INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Potential Benefit of Statin Therapy for Dyslipidemia with Chronic Kidney Disease: Fluvastatin Renal Evaluation Trial (FRET)

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Abstract

Background Dyslipidemia is a common complication of chronic kidney disease (CKD) and contributes to cardiovascular morbidity and mortality of CKD patients.

Aim The aim of the present study was to determine whether fluvastatin, which is mostly characterized by its pleiotropic anti-oxidant effects, has renoprotective effects in dyslipidemic patients with CKD.

Methods In 43 dyslipidemic patients with CKD taking fluvastatin 10 mg/day, 20 mg/day or 30 mg/day, renal functions as well as lipid profiles were assessed.

Results After 3 months of treatment with fluvastatin, LDL-cholesterol level significantly decreased. Serum creatinine level, estimated glomerular filtration rate (eGFR), urinary albumin excretion (UAE), urinary liver-type fatty acid binding protein (L-FABP) level and urinary 8-hydroxydeoxyguanosine (8-OHdG) level did not change in overall patients. However, in patients with microalbuminuria (baseline UAE≥30 mg/g·creatinine; n=23), the UAE significantly decreased [2.43±0.67 to 1.98±0.80 log(mg/g·creatinine), p=0.01]. In patients with high L-FABP group (baseline L-FABP≥11 μg/g·creatinine; n=18), the urinary L-FABP level was significantly decreased (1.52±0.45 to 1.26±0.43 μg/g·creatinine, p<0.01). In the limited 23 patients with microalbuminuria, the L-FABP level was significantly decreased [1.20±0.62 to 1.03±0.49 log(μg/g·creatinine), p=0.042], although the LDL-cholesterol level (139±28 to 129±23 mg/dL, p=0.08) only showed a tendency to decrease. The 8-OHdG level also was significantly decreased (13.6±9.6 to 9.8±3.8 ng/g·creatinine, p=0.043). In the overall patients, changes in the values for UAE and urinary L-FABP were not correlated with the changes in LDL-levels.

Conclusion Fluvastatin reduces both UAE and the urinary L-FABP level, and thus, has renoprotective effects, independent of its lipid lowering effects in dyslipidemic patients with CKD.

Key words: statin, chronic kidney disease, oxidative stress, urinary albumin excretion, L-FABP

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Introduction

Chronic kidney disease (CKD) in the community is associated with a significant burden of cardiovascular disease risk factors (1). The prevalence of dyslipidemia in CKD patients is much higher than in the general population whilst elevated cholesterol and triglyceride levels are associated with more rapid deterioration of kidney function (2). Thus, CKD is a "high risk" category for cardiovascular events and aggressive therapeutic intervention should be initiated to reduce the risk (3). Recently, Sandhu et al reported that ther-

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Table 1. Patient Characteristics (n=43)

Age; years	75±9
Sex; male/female	21/22
Hypertension; n (%)	33 (76)
Diabetes; n (%)	14 (33)
Smoking; n (%)	5 (12)
Cadriovascular diseases; n (%)	9 (21)
Basal diseases of CKD	
Hypertensive nephropathy; n (%)	27 (63%)
Diabetic nephropathy; n (%)	8 (19%)
Either or both of HN and/or DN ; n (%)	6 (14%)
Chronic glomerulonephritis; n (%)	2 (4%)
Fluvastatin dose	
10 mg/day; n (%)	7 (16)
20 mg/day; n (%)	31 (72)
30 mg/day; n (%)	5 (12)
ACEI or ARB; n (%)	30 (70)
Ca channel blocker; n (%)	26 (60)
Anti-diabetic drugs; n (%)	11 (26)
Aspirin; n (%)	4 (9)

HN=hypertensive nephropathy, DN=diabetic nephropathy, ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker

apy with cholesterol lowering drugs, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, i.e., statins resulted in a modest reduction in proteinuria and protected renal function in a meta-analysis comprising 39,704 participants (4).

Among the various statins, fluvastatin is primarily characterized by its pleiotropic anti-oxidant effects (5, 6). Since oxidative stress produces renal glomerular injury and tubulointerstitial damage (7), we hypothesize that fluvastatin may have specific beneficial effects to improve renal function. To test this hypothesis, we designed a single arm multi-center study, the Fluvastatin Renal Evaluation Trial (FRET), to assess the effects of fluvastatin on renal function in dyslipidemic patients with CKD.

Methods

For the FRET trial, patients with dyslipidemia along with CKD over the age of 20 years old were recruited from 8 practitioners belonging to Saga Medical Association. Dyslipidemia and CKD were defined based upon the criteria of the Japanese Atherosclerosis Society and the Japanese Society of Nephrology, respectively. Patients who had cardiac, liver, gastrointestinal, or collagen disease, malignancy, or a history of previously receiving any lipid lowering drugs were excluded. All of the patients were prescribed 10 mg, 20 mg or 30 mg fluvastatin. The dose of fluvastatin was dependent upon the judgment of each attending physician. We monitored blood pressure, lipid profiles such as serum low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol and triglyceride levels, and renal function markers such as serum creatinine level, urinary albumin excretion (UAE) and urinary liver-type fatty acid binding protein (L-FABP) level prior to the fluvastatin prescription and 3 months after the fluvastatin treatment. Estimated glomerular filtration rate (eGFR) was calculated based on the Japanese Society of Nephrology CKD Practice Guide. In addition, urinary 8-hydroxydeoxyguanosine (8-OHdG) was simultaneously measured as an oxidative stress marker. L-FABP levels were measured by a specific ELISA method as previously described (8-10). 8-OHdG levels were measured by a specific ELISA kit as previously described using a highly sensitive monoclonal antibody (8-OHdG Check, Nikken Foods, Fukuroi, Shizuoka, Japan) (11).

Normality of the distribution of variables was assessed using Kolmogorov-Smirnov test with Lilliefors' correlation. Since values of UAE and L-FABP were non-parametric, the values were transformed into logarithmic values. Then the data were expressed as mean±SD. The changes in the values after 3 months treatment of fluvastatin were assessed using paired t test. Correlations were assessed using simple linear regression. The P value less than 0.05 was considered to be statistically significant.

Results

A total of 43 patients (21 males and 22 females; 75±9 years) were eligible for the FRET trial. Patient characteristics are shown in Table 1. Complications with cardiovascular diseases were seen in 9 patients (21%) (ischemic heart disease in 3; 7%, arrhythmia in 5; 12%, hypertensive heart disease in 1; 2% and cerebrovascular disease in 3; 7%). Basal diseases of CKD were hypertensive nephropathy in 27 (63%), diabetic nephropathy in 8 (19%), either or both hy-

Table 2. Changes in the Measurements after 3 Months' Treatment with Fluvastatin

	Baseline	3 months	p value
Systolic blood pressure; mmHg	137±15	135±13	0.0792
LDL-cholesterol; mg/dL	131±30	119±22	0.0097
HDL-cholesterol; mg/dL	50±11	48±12	0.1521
Triglyceride; mg/dL	178±90	160±89	0.0950
Fasting blood glucose; mg/dL	110±30	114±30	0.2696
HbA_1C; %	5.9±1.1	5.9±1.0	0.2157
Creatinine; mg/dL	1.16±0.48	1.18±0.54	0.3419
eGFR; ml/min/1.73m^2	40±14	40±14	0.6800
UAE (n=36); mg/g•creatinine	72.2 [10.0, 355.3]	49.4 [12.5, 282.3]	0.0937
log(mg/g•creatinine)	1.84±0.84	1.75±0.77	0.1662
L-FABP (n=36); mg/g•creatinine	10.5 [4.0, 26.3]	7.4 [4.0, 17.7]	0.1447
log(mg/g•creatinine)	1.07±0.54	0.98±0.43	0.1059
8-OHdG (n=36); ng/mg•creatinine	12.7±8.0	10.9±4.1	0.1705

Data are expressed as mean ± standard deviation or median value and interquartile range. LDL=low density lipoprotein, HDL=high density lipoprotein, HbA1C=hemoglobin A1C, eGFR=estimated glomerular filtration rate, ACEI=angiotensin converting enzyme inhibitor, UAE=urinary albumin excretion, L-FABP=liver type fatty acid binding protein, 8-OHdG=8-hydroxy deoxiguanosine

pertensive nephropathy and/or diabetic nephropathy in 6 (14%) and chronic glomerulonephritis in 2 patients (4%). The dose of fluvastatin was 10 mg/day in 7 (16%), 20 mg/day in 31 (72%) and 30 mg/day in 5 patients (12%). Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) was given in 30 patients (70%). Although anti-diabetic drugs were given in 11 patients (26%), no patient received thiazolidinediones such as pioglitazone.

Table 2 shows the comparison of measured variables in the baseline before fluvastatin administration and those after 3 months of treatment with fluvastatin in overall patients. After the 3 months of treatment, the LDL-cholesterol level was significantly decreased (131±30 to 119±22 mg/dL, $p<0.01$). However, the levels of HDL-cholesterol and triglyceride did not change. Concerning renal function, the serum creatinine level and eGFR did not change significantly. The UAE, urinary L-FABP level and urinary 8-OHdG level also did not change in 36 patients, in whom these markers could be measured at both baseline and at 3 months after treatment. If these patients are divided into patients with microalbuminuria (baseline UAE≥30 mg/g·creatinine; n=23) and patients without microalbuminuria (baseline UAE<30 mg/g·creatinine; n=13), based on the cut-off value of 30 mg/g·creatinine according to guideline of Japanese Society of Hypertension, the UAE value was significantly decreased in the patients with microalbminuria [2.43±0.67 to 1.98±0.80 log(mg/g·creatinine), p=0.01], although the value did not change in the patients without microalbuminuria [0.96±0.29 to 1.08±0.24 log(mg/g·creatinine)] (Fig. 1). If these patients are divided into two subgroups, a low L-FABP group (baseline L-FABP <11 μg/g·creatinine; n=18) and a high L-FABP group (baseline L-FABP≥11 μg/g·creatinine; n=18), based on the cut-off value of 11 μg/g·creatinine as the median value, the L-FABP level was significantly decreased in the high L-FABP group [1.52±0.45 to 1.26±0.43 log(μg/g·creatinine), $p<0.01$], although the level did not change in the low L-FABP group [0.64±0.11 to 0.72±0.27 log(μg/g·creatinine)] (Fig. 2). In the limited 23 patients with microalbuminuria, the L-FABP level was also significantly decreased [1.20±0.62 to 1.03±0.49 log(μg/g·creatinine), p=0.042], although LDL-cholesterol level (139±28 to 129±23 mg/dL, p=0.08) showed only a tendency to decrease. In these limited patients, the 8-OHdG level was also significantly decreased (13.6±9.6 to 9.8±3.8 ng/g·creatinine, p=0.043) (Fig. 3).

In overall patients, the changes in the values (baseline values minus values after 3 months of treatment) for UAE and urinary L-FABP level were not correlated with the changes in LDL-cholesterol level (R=0.19 and R= 0.15, respectively). The changes in UAE and L-FABP level were also not correlated with the changes in urinary 8-OHdG level (R=0.09, R=0.04, respectively). In the limited 23 patients with microalbuminuria, the changes in the values for UAE and L-FABP level were not correlated with the changes in LDL-cholesterol levels (R=0.09 and R= 0.13, respectively) as well as the changes in 8-OHdG level (R=0.02 and R= 0.10, respectively).

Among patient groups of the fluvastatin dose of 10 mg/day (n=6), 20 mg/day (n=25) and 30 mg/day (n=5), there were no differences in the changes for UAE [0.02±0.38, 0.19±0.19, 0.26±0.30 log(mg/g·creatinine) in the 10 mg/day, 20 mg/day and 30 mg/day groups, respectively] and urinary L-FABP level [0.04±0.56, 0.23±0.29, 0.73±0.37 log(μg/g·creatinine) in the 10 mg/day, 20 mg/day and 30 mg/day groups, respectively]. Between 27 patients receiving ACEIs or ARBs and the remaining 9 who did not receive them, there were no differences in the changes for UAE [0.16±0.28 vs 0.10±0.39 log(mg/g·creatinine)] and urinary L-FABP

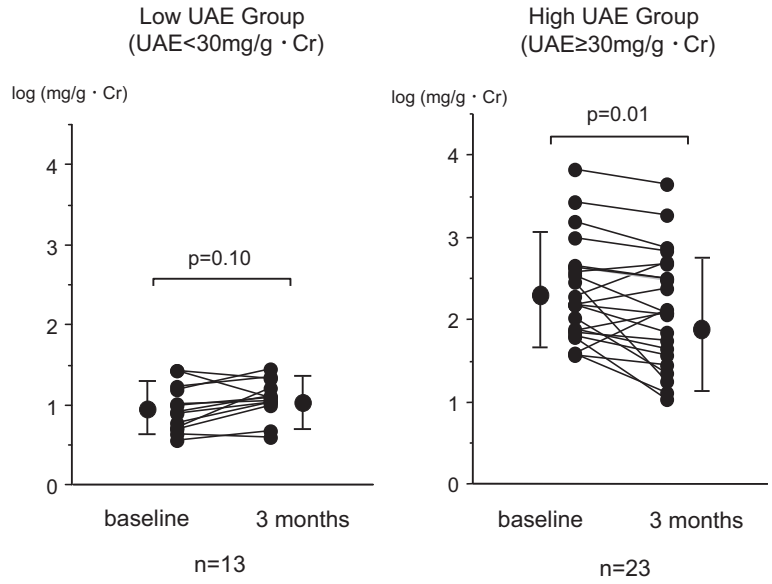

Figure 1. **Change in urinary albumin excretion (UAE), separately shown in patients with (right panel) and without (left panel) microalbuminuria. The values were log-transformed.**

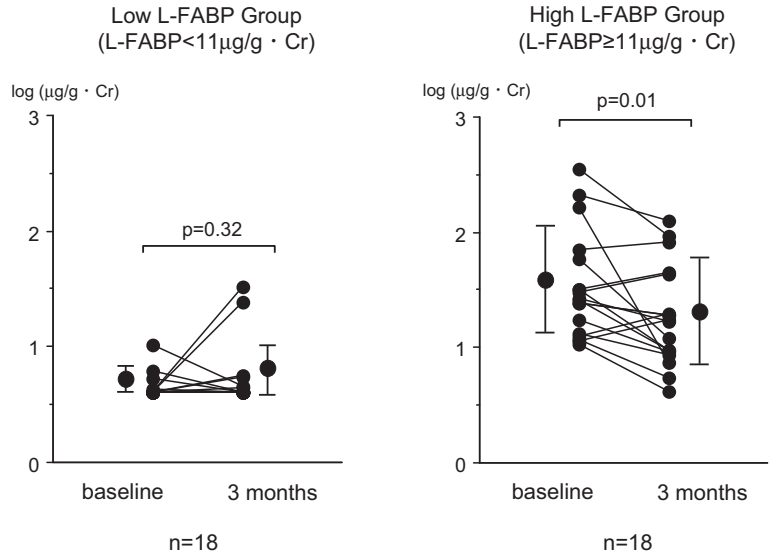

Figure 2. **Changes in urinary liver-type fatty acid binding protein (L-FABP) separately shown in subgroups of high (right panel) and low (left panel) L-FABP level. The values were log-transformed.**

level [0.55±0.66 vs 0.62±0.48 log(μg/g·creatinine)].

Discussion

In the FRET trial, in dyslipidemic patients with CKD we demonstrated that 3 months of treatment with fluvastatin reduced UAE in patients with microalbuminuria and also reduced urinary L-FABP level in the patients with microalbuminuria as well as in the subgroup of a high baseline L-FABP level. These results suggest that fluvastatin might be potentially effective to improve renal function in addition to its cholesterol lowering effect.

CKD is a potent risk factor for cardiovascular disease with an increased risk of cardiovascular events associated with even mild CKD. Cardiovascular death rather than progression to end-stage renal disease is a common outcome in patients with CKD (12). Abnormal lipid metabolism and dyslipidemia is considered to be an important promoter of renal dysfunction (13) with potential pathogenic mechanisms including not only theacceleration of atherosclerosis of the renal vasculature but also glomerular injury and tubulointerstitial damage. Although the underlying pathophysiological mechanisms are not yet fully understood, there are increasing numbers of data indicating that oxidative stress may mediate the lipid-induced renal damages. There is evidence that circulating lipids bind to and become trapped by cell membranes and extracellular matrix molecules (14), where they undergo oxidation increasing the formation of reactive oxygen species such as superoxide anion and hydrogen peroxide.

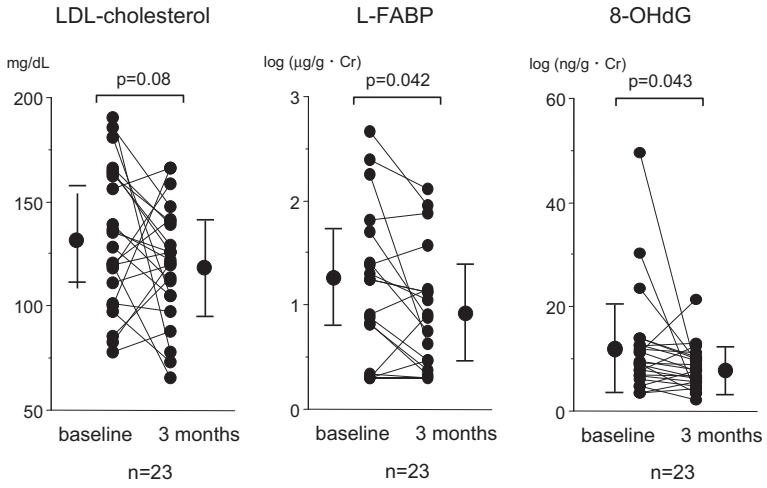

Figure 3. Changes in the levels of low density lipoprotein (LDL)-cholesterol, L-FABP and 8-hydroxydeoxyguanosine (8-OHdG) in the limited 23 patients. Although LDL-cholesterol level showed only the tendency for a decrease (left); the L-FABP (mid) and 8-OHdG (right) levels were significantly decreased. The values for L-FABP and 8-OHdG were log-transformed.

Recently, statins have been demonstrated to yield beneficial effects in different models of progressive renal failure. Although there is not yet a large interventional study on the effect of statin therapy in the progression of renal damage, there is evidence from post-hoc analyses to suggest that statins are likely to be effective in the treatment of renal disease (15). Statins are experimentally shown to have an antiproteinuric effect (16), as shown clinically in our FRET trial that demonstrated the improvement of microalbuminuria by fluvastatin. Since lipid lowering by statins reduces lipid trapping in renal tissues, the lipid lowering itself may contribute to renoprotective effects. However, some of the renoprotective effects of statins can be seen independent of the cholesterol reduction. In the FRET trial, the changes in the values for UAE and urinary L-FABP level were not correlated with the changes in LDL-cholesterol level not only in overall patients but also in the limited patients with microalbuminuria. These results suggest that fluvastatin might have a renoprotective effect beyond lipid lowering. Among various statins, fluvastatin is thought to be the most powerful anti-oxidant (5, 6). Different from other statins, fluvastatin has lipid-independent strong radical scavenging action and reduces superoxide anion formation both in vitro and in vivo (5). Fluvastatin has an indole ring in its structure, which is believed to be important for manifestation of these actions (17-19). L-FABP, which has high affinity for long-chain fatty acid oxidation products, may be an effective endogenous anti-oxidant. Since renal L-FABP reduces oxidative stress, ameliorating tubulointerstitial damage, urinary L-FABP, increased in association with renal dysfunction, is a potential marker of oxidative tubulointerstitial damage (20). In addition to the reduction of urinary L-FABP level not only in the high baseline L-FABP subgroup but also in the patients with microalbuminuria, our FRET trial showed the reduction of urinary 8-OHdG level, which is a marker for oxidative DNA damage, by 3 months of fluvastatin treatment in the patients with microalbuminuria. From our results, we can envision that the renoprotective effect of fluvastatin might be due to its anti-oxidative effect, although the changes in the urinary L-FABP level as well as UAE after fluvastatin treatment were not correlated with the changes in urinary 8-OHdG level not only in overall patients but also in the limited patients with microalbuminemia. Anyway, the results of FRET alone cannot determine the mechanism, by which fluvastatin ameliorates renal function.

Potential limitations

The FRET study has several potential limitations. This study was performed in a single arm no-controlled design with a small number of patients. Since comparisons with other statins were not performed, it was not elucidated whether the effects of fluvastatin on renoprotection are fluvastatin-specific effects or the class effects of statins. However, we believe it should be appreciated that this study was performed only by practitioners belonging to Saga Medical Association, because efforts of practitioners to prevent progression of CKD will be important for the improvement of cardiovascular mortality and morbidity of the CKD patients.

The authors state that they have no Conflict of Interest (COI).

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