermore, an increased CCA-IMT is associated with major cardiovascular risk factors and is a powerful predictor of cardiovascular events, particularly those associated with ischaemic heart disease (IHD).6–9 In 133 patients the severity of coronary disease, as shown by coronary angiography, was significantly correlated with the CCA-IMT when measured by ultrasonography.10 Increased CCA-IMT is strongly associated with a risk of stroke11 and small changes in the CCA-IMT were also associated with clinically significant atherosclerosis in the peripheral arteries.12 There are only a few studies involving the common femoral artery IMT (CFA-IMT). They showed that the combined assessment of the carotid and femoral arterial walls provides a more accurate estimate of the atherosclerotic burden in patients with familial hyperlipidaemia.13 The femoral and carotid IMT was also increased in smokers without other vascular risk factors.14,15 B-mode (two-dimensional) duplex ultrasound is also increasingly used for non-invasive visualisation and monitoring of atherosclerotic changes in the vasculature. Its use in measuring the CCA-IMT is now established as a method.16–19 It can be concluded from these studies that the IMT may represent the sum of the cardiovascular risk in an individual. Therefore, the IMT is expected to be increased in those with established vascular disease.

Cholesterol-lowering treatment effectively prevents IHD-related events and strokes10,21 and also significantly reduces overall mortality in patients with established IHD.22 In turn, hyperlipidaemia predisposes to an increased CCA-IMT23 and cholesterol-lowering treatment causes CCA-IMT regression.24,25 Therefore, we monitored the CCA-IMT and CFA-IMT...
Intima Media Thickness and Lipid-lowering Treatment

Table 1. Baseline characteristics of the patients. Values are expressed as mean (SD) unless otherwise stated.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>25</td>
</tr>
<tr>
<td>Age median (range) (years)</td>
<td>69 (48–81)</td>
</tr>
<tr>
<td>Gender (M,F)</td>
<td>14,11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5 (2.8)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>145 (10)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>87 (8)</td>
</tr>
<tr>
<td>No. of current smokers (%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>No. of ex-smokers (%)</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>No. of patients on aspirin (%)</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>No. of patients on antihypertensives (%)</td>
<td>20 (80%)</td>
</tr>
</tbody>
</table>

BMI = body mass index.

in patients with peripheral vascular disease (PVD) and raised serum cholesterol 4 and 8 weeks after treatment with atorvastatin. The aim of the study was to establish whether the IMT was significantly changed within this short period.

Methods

A total of 25 patients (14 men and 11 women), median age 69 years (range: 48–81) were recruited. Their pre-treatment characteristics are shown in Table 1. The study population consisted of patients who were referred to a university hospital vascular surgery clinic with stable PVD and who were found to have a serum cholesterol level ≥ 5.5 mmol/l. PVD was defined as stable uncomplicated intermittent claudication with an ankle/brachial pressure index <0.08.

Exclusion criteria

Patients with critical leg ischaemia, significant carotid artery disease (>70% stenosis) or previous carotid surgery, diabetes mellitus, poorly controlled hypertension, serum creatinine level above the upper limit of the reference range (120 μmol/l) and patients receiving lipid-lowering treatment were excluded.

Blood samples and measurements

A fasting (12 h) venous sample was obtained to assess: (1) Lipid profile, (2) haematological and biochemical profile, (3) plasma fibrinogen and factor XII levels (as indices of the coagulation system), and (4) renal and liver function tests.

Carotid and femoral artery IMT measurements and trial design

A variety of IMT measurement protocols, based on different ultrasound methods, have been developed in order to obtain reliable and reproducible results.16 We used an automatic technique,17 that has been validated against the conventional manual technique; there was a significant correlation between the two methods.27 This technique has been described elsewhere in detail;17,27 in brief, patients were scanned in the supine position and electrocardiographic (ECG) leads were placed appropriately on the chest wall for ECG R-wave triggered measurements. A longitudinal B-Mode image of the blood vessel was visualised using a duplex ultrasonography scanner with a 7.5 MHz linear-transducer (Scanner 350, Pie Medical System, Maastricht, The Netherlands), then switched to echo M-mode with a high pulse-repetition frequency and a short activation pulse. The radio frequency (RF) signals were transferred to a computer with wall tracking software and the IMT was determined automatically (WTS ver 2.0, Pie Medical System, Maastricht, The Netherlands).17

The IMT was measured at the posterior wall, because the trailing edge of the adventitia signal of the anterior wall will obscure the media and influence the measurement of this IMT. On the other hand the far wall is well visualised and likely to show the earliest atherosclerotic changes.17 The same locations of arteries were scanned pre-treatment as well as at 4 and 8 weeks after treatment with atorvastatin (Lipitor™) 20 mg/day.

The IMT measurements were taken 2 cm proximal to the carotid bifurcation. The IMT was expressed as the mean of six measurements taken at each visit; these were blindly analysed. The same method was used for the femoral artery measurements, which were taken 2 cm proximal to the origin of the superficial femoral artery.

Ethics, data collection and statistical analysis

The Ethics Committee of the Royal Free Hospital NHS Trust approved the study and written consent was obtained from each patient. The data was blindly analysed by giving random numbers to each measurement of IMT and each blood sample. Paired t-tests were used to check if the changes in IMT (pre-treatment vs 4 weeks and pre-treatment vs 8 weeks) and lipid profile (pre-treatment vs 8 weeks) were significant. The multivariate ANOVA test was used to assess the
Table 2. Changes in serum creatinine, serum urea, serum urate, plasma fibrinogen and plasma factor XII after 8 weeks of treatment with 20 mg/day of atorvastatin. The results are expressed as median and range.

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-treatment</th>
<th>8 weeks</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (n=25)</td>
<td>87 (67–114)</td>
<td>84 (64–112)</td>
<td>0.007</td>
</tr>
<tr>
<td>Patients with the highest 12 creatinine values*</td>
<td>98 (89–114)</td>
<td>91 (83–112)</td>
<td>0.008</td>
</tr>
<tr>
<td>Patients with the lowest 13 creatinine values*</td>
<td>77 (67–84)</td>
<td>77 (64–85)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum urate (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (n=25)</td>
<td>0.33 (0.17–0.43)</td>
<td>0.32 (0.19–0.40)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients with the highest 12 creatinine values*</td>
<td>0.33 (0.24–0.43)</td>
<td>0.32 (0.22–0.40)</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with the lowest 13 creatinine values*</td>
<td>0.29 (0.17–0.40)</td>
<td>0.30 (0.19–0.35)</td>
<td>NS</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (n=25)</td>
<td>5.7 (1.9–9.6)</td>
<td>5.4 (1.8–9.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Fibrinogen (mg/l)</td>
<td>323 (216–565)</td>
<td>304 (194–494)</td>
<td>NS</td>
</tr>
<tr>
<td>Factor XII (ng/ml)</td>
<td>1.7 (0.7–2.8)</td>
<td>1.2 (0.7–4.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant, * pre-treatment.

Table 3. Changes in the lipid profile after 8 weeks treatment with atorvastatin 20 mg/day.

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-treatment</th>
<th>8 weeks</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.0 (0.3)</td>
<td>4.3 (0.8)</td>
<td>0.0004</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>3.7 (0.2)</td>
<td>2.2 (0.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.8 (0.6)</td>
<td>2.0 (0.5)</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.3 (0.4)</td>
<td>0.8 (0.3)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

LDL = low density lipoprotein cholesterol, HDL = high density lipoprotein cholesterol, TG = triglycerides.

Results

Biochemical results

There was no statistical difference in the haematological profile between visits at 0 and 8 weeks (results not shown). There was a significant (p = 0.007) decrease in serum creatinine values. The patients were divided into two halves, one with the highest serum creatinine levels (n = 12) and the other (n = 13) with the lowest serum creatinine levels. The decrease in serum creatinine was only significant (p = 0.008) in the “higher creatinine” group. Similarly, there was fall in the serum uric acid value in the group with a higher creatinine. There were no significant changes in liver function tests, creatine kinase, fibrinogen, urea and factor XII levels (Table 2).

Changes in the lipid profile

Table 3 summarised the lipid profile data. After 8 weeks of treatment there was a significant reduction in total cholesterol (p = 0.0004) and in low density lipoprotein cholesterol (LDL) (p = 0.0001). There was no significant change in the HDL level. The triglyceride levels decreased significantly (p = 0.05). After 8 weeks treatment all the patients had a LDL level <3.0 mmol/l, the UK guideline value for patients with vascular disease.

Changes in carotid and femoral IMT

The ANOVA test for the trend was significant (p = 0.024) for the CCA-IMT and for the CFA-IMT (p = 0.0003). The changes in CCA-IMT and CFA-IMT were not significant when the pre-treatment and 4-week values were compared. However, they were significant (p = 0.01 CCA-IMT; p = 0.005 CFA-IMT) when the pre-treatment and 8-week values were compared (Table 4). There was no significant correlation between the carotid and the femoral IMT values pre-treatment or at the end of the 8 weeks treatment. A decrease of the CCA-IMT by >0.1 mm was noted in 10 patients (40%) after 4 weeks and in 18 patients (72%) after 8 weeks of treatment. For the CFA-IMT the corresponding figures were 8 (32%) and 19 (76%) patients, respectively (Fig.
Table 4. Right common carotid artery (CCA) and right common femoral artery (CFA) IMT before and after treatment with 20 mg/day atorvastatin.

<table>
<thead>
<tr>
<th>Arteries</th>
<th>Pre-treatment</th>
<th>4WP</th>
<th>8WP</th>
<th>*p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCA-IMT</td>
<td>0.79 (0.21)</td>
<td>0.75 (0.22)</td>
<td>0.64 (0.15)</td>
<td>0.024</td>
</tr>
<tr>
<td>CFA-IMT</td>
<td>0.83 (0.13)</td>
<td>0.80 (0.09)</td>
<td>0.69 (0.14)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

* ANOVA test for the trend over the 8 week treatment period. 4WP, 4 weeks post-treatment; 8WP, 8 weeks post-treatment. The IMT (mm) is expressed as mean ± SD.

1). There was no correlation between the changes in the lipid levels and the IMT.

Side effects

There were no side effects, vascular events or dropouts during this 8-week study.

Discussion

Achieving U.K. guideline values for LDL (<3.0 mmol/l) within 8 weeks using atorvastatin (20 mg/day) in patients with PVD was associated with a significant decrease in the CCA-IMT and CFA-IMT. These findings confirm those of our preliminary study where we only assessed the CCA-IMT under similar circumstances.25

We attributed this rapid improvement to anti-inflammatory changes25 because it is unlikely that in this short time span there could be a significant reduction in lipid deposits in the intima and media. Our conclusion is based on the findings of an experimental model of carotid injury. In this model, a decrease in intimal thickening, smooth muscle cell proliferation and infiltration by macrophages was noted after the administration of a statin for 2 weeks.29 Furthermore, there is evidence that atorvastatin can significantly reduce the circulating levels of C-reactive protein in patients with combined hyperlipidaemia after treatment for 6 weeks.30 Improvement in endothelial function is also reported within 1 month of lipid lowering treatment.31,32

Observing a trend as early as 4 weeks after commencing atorvastatin supports the rapidity of the effect of lipid lowering treatment on the IMT. Although the 4-week IMT measurements were not significantly decreased when directly compared with pre-treatment values, they were included as part of the ANOVA analysis. This latter analysis was significant for both the CCA-IMT (p = 0.024) and CFA-IMT (p = 0.0003). This difference in significance suggests that these arteries may not respond at the same rate to lipid lowering. Indeed a greater decrease in the CFA-IMT compared with the CCA-IMT was reported after statin treatment (mainly with pravastatin or simvastatin) for a period of 1 year.33 An alternative explanation is that the CFA-IMT is a more relevant measurement in patients with PVD. Others have proposed that initial lipid-lowering therapy is associated with a greater improvement in the CFA-IMT and CCA-IMT than when this form of treatment was intensified in patients already taking statins.33 The baseline lipid levels were similar in both these treatment groups and the CFA-IMT and CCA-IMT were assessed after treatment with statin for 1 year.

It is important to consider that rapid changes in endothelial function (within as little as 1 month) have been reported.25,31,32 Furthermore, in the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study there was an unexplained significant (p = 0.045) and marked (50%) reduction in strokes in patients with acute coronary syndrome who were treated for 16 weeks with atorvastatin (80 mg/day). MIRACL was a placebo controlled, double blind, randomised study and it included >3000 patients.34 Clearly there is a need to further investigate the rapid changes in the vasculature that follow lipid lowering treatment. This (unfortunately) should include animal-based studies so as to allow for the extensive histological and functional investigation of several arteries.

A decrease in carotid artery IMT with atorvastatin has been previously documented but the time scale was of the order of 12–24 months.35,36 The patients had familial hypercholesterolaemia and the dose of atorvastatin was considerably higher (80 mg/day) compared to what we used in the present study (20 mg/day).

The significant (p = 0.007) fall in serum creatinine levels was relatively unexpected. However, we assessed that variable on the basis of anecdotal observations in patients with PVD after correcting their dyslipidaemia. We also previously reported similar changes in serum uric acid in dyslipidaemic patients treated with atorvastatin.37 We interpret these findings as indicating an increase in renal perfusion following lipid-lowering treatment. This improvement was most evident (p = 0.008) in the 50% of our study population with the highest pre-treatment serum creatinine values. In this context, it is relevant that others have proposed that the improvement in microalbuminuria (and blood pressure) after treatment with statins is related to an increased production of nitric oxide (NO) in the kidney.38 NO is a vasodilator and may well
improve renal blood flow.\textsuperscript{38} It is also of interest that microalbuminuria is associated with an increased carotid IMT.\textsuperscript{39} A further possible effect of statin treatment is a reduction or stabilisation of plaque in the renal arteries. Localised renal atherosclerosis is probably present to a variable degree in patients with PVD.\textsuperscript{40} The hypothesis that improved renal blood flow was responsible for our observations requires confirmation in larger placebo-controlled studies with a randomised design. These studies should also include a more detailed assessment of renal function. However, these changes may be restricted to a specific patient population.

Our findings have several limitations. Our study was not placebo controlled or randomised and the number of patients was small ($n=25$). We selected a
more homogeneous group of PVD patients by defining several exclusion criteria. However, future studies should also consider further selection; for example by gender. The smoking status is also known to adversely influence the benefit derived from treatment with statins.41

In concordance with some but not all other studies,42 we did not observe a rise in plasma fibrinogen concentration after using atorvastatin. Equally, there was no rise in coagulation factor XII. There is also evidence that statins may differ in their effect on HDL1996; gender. The smoking status is also known to adversely Y.


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Acknowledgements

We thank Pfizer Ltd for providing atorvastatin (Lipitor™) and an unrestricted grant. We also thank the vascular studies technologists at the Royal Free Hospital for their help.

References


Accepted 24 January 2002