

## Effects of Long-Term Fenofibrate Treatment on Markers of Renal Function in Type 2 Diabetes: FIELD Helsinki Substudy

Hiukka A et al.: Renal effects of fenofibrate in type 2 diabetes

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**Objective.** Although fenofibrate was associated with less progression of albuminuria in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study, it is unknown if it has any effect on renal function. We explored if there were changes in commonly available markers of renal function during fenofibrate treatment in the FIELD Helsinki cohort excluding statin users.

**Research Design and Methods.** 170 subjects with type 2 diabetes were randomly assigned to micronised fenofibrate 200 mg/day or placebo for 5 years. In this substudy, we measured several markers of albumin excretion and renal function.

**Results.** Following intensified treatment, blood pressure and fasting glucose decreased in both groups while HbA<sub>1c</sub> remained at 7.2%. Plasma creatinine increased with fenofibrate while urine creatinine remained comparable between the groups, resulting in significant decreases in both creatinine clearance and estimated glomerular filtration rates (eGFR) by the MDRD-4 and Cockcroft-Gault equations in the fenofibrate group. Cystatin C increased during fenofibrate treatment. Urinary albumin/creatinine ratio and diurnal urine protein remained unchanged, whereas overnight urinary albumin excretion rate showed minor decreases in both groups.

**Conclusions.** We report concomitant decreases in creatinine clearance and eGFR by fenofibrate. These changes complicate the clinical surveillance during fenofibrate treatment. We could not demonstrate beneficial effects of fenofibrate on albumin excretion. A novel finding is increase of cystatin C in type 2 diabetic patients during fenofibrate treatment. The clinical relevance of the changes needs to be assessed in a long-term outcome study of renal function.

Clinical Trial Registry Number: ISCRTN: 64783481

**D**iabetic nephropathy associates with a marked increase of cardiovascular disease (CVD) (1, 2). Part of this risk has been explained by concomitant dyslipidemia that is further aggravated in patients who develop diabetic nephropathy. This is in particular reflected in decreased HDL-cholesterol and increased triglyceride levels. Interestingly, hypertriglyceridemia seems to associate with the development and the progression of non-diabetic (3, 4) as well as diabetic kidney disease (5, 6). Fibrates are peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) agonists, designed to decrease triglycerides, LDL-cholesterol and to increase HDL cholesterol. Fenofibrate has been shown to reduce the progression of microalbuminuria in patients with type 2 diabetes in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and the Diabetes Atherosclerosis Intervention Study (DAIS) (7, 8). In these studies, data on albuminuria were analyzed using a change between different albuminuria categories as an indicator of progression or regression. More patients showed regression to a lower level and fewer patients progression to a higher level of albuminuria in the fenofibrate group. Such categorical analysis is sensitive to changes in the variance of the data, and thus the results should be interpreted cautiously. In fact, the absolute values of albumin/creatinine -ratio (ACR) and albumin excretion rate (AER) did not change during FIELD (unpublished data) and the DAIS (15.2 vs. 12.7  $\mu\text{g}/\text{min}$ ,  $p=\text{NS}$ ).

Plasma creatinine levels seem to increase with the use of fibrates. The exact mechanism for this increase is not

known. In a two-week study in dyslipidemic subjects ( $n=13$ ) there was no effect of fenofibrate on creatinine clearance, explained by an increased urinary excretion of creatinine, and thus no subsequent change in the creatinine clearance (9). A recent study, however, reported that the urinary excretion of creatinine remained unchanged, even though para-aminohippurate clearance was decreased and cystatin C increased (10). Thus available data are rather confusing and furthermore do not address the important question whether the fenofibrate-induced increase in plasma creatinine is detrimental or not.

In this pre-specified FIELD substudy, we used several markers of albuminuria and renal function, including cystatin C, to further elucidate the existing controversy of fenofibrate therapy.

## **METHODS**

**Subjects.** The FIELD study design has been described in detail (11). Briefly, men and women aged 50 to 75 years with type 2 diabetes, with or without prior coronary heart disease, were eligible using the following lipid criteria: serum (S-) cholesterol 3.0 to 5.5 mmol/L, plus either S-triglycerides (TG) 1.0 to 5.0 mmol/L or S-cholesterol/HDL cholesterol ratio over 4. Patients with hepatic or renal (S-Creatinine  $>130 \mu\text{mol}/\text{L}$ ) dysfunction, gallstones, lipid-lowering medication, cyclosporin, alcohol abuse, and other severe mental or physical illness were excluded. Patients were randomly assigned to receive in a double-blind design either placebo or micronized fenofibrate (200mg daily) for 5 years. In randomisation, patients were stratified within the country stratum for prognostic factors, such as age, sex, previous myocardial infarction, lipid levels, and

urinary albumin concentration. A total of 270 type 2 diabetic patients were recruited to the FIELD study at the Helsinki Centre (Finland). Of these patients, 239 volunteered to participate in this substudy and 228 were randomized to placebo or fenofibrate groups (Figure 1.). There were 2 deaths and 12 serious adverse events (SAEs) in the placebo group and 5 deaths and 15 SAEs in the fenofibrate group. We excluded patients who had statin added to their medication during the study course, since this was considered a confounding factor. We further excluded from the analysis one patient who developed diabetic nephropathy and overt proteinuria (3g/24h) early during the study, and who was thus a clear outlier in our study population. Consequently, 170 patients were eligible for the analysis (placebo group: men/women 62/21, fenofibrate group: men/women 63/24). All patients signed informed consent forms. The Ethics Committee of the Helsinki University Central Hospital approved the substudy protocol.

**Laboratory analyses.** Baseline examinations were performed during the placebo run-in period of the FIELD study before any fenofibrate intervention. Blood samples were obtained after an overnight fast. Serum and EDTA plasma were separated by centrifugation and stored at -80°C until analyzed. Lipids were measured in lipoprotein fractions isolated by ultracentrifugation. Enzymatic colorimetric assays were used to measure cholesterol (Unimate 7 CHOL, Hoffman-La Roche, Basel, Switzerland for baseline samples and later ABX Diagnostics Cholesterol and ABX Pentra Cholesterol, HORIBA ABX, Montpellier, France) and triglyceride (Unimate 7 TRIG, Hoffman-La Roche, Basel, Switzerland for baseline samples and

later ABX Diagnostics Triglycerides and ABX Pentra Triglycerides, HORIBA ABX, Montpellier, France) concentrations in whole sera or lipoprotein fractions using a Cobas Mira automatic analyzer (Hoffman-La Roche, Basel, Switzerland). Plasma glucose concentrations were analyzed by a glucose dehydrogenase method (Precision-G Blood Glucose Testing System, Abbott, Abbott Park, IL, USA). HbA<sub>1c</sub> was measured using a commercially available kit (DCA 2000 Analyzer, Bayer Diagnostics, NY, USA). Serum/plasma/urine creatinine was measured using the Jaffe's method and later using an enzymatic method in the laboratory of Helsinki University Central Hospital. Samples were randomly selected to perform parallel analysis with Jaffe's method and enzymatic method. The values from the two methods were highly correlated with R<sup>2</sup>=0.977, and their relationship was formulated as serum creatinine (μmol/L, enzymatic method)=1.07 x serum creatinine (μmol/L, Jaffe's method) -21. Due to approximately 15% lower levels of creatinine with the enzymatic method, a conversion factor of 0.85 was used for values measured with Jaffe's method. The timed overnight urine samples were analyzed for albumin concentration by an immunoturbidimetric method. At baseline, AER was collected during three consecutive nights, and the median of these results was used in the analysis. At the 2<sup>nd</sup> year and at the 5<sup>th</sup> year, an additional AER was collected. The patients collected a 24h urine sample at each study visit and urinary protein excretion rate (measured by a turbidimetric benzetoniumchloride method) and creatinine clearance was calculated from the same sample. Estimated GFR was calculated both by the Cockcroft-Gault equation and MDRD-4. The eGFR estimates and the

calculated creatinine clearance were normalized to body surface area by DuBois formula. We also used the data on ACR which was determined from a spot sample in the main FIELD study. Cystatin C was measured by an immunoprecipitation method (Thermo Fisher Scientific, Vantaa, Finland).

**Statistical analysis.** The statistical analysis was performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, USA) and CIA 2.1.2 ([www.som.soton.ac.uk/cia/](http://www.som.soton.ac.uk/cia/)). Most of the variables were non-normally distributed and their results are shown as median (+SEM) in Figure 2. and median with interquartile range (IQR) in Tables. For normally distributed variables, mean (+SEM) is used in Figure 2 and mean  $\pm$ STD is used in Tables. We used repeated measures ANOVA with log-transformed values or the Mann-Whitney U-test to compare changes between the treatment groups and Wilcoxon Signed Rank test for matched pairs to compare the changes within the groups. When testing variables of renal function, we included covariates of glucose, blood pressure, LDL cholesterol, and triglycerides to the ANOVA model. Qualitative variables are presented as N (%) and their changes are compared by the 2x2 likelihood ratio test for transition probability matrices (<http://www.kttl.helsinki.fi/sarna/Stats/LRtest2x2.xls>) or chi-square test. Correlations were studied using Spearman correlation coefficient. A p-value of <0.05 was considered significant in all analyses.

## RESULTS

**Characteristics of patients.** The mean age of subjects was  $61.3 \pm 6.7$  yrs in the placebo and  $62.5 \pm 6.3$  yrs in the fenofibrate group (NS). Median duration

of diabetes was 5 (2-10) yrs in the placebo group and 6 (3-11) yrs in the fenofibrate group. The majority of the patients were non-smokers (42%) or ex-smokers (43%), and there were no significant differences between the groups during the study. A history of CVD was reported by 25% in the placebo group and by 33% in the fenofibrate group (p=NS). In both groups 13% of patients had retinopathy. Fasting serum glucose values decreased slightly in both groups, with no change in HbA<sub>1c</sub> (Table 1 and Supplement Table 1 in the online appendix which is available at <http://care.diabetesjournals.org>). The use of antihypertensive treatment increased in both groups, and systolic blood pressure was decreased in both groups (Table 1). Our study cohort was similar to the whole Finnish FIELD study cohort, and had a greater proportion of men and of patients with pre-existing cardiovascular disease compared to the whole FIELD study cohort. The use of betablockers, diuretics, aspirin, and oral antihyperglycaemic agents were more common in our cohort compared to the whole FIELD study cohort (data not shown).

Markers of renal function and albuminuria. Plasma creatinine increased during fenofibrate treatment (Figure 2a.), similarly to the main FIELD study. However, urine creatinine levels remained comparable between the treatment groups (Fig. 2b). This obviously resulted in a decrease in calculated creatinine clearance and eGFR (Fig. 2c-e) in the fenofibrate treatment group. There were no differences in 24h urine protein excretion (dU-Prot), AER, or ACR between the treatment groups at study close-out (Table 2). Cystatin C increased in the fenofibrate treatment group by 14.1% during the study, compared to the 3.6% increase in the placebo group

( $p < 0.001$ ). Of the albuminuria markers, AER decreased in both groups whereas ACR remained stable.

## DISCUSSION

We here report by using several markers that fenofibrate reduces measures of renal function to a greater extent than placebo. In addition, our study showed that long-term fenofibrate treatment had no effect on albumin excretion rate. This finding is in agreement with the lack of changes in the mean values of ACR and AER attributable to fenofibrate in the FIELD and the DAIS studies, respectively. In the FIELD study, the allegedly beneficial renal outcome was based on 2.6% more patients allocated to fenofibrate than placebo regressing or not progressing in a categorized albuminuria variable ( $p = 0.002$ ). This benefit is rather modest and the clinical relevance should be evaluated in a long-term outcome study of renal function.

In the placebo group systolic and diastolic blood pressures decreased by 2 and 8 mmHg, respectively, and in the fenofibrate group by 6 and 8 mmHg, respectively. These changes in blood pressure may explain the decrease in AER in both groups. Further, the increased use of renin-angiotensin system blockers in both groups may have had nephroprotective effects beyond arterial blood pressure lowering. It should also be recognized that glycemic control did not worsen during the 5 years of our study. These variables, together with triglycerides and LDL-cholesterol, were included in the repeated measures ANOVA and were found not to account for the changes in renal function. Overall, these factors may explain the modest annual reduction of eGFR seen in placebo group.

The increase in plasma creatinine by fenofibrate is a well established phenomenon. In contrast, the reduction in renal function has been observed previously as a decrease of para-aminohippurate clearance and increase of cystatin C in non-diabetic subjects (10). Since urinary creatinine levels remained unchanged in both studies, there was an obvious reduction in creatinine clearance. The MDRD and Cockcroft-Gault estimates express variability and tend to underestimate renal function in subjects with relatively normal renal function. In these patients, creatinine clearance is more reliable measure of renal function. As cystatin C is considered to be the best marker of renal function (12, 13), we used it as a creatinine-independent marker of renal dysfunction during fenofibrate treatment. We observed a 14% increase of cystatin C levels in fenofibrate group, suggesting impairment of renal function. It has been suggested that fibrates increase the production of creatinine (9) with no adverse effect on renal function. This seems unlikely, since an increase of creatinine excretion has not been observed (10), which was confirmed in our study. Thus, we cannot exclude the option that the increase of creatinine is caused by the decrease in creatinine clearance. Another hypothetical option is that fenofibrate might have an inhibitory effect on the excretion of creatinine via the kidneys, requesting higher blood concentration of creatinine to maintain normal excretion. Finally, fenofibrate may increase the flow of creatinine from the muscle. If fenofibrate increases creatinine outflow from the muscle, muscle damage cannot be ruled out. However, in this study creatine phosphokinase levels were lower in the fenofibrate group. Likewise increased flux of creatinine from muscle should be reflected in increased excretion

of creatinine, which was not seen in this study.

This study was a pre-specified FIELD substudy addressing renal function using several markers, but not an intention to treat analysis as several patients were excluded. In this substudy direct measures of GFR could not be used due to multiple visits and a cumbersome study protocol. However, the size of our study cohort gives enough statistical power, despite potential day-to-day variations in the measured variables. The strength of our study is that all used parameters of albumin excretion and renal function showed parallel results in the fenofibrate group.

In conclusion, our results do not support the benefits of fenofibrate on progression of albuminuria. Available data do not allow us to conclude whether the fenofibrate-induced increase in creatinine and cystatin C are relevant for the prognosis of these patients but obviously the changes in the estimates of GFR impair the follow-up of renal function in clinical practice. The results of the lipid-lowering arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial may clarify the issue (14). Currently, the use of fenofibrate for

cardiovascular protection should be considered in the context of the increases of both creatinine and cystatin C.

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## FIGURE LEGENDS

**Figure 1.** Consort flow of the study patients.

**Figure 2.** Creatinine levels in plasma and urine, and markers of renal function during the study in placebo and fenofibrate groups. White bars present baseline, hatched bars 2<sup>nd</sup> year and black bars 5<sup>th</sup> year data (median). The change during study is expressed as total change for plasma and urine creatinine and as annual change for the markers of renal function. The changes have been compared by the Mann-Whitney U-test.

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**Table 1.** Characteristics of the patients at baseline and at 5<sup>th</sup> year.

	Baseline	5th yr	Baseline	5th yr	P-value §
	Placebo	Placebo	Fenofibrate	Fenofibrate	
	(n=83)	(n=83)	(n=87)	(n=87)	
BMI (kg/m <sup>2</sup> )	29.7(26.8-33.0)	29.5(26.6-32.9)	29.1(26.3-32.5)	28.6 (26.3-33.4)	NS
Glucose (mmol/L)	7.7 (6.5-8.7)	7.1 (6.0-8.8)	7.9 (6.8-9.1)	7.2 (6.0-8.6)‡	NS
HbA <sub>1c</sub> (%)	7.0 (6.3-8.1)	7.0 (6.4-7.7)	7.2 (6.6-8.0)	7.3 (6.6-8.1)	NS
Syst BP (mmHg)	140 (132-150)	138 (126-148)‡	142 (134-152)	136 (126-142)*	NS
Diast BP (mmHg)	87 ± 9	80 ± 9*	88 ± 9	78 ± 10*	0.047
S-Chol (mmol/L)	4.9 ± 0.7	5.0 ± 0.6	5.2 ± 0.7	4.3 ± 0.8*	<0.001
LDL Chol (mmol/L)	3.0 ± 0.6	3.0 ± 0.6	3.3 ± 0.6	2.7 ± 0.7*	<0.001
TG (mmol/L)	1.7 (1.3-2.1)	1.6 (1.2-2.2)	1.5 (1.1-2.2)	1.1 (0.8-1.7)*	<0.001
HDL Chol (mmol/L)	1.1 (1.0-1.3)	1.2 (1.0-1.4)*	1.1 (1.0-1.4)	1.1 (1.0-1.4)	NS

BMI, body mass index; BP, blood pressure; Syst, systolic; Diast, diastolic; Chol, cholesterol; TG, triglycerides

Data are mean±STD or median (IQR).

§, p-value from the repeated measures ANOVA.

Between baseline and 5<sup>th</sup> yr within each group, p-values with Wilcoxon Signed Rank test for 2 related variables: \*, p<0.001; †, p<0.01; ‡,p<0.05.

**Table 2.** Markers of albuminuria and renal function at baseline and at 5<sup>th</sup> year.

	Baseline	5th yr	Baseline	5th yr	P-value §
	Placebo	Placebo	Fenofibrate	Fenofibrate	
	(n=83)	(n=83)	(n=87)	(n=87)	
P-Creatinine (µmol/L)	73 (66-78)	75 (63-85)	73 (68-85)	87 (75-101)*	<0.001
U-Creatinine (mmol/24h)	13.0 (10.8-15.5)	12.9 (10.0-15.5)	13.2 (10.8-15.6)	14.0 (10.0-16.4)	NS
Creatinine clearance (ml/min/1.73m <sup>2</sup> )	108 (95-119)	104 (89-127)	102 (87-118)	95 (77-112)*	0.027
eGFR-CG (ml/min/1.73m <sup>2</sup> )	95 (83-109)	90 (75-108)	93 (80-104)	76 (59-89)*	<0.001
eGFR-MDRD (ml/min/1.73m <sup>2</sup> )	95 ± 15	95 ± 23	91 ± 16	78 ± 20*	<0.001
Cystatin C (mg/L)	0.85 ± 0.13*	0.91 ± 0.17	0.92 ± 0.17	1.05 ± 0.25*	<0.001
AER (µg/min)	6.5 (5-11)	4 (2-11) ‡	6 (4-12)	4 (2-13)	NS
dU-Prot (mg/d)	105 (82-190)	100 (70-150)	123 (78-184)	110 (73-190)	NS
ACR (mg/mmol)	1.0 (0.7-2.3)	1.1 (0.4-2.9)	1.1 (0.6-2.8)	1.0 (0.0-3.3)	NS
CPK (U/L)	92 (61-134)	98 (70-150)	84 (60-133)	84 (55-115)	0.05

ACR, albumin/creatinine –ratio; AER, albumin excretion rate; CPK, creatine phosphokinase; dU-Prot, 24h urine protein excretion.

Data are mean±STD or median (IQR).

§, p-value from the repeated measures ANOVA, except for nU-AER for which Mann-Whitney U-test was used to compare relative changes from baseline to 5<sup>th</sup> year between the groups.

Between baseline and 5<sup>th</sup> yr within each group, p-values with Wilcoxon Signed Rank test for 2 related variables: \*, p<0.001; †, p<0.01; ‡,p<0.05.

Figure 1

## FIELD Helsinki Renal Substudy

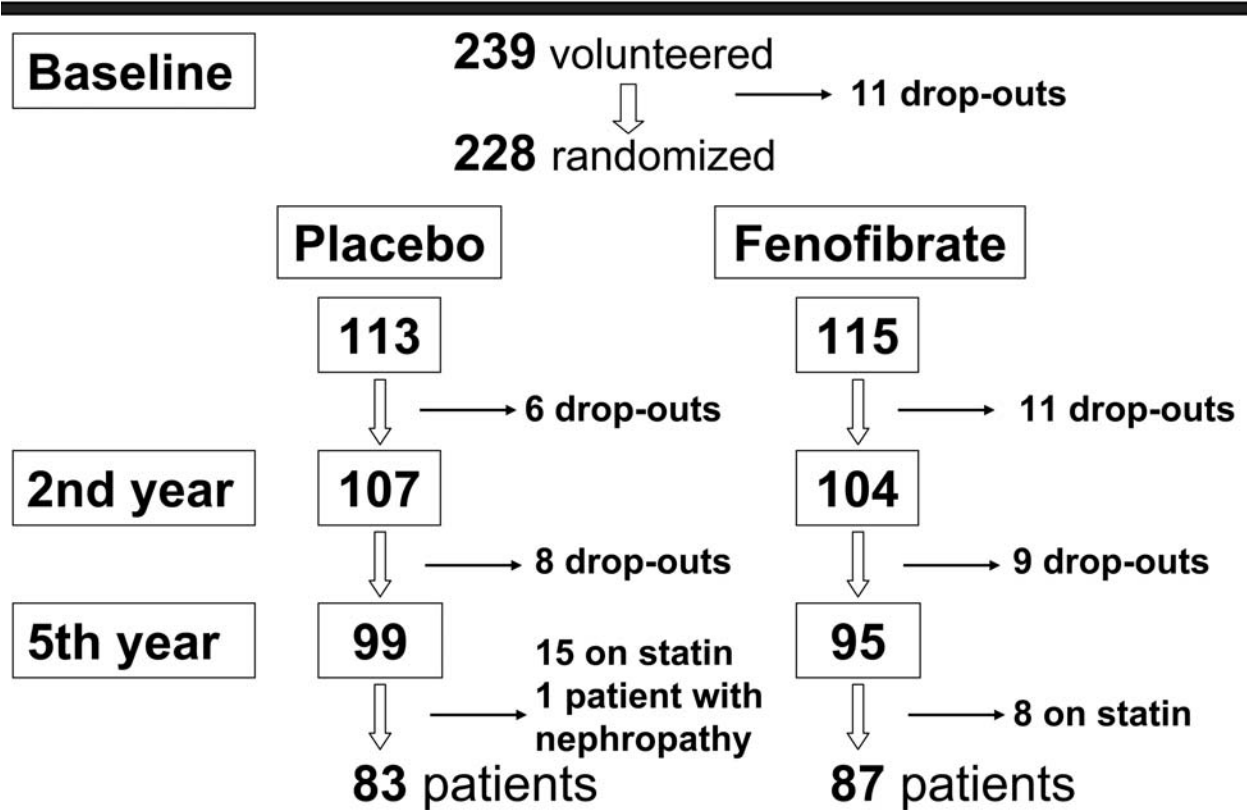


Figure 2

