Effect of fluvastatin on endothelium-dependent brachial artery vasodilation in patients after renal transplantation

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Background. Hypercholesterolemia may affect both endothelial function and arterial distensibility (DC). Renal transplant recipients (NTX) exhibit advanced structural and functional alterations of arterial vessel walls. The aim of this double-blind, randomized trial was to evaluate the effects of fluvastatin (FLU) on brachial artery flow-mediated vasodilation (FMD) and DC in hypercholesterolemic NTX.

Methods. Eighteen NTX received FLU 40 mg/day and 18 NTX placebo (PLA). Before and after six months of treatment, the brachial artery diameter and DC at rest were measured by a Doppler frequency analysis in the M mode, and then changes in diameter during reactive hyperemia (to assess endothelial-dependent FMD) and after 400 μg sublingual nitroglycerin (to assess endothelium-independent vasodilation—NMD).

Results. FLU, but not PLA, treatment resulted in significant decreases in total (from 288 ± 10 to 239 ± 8 mg/dL, $P < 0.05$) and low-density lipoprotein cholesterol (from 182 ± 779 to 138 ± 8 mg/dL, $P < 0.05$). Blood pressure did not differ between FLU- and PLA-treated patients and was not affected by either treatment. Also, the brachial artery baseline diameter was not different between groups and was not affected by FLU or PLA. Brachial artery flow at rest and during reactive hyperemia as measured by pulsed Doppler did not differ between groups. Brachial artery FMD increased with FLU from 0.23 ± 0.08 to 0.54 ± 0.08 mm ($P < 0.05$), whereas PLA did not alter FMD (0.22 ± 0.07 vs. 0.14 ± 0.05 mm at baseline and after six months of PLA treatment, respectively, $P =$ NS). In contrast, NMD did not change significantly with either treatment (0.76 ± 0.13 vs. 0.83 ± 0.15 mm at baseline and after 6 months of FLU treatment, respectively, $P =$ NS, and 0.64 ± 0.09 vs. 0.66 ± 0.10 mm at baseline and after 6 months of PLA treatment, respectively, $P =$ NS). Also, brachial artery DC was not altered by FLU (6.4 ± 1.0 vs. $5.8 \pm 0.6 \times 10^{-3}$/kPa, $P =$ NS) or PLA treatment (5.8 ± 0.6 vs. $6.8 \pm 0.8 \times 10^{-3}$/kPa, $P =$ NS).

Conclusions. In hypercholesterolemic NTX, the HMG-CoA reductase inhibitor FLU significantly improves brachial artery

FMD as a measure of endothelial function after six months of treatment. In contrast, FLU does not have a beneficial effect on brachial artery DC.

Cardiovascular disease is a major cause of morbidity and mortality in patients after renal transplantation and one of the most important determinants of long-term outcome of transplantation [1–3]. The functional and structural alterations of large arteries leading to cardiovascular disease begin in the early stages of renal disease, and by the time of renal transplantation, arterial disease is already advanced in the majority of even clinically asymptomatic renal transplant recipients [1, 4]. The atherosclerotic process covers a spectrum extending from endothelial dysfunction to structural alterations of the arterial wall with eventually occlusion of the artery leading to ischemia and infarction [1]. Endothelial dysfunction and disturbed cushioning function of large arteries are generally observed after renal transplantation [5], but are also found in patients without clinical symptoms of cardiovascular disease and are associated with substantial structural vessel wall alterations such as intima media thickening and atherosclerotic plaque formation [4]. Hypercholesterolemia is observed in the majority of patients after renal transplantation [6] and may be a major contributor to the previously mentioned vessel wall alterations [7]. In hypercholesterolemic humans without cardiovascular disease, endothelial dysfunction is improved by treatment with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors [8–10]. Also, in patients with documented coronary artery disease, HMG-CoA reductase inhibitors may have beneficial effects on endothelial function [11]. Finally, HMG-CoA reductase inhibitor treatment in patients with familiar hypercholesterolemia may improve elastic properties of large arteries [12]. Until the present, there are no studies investigating the effects of HMG-CoA reductase inhibitor therapy on endothelial function and elastic properties of large arteries in patients with end-stage renal failure

and after renal transplantation. The present study was therefore designed to test the hypothesis that the HMG-CoA reductase inhibitor fluvastatin (FLU) can improve endothelial function and arterial distensibility in patients after renal transplantation. In the present prospective, double-blind, randomized study, flow-mediated vasodilation (FMD) and distensibility of the brachial artery were measured by high-resolution ultrasound and Doppler frequency analysis of vessel wall movements in M mode as indices of endothelial function and mechanical vessel wall properties, respectively, in placebo and FLU-treated renal transplant recipients.

METHODS

We performed a randomized, prospective, double-blind, placebo-controlled trial that was approved by the ethics committee of the University of Münster School of Medicine. All patients gave their written informed consent. Eligible patients were between 18 and 60 years of age and had received a kidney from a cadaveric donor at least six months earlier. At the time of transplantation, all patients had been instructed to follow a reduced cholesterol (American Heart Association step 1 diet). Renal transplant function was stable, and the serum creatinine level was below 2.5 mg/dL in all patients at entry into study. Patients with serum cholesterol levels above 200 mg/dL and below 350 mg/dL were included into study. Subjects with prior HMG-CoA reductase inhibitor or other anti-lipidemic medication were excluded. Blood pressure was controlled in hypertensive renal transplant recipients by antihypertensive drugs, and blood pressure levels were below 160 mm Hg systolic and 90 mm Hg diastolic in all patients at randomization. Patients with clinical evidence of cardiovascular disease or diabetes mellitus were excluded. An immunosuppressive drug regimen with cyclosporine A and prednisolone (5 to 10 mg/day) was used. Cyclosporine whole-blood trough concentrations (measured by high-performance liquid chromatography) were maintained at 75 to 150 μg/L by dose adjustment.

A total of 40 patients was included into the study. Causes of renal failure were chronic glomerulonephritis in 21 cases, chronic interstitial nephritis in 7 cases, glomerulosclerosis in 2 cases, polycystic renal disease in 4 cases, hydronephrosis in 1 case, Alport's disease in 1 case, and unknown in 4 cases. Antihypertensive therapy consisted of β blockers (21 patients), calcium antagonists (25 patients), angiotensin-converting enzyme (ACE) inhibitors (19 patients), α blockers (4 patients), and loop diuretics (21 patients). Antihypertensive treatment was not changed in any patient during the six-month observation period.

Patients were randomly assigned to six months of treatment with FLU 40 mg or matching PLA taken once daily with dinner. Patients were studied twice: at entry into the study and after the six-month observation period.

Measurements

All studies were performed between 8 and 12 a.m. Twelve to 14 hours had elapsed between the measurements and previous intake of cyclosporine or antihypertensive drugs. Only patients without an arteriovenous fistula or previous vascular surgery on the right arm were included into study. Following blood sampling and routine clinical examination, blood pressure, distensibility (DC), as well as flow-mediated and nitroglycerin-mediated vasodilation of the brachial artery were studied as described earlier [5], after a rest of at least 15 minutes in a supine position. In brief, brachial artery blood pressure was measured using an automatic sphygmomanometer, and heart rate was determined using an echocardiogram monitor. After blood pressure measurements, the brachial artery of the right arm was visualized in a longitudinal section 2 to 6 cm above the elbow using a 7.5 MHz linear array transducer and a standard Toshiba ultrasound system. The brachial artery was displayed in B and M modes. Vessel diameter was then analyzed using a multigate pulsed Doppler system. Low-frequency Doppler signals originating from the sample volumes coinciding with the arterior and posterior vessel walls were processed. The positions of sample volumes were continuously adjusted according to the displacement of the wall. Using the echocardiogram trigger, the end-diastolic diameter and distention (diastolic–systolic diameter change) of the brachial artery were measured. Coefficient of variation was 4.5% for the end-diastolic diameter ($N = 26$) and $9.6 \pm 1.6\%$ ($N = 26$) for the relative distention of the brachial artery. After two measurements of end-diastolic diameter at baseline were taken, a cuff placed on the forearm was inflated at 300 mm Hg during four minutes. During the last minute of cuff inflation and at 1, 3, 5, 7, and 10 minutes after cuff release, further measurements of brachial end-diastolic diameter were taken. Brachial artery flow at baseline and during the initial 15 seconds of reactive hyperemia was estimated using a pulsed Doppler. Eleven minutes after cuff release and return of the brachial artery diameter to baseline values, 400 μg of glycerol trinitrate were administered sublingually, and further scans of the brachial artery were taken after one, three, and five minutes. Ultrasound measurements were taken by two investigators (M.H. and M.B.); however, in each patient, both measurements were taken by the same investigator.

Analyses

From the end-diastolic diameter (d), the relative systolic increase of vessel diameter (relative distention = $\Delta d \times d^{-1}$) and from the SBP and diastolic blood pressure

Table 1. Demographic data

	FLU (N = 18)	PLA (N = 18)	P
Age *years*	50 ± 2	47 ± 3	NS
Time after transplantation *years*	4.9 ± 0.7	4.0 ± 0.8	NS
Patients on ACE inhibitor therapy	9	8	NS
Smoker/nonsmoker	3/15	5/13	NS
Gender *male/female*	13/5	13/5	NS
Body mass index *kg/m²*	26 ± 1	23 ± 1	NS

Displayed are age, time after transplantation, smoking habits, gender and body mass index of patients treated with fluvastatin (FLU) or placebo (PLA). Data are means ± SEM.

(DBP), arterial wall DC was calculated (DC coefficient $DC = 2 \Delta d \times d^{-1} \times (SBP - DBP)^{-1} [10^{-3} \text{ kPa}]$).

Flow-mediated vasodilation was calculated as the maximum increase in brachial artery end-diastolic diameter during reactive hyperemia. Nitroglycerine-mediated vasodilation was accordingly calculated as the maximum increase in brachial artery end-diastolic diameter after sublingual glycerol trinitrate.

Data were expressed as mean ± SEM. A statistical comparison between the FLU-treated and PLA-treated groups was carried out using the Student *t* test for continuous variables and the chi-square test for qualitative variables. To test the effects of a sixth-month therapy with FLU or PLA, repeated measures of analysis of variance with adjustment for covariates (ANCOVA) was used. Within- and between-group comparisons were made with post hoc tests (planned contrasts).

RESULTS

Four of the 40 included patients dropped out during follow-up, and a second measurement of vessel wall properties could not be obtained. One patient (PLA group) developed bronchial carcinoma. One patient (FLU group) developed myalgias, and two patients (one in each group) withdrew consent. The following analysis, therefore, is confined to the remaining 36 patients available for according-to-protocol analysis.

Baseline characteristics of the two groups are shown in Table 1. There were no significant differences between FLU- and PLA-treated patients with respect to age, time after transplantation, number of smokers, gender, and body mass index.

Biochemical parameters at entry and after six months of therapy are shown in Table 2. Cyclosporine and serum creatinine levels at entry and after six months were comparable in the FLU- and the PLA-treated groups (Table 2). The same was true for glucose, bilirubin levels, and creatine kinase activity. Total serum cholesterol and low-density lipoprotein (LDL) cholesterol levels at entry were not significantly different in the group treated with FLU when compared with the PLA-treated group (Table 2). As expected, there was a significant decrease of total serum cholesterol and LDL cholesterol level in FLU-treated patients when compared with PLA-treated patients ($P < 0.001$; Table 2). In the PLA-treated group, total serum cholesterol and LDL cholesterol level remained unchanged after six months when compared with baseline levels. High-density lipoprotein (HDL) cholesterol levels at entry and after six months of therapy did not differ between both study groups. There was no significant difference of triglyceride levels at baseline between both study groups, and therapy with either FLU or PLA did not significantly alter triglyceride levels.

The results of blood pressure measurements and the vessel parameters are shown in Table 3 and Figures 1 and 2. Blood pressure at baseline was not significantly different between FLU- and PLA-treated patients and remained unchanged after six months of therapy. The same was true for pulse pressure and heart rate.

The end-diastolic diameter of the brachial artery at baseline was not significantly different in FLU-treated patients when compared with PLA-treated patients. There was no significant effect of either treatment on end-diastolic diameter of the brachial artery. Brachial artery distention and DC coefficients were also comparable in both study groups at baseline and not significantly influenced by either treatment.

Flow-mediated vasodilation at baseline was similar in both study groups. However, FMD of the brachial artery significantly improved after six months of treatment with FLU. In contrast, FMD of the brachial artery did not change from baseline values after six months of PLA therapy. Improved FMD in FLU-treated patients was not related to changes in brachial artery blood flow. Resting brachial blood flow at baseline and after six months of therapy was not different between both study groups. Peak blood flow after release of forearm occlusion was also comparable between both study groups at baseline and after six months of therapy. The effect of FLU as compared with PLA on brachial artery FMD also remained statistically significant after adjustment for brachial artery diameter ($P < 0.05$) as analyzed by ANCOVA.

Endothelium-independent nitroglycerin-induced vasodilation was similar in FLU-treated and in PLA-treated patients at baseline and after six months of therapy.

Changes in brachial artery flow-mediated dilatation were not related to changes in serum cholesterol levels in either group (Fig. 3) and were also not related to changes in LDL cholesterol levels after FLU or PLA treatment ($r = 0.29$ for the FLU group and $r = 0.16$ for the PLA group, both $P = NS$).

DISCUSSION

The present randomized, double-blind, PLA-controlled study shows that six months of therapy with the HMG-

Table 2. Biochemical data

Time *months*	FLU ($N = 18$)		PLA ($N = 18$)		P
	0	6	0	6	
Cyclosporine *ng/mL*	91 ± 9	97 ± 7	94 ± 12	94 ± 8	NS
Creatinine *mg/dL*	1.4 ± 0.1	1.5 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	NS
Glucose *mg/dL*	91 ± 3	96 ± 3	92 ± 4	87 ± 3	NS
Bilirubin *mg/dL*	0.7 ± 0.1	0.7 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	NS
CK *U/L*	38 ± 4	46 ± 6	39 ± 4	45 ± 6	NS
Cholesterol *mg/dL*	288 ± 8	239 ± 9 [a]	266 ± 7	267 ± 9	<0.001
HDL cholesterol *mg/dL*	67 ± 5	72 ± 8	63 ± 4	67 ± 8	NS
LDL cholesterol *mg/dL*	182 ± 9	138 ± 8 [a]	173 ± 7	166 ± 9	<0.001
Triglycerides *mg/dL*	182 ± 24	163 ± 25	161 ± 15	169 ± 14	NS

Values are shown for cyclosporine whole blood trough levels, serum concentrations of creatinine, glucose, bilirubin, creatine kinase (CK), total cholesterol, high (HDL) and low (LDH) lipoprotein, and triglycerides at baseline and after 6 months of treatment with fluvastatin (FLU) or placebo (PLA). Data are mean ± SEM. P values are for group × time interaction.
[a] $P < 0.05$ versus baseline value

Table 3. Hemodynamic and ultrasound measurements at baseline and after six months

	FLU ($N = 18$)		PLA ($N = 18$)		P
	0	6	0	6	
Blood pressure *mm Hg*					
Systolic	138 ± 4	139 ± 4	133 ± 4	136 ± 4	NS
Diastolic	83 ± 3	82 ± 2	83 ± 3	83 ± 2	NS
Pulse pressure *mm Hg*	55 ± 3	57 ± 31	50 ± 2	52 ± 3	NS
Heart rate *min^{-1}*	69 ± 4	70 ± 4	67 ± 2	64 ± 2	NS
BA diameter *mm*	4.5 ± 0.2	4.4 ± 0.1	4.0 ± 0.2	4.0 ± 0.2	NS
BA relative distention %	2.4 ± 0.5	2.0 ± 0.2	1.9 ± 0.2	2.3 ± 0.3	NS
BA baseline flow *mL/min*	109 ± 14	121 ± 12	113 ± 16	111 ± 12	NS
BA peak flow *mL/min*	571 ± 60	638 ± 86	527 ± 54	608 ± 45	NS

Systolic and diastolic blood pressure, pulse pressure, heart rate, brachial artery (BA) end-diastolic diameter, relative distention, baseline blood flow and peak flow during reactive hyperemia, at baseline and after 6 months of treatment with fluvastatin (FLU) or placebo (PLA). Data are mean ± SEM. P values are for group × time interaction.
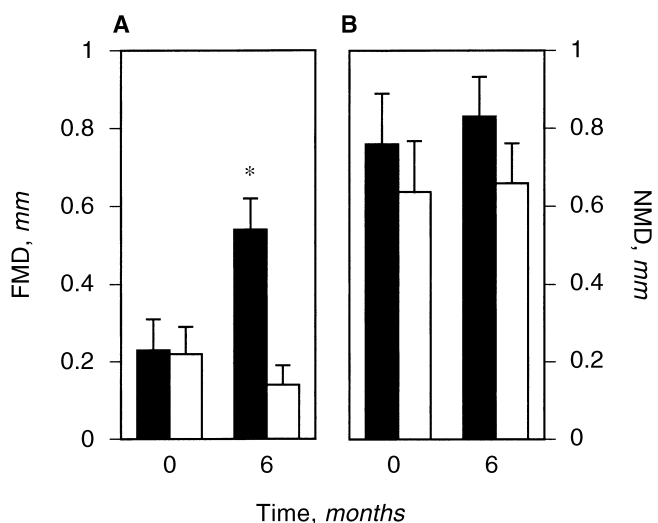

Fig. 1. Displayed are flow-mediated (FMD, left panel) and nitroglycer-ine-mediated vasodilation (NMD, right panel) of the brachial artery at baseline and after six months of treatment with fluvastatin (FLU; ■) or placebo (PLA; □). Data are mean ± SEM. *$P < 0.01$ vs. baseline and $P < 0.05$ for group × time interaction.
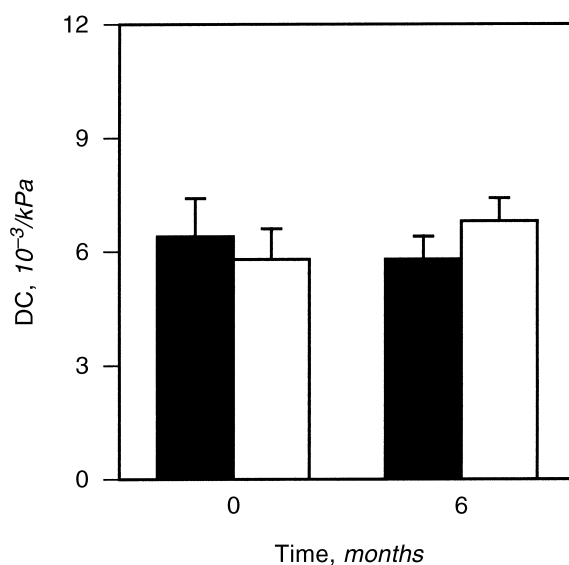

Fig. 2. Brachial artery distensibility coefficient (DC) at baseline and after six months of fluvastatin treatment (FLU; ■) or placebo treatment (PLA; □). Data are mean ± SEM.
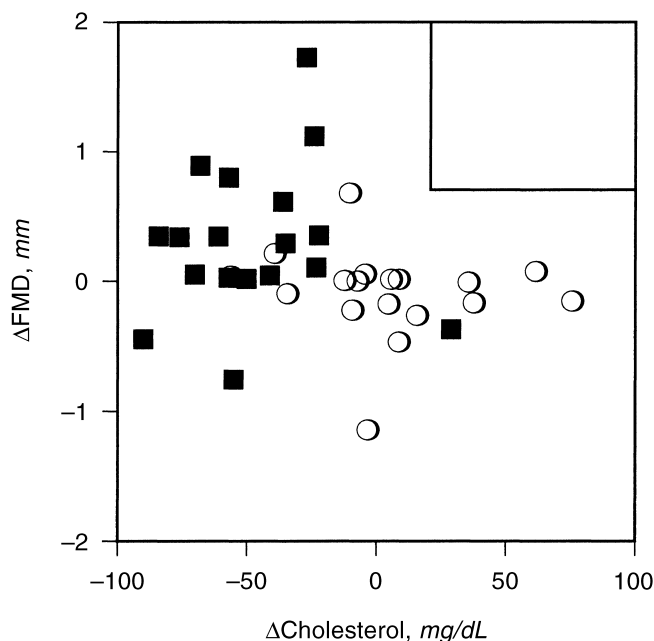
Fig. 3. Change in brachial artery flow-mediated vasodilation (FMD) plotted against change in total serum cholesterol after six months of treatment with fluvastatin (FLU; ■) or placebo (PLA; ○). Neither in FLU- nor in PLA-treated patients was there a significant correlation between the change in serum cholesterol and the change in FMD ($r = 0.29$, $P =$ NS for FLU, and $r = 0.16$, $P =$ NS for PLA).

CoA reductase inhibitor FLU can significantly improve endothelial function in patients after renal transplantation. FMD of the brachial artery significantly improved with FLU when compared with PLA treatment. The data of the present study therefore suggest that endothelial dysfunction is reversible in patients after renal transplantation despite substantial structural wall alterations of large arteries, which often are found in these patients even in the absence of clinical evidence of cardiovascular disease [4]. In contrast, FLU failed to improve mechanical wall properties of the brachial artery in renal transplant patients.

Several studies have shown convincingly that already short-term HMG-CoA reductase inhibitor therapy can improve endothelial dysfunction in patients with hypercholesterolemia free of cardiovascular disease or diabetes mellitus. This has been shown for the forearm vascular bed [8, 9] as well as for the coronary vessels [13]. Also, in patients with coronary artery disease, recent observations indicate an improvement of endothelial dependent vasodilation by HMG-CoA reductase inhibitors [11, 14]. Improvement of endothelial dysfunction is suggested to be a major factor that explains the success of HMG-CoA reductase inhibitors in the primary and secondary prevention of cardiovascular disease [15]. To our knowledge, the current study is the first report of improvement of endothelial dependent vasodilation by an HMG-CoA

reductase inhibitor in patients with end-stage renal disease. Since there is a close correlation between endothelial-mediated vasodilation of peripheral and coronary arteries [16], our finding of improved endothelial-mediated brachial artery vasodilation in renal transplant patients suggests a beneficial effect of FLU treatment on the excess cardiovascular morbidity and mortality in this patient group [3]. Prospective studies investigating this issue are in progress (for example, ALERT study), however, results are not available yet.

The observed improvement of endothelial function in renal transplant patients with FLU could also relate to improved graft survival [17]. Katznelson and Kobashigawa observed a decreased incidence of acute rejections in renal transplant patients treated with pravastatin, which was accompanied by an inhibition of cytotoxic killer cell activity [18]. It has recently been shown that FLU inhibits the expression of adhesion molecules in human monocyte cell lines [19], which may be of importance for both immunologic processes in allograft rejection and progression of atherosclerotic lesions. We did not observe any effect of FLU on graft function or on the incidence of acute rejection. This may be explained by the selection of patients at least six months after transplantation who had excellent graft function and by the relatively short observation period.

We did not observe a correlation between the reduction in serum total cholesterol or LDL cholesterol concentrations and the achieved increase in brachial artery flow-mediated dilation. This could indicate a cholesterol-independent effect of FLU on endothelial function in renal transplant recipients [15]. In patients with coronary artery disease, Jarvisalo et al found brachial artery flow-mediated dilation to be significantly better in patients on HMG-CoA reductase inhibitor medication than in patients without HMG-CoA reductase inhibitor therapy, despite similar cholesterol levels. The effect on FMD was dose dependent [11]. This could be explained by the observation of Laufs et al, who reported a direct up-regulation of endothelial nitric oxide synthase by HMG-CoA reductase inhibitors [20]. Recently, the cellular uptake mechanism for FLU in endothelial cells of the human aorta could be characterized suggesting that also FLU may have a direct effect on the expression of endothelial nitric oxide synthase [21].

Recent observations suggest that an altered expression of angiotensin II type 1 (AT$_1$) receptors may contribute to the improved endothelial function with statin therapy [22]. In the present study, patients receiving FLU and patients receiving PLA did not differ significantly in their antihypertensivie medication, particularly not in angiotensin-converting enzyme inhibitor use. Antihypertensive medication was not changed in any of the patients during the six months of follow-up.

It has been shown that apart from its effects on endo-

thelial function hypercholesterolemia also affects mechanical vessel wall properties of large [23] and medium-sized arteries [24]. In contrast to the beneficial effects of FLU on brachial artery FMD, we did not observe an improvement of brachial artery distensibility with FLU. It has to be noted that fewer atherosclerotic lesions are found in the brachial artery than in large elastic-type arteries [25, 26] and that brachial artery elastic wall properties are largely determined by blood pressure [27]. Therefore, FLU treatment could have resulted in improved DC of elastic type arteries, for example, the common carotid artery, which is prone to atherosclerosis and in which the elastic properties are influenced by hypercholesterolemia [23]. However, our observations are consistent with the report of Kool et al, who did not observe improvements of either the carotid, femoral or brachial artery elastic properties in hypercholesterolemic subjects after eight weeks of HMG-CoA reductase inhibitor therapy [28]. It is conceivable that the observation period of six months was too short to observe improvements in large artery DC with FLU. In support of this hypothesis, Giannattasio et al observed an improvement of radial artery compliance in seven patients with familial hypercholesterolemia not after 6 months, but only after 24 months of therapy with simvastatin [12].

Despite the success of HMG-CoA reductase inhibitors with respect to primary and secondary prevention of cardiovascular events in the general population, these drugs are used with great caution in renal transplant patients. The reasons are as follows: First, the benefit of lipid-lowering therapy with respect to prevention of cardiovascular disease in renal transplant patients has not yet been proven. Retrospective analyses show equivocal data [3, 29], and the results of prospective studies with statins are not yet available. Second, a redoubtable side effect of HMG-CoA reductase inhibitors is the development of myopathy, which may extend to often lethal rhabdomyolysis. The latter was particularly described in patients with concomitant HMG-CoA reductase inhibitor and cyclosporine therapy [30]. The present report, however, is consistent with previous reports showing that FLU can be safely used in renal transplant recipients receiving cyclosporine [31, 32]. Only one patient developed myalgia while on FLU therapy; however, causality could not be firmly established. We did not observe an increase in creatine kinase activity in FLU-treated patients when compared with patients receiving PLA.

Conclusions

The present study investigated the effects of FLU on endothelial function and large artery mechanical wall properties in patients after renal transplantation. The data show that six months of therapy with FLU improved FMD of the brachial artery in renal transplant recipients when compared with PLA-treated patients. To our knowledge, this is the first report demonstrating improved endothelial function with HMG-CoA reductase inhibitor treatment in end-stage renal disease. This is an important finding since renal allograft recipients even without clinical evidence of cardiovascular disease already exhibit substantial structural alterations of large arteries, which differ from those observed in patients with hypercholesterolemia [1], and this finding may be of prognostic relevance. In contrast, FLU did not improve elastic properties of the brachial artery in renal allograft recipients.

APPENDIX

Abbreviations used in this article are: ACE, angiotensin-converting enzyme; AT_1, angiotensin II type 1 (receptor); CK, creatine kinase; DBP, diastolic blood pressure; DC, distensibility coefficient; FLU, fluvastatin; FMD, flow-mediated vasodilation; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HPLC, high-pressure liquid chromatography; LDL, low-density lipoprotein; NTX, renal transplant recipients; PLA, placebo; SBP, systolic blood pressure.

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