Fibrates in Chronic Kidney Disease Patients: A Controversial Issue

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ABSTRACT

Background: Fenofibrates were not previously known to affect renal function tests until some reports indicated that these drugs may lead to a decrease in renal function. Likewise, the nephrotoxic effect of fibrates remains to be vague and unclear. Guidelines regarding fenofibrate dosing in renal impairment vary internationally.

Patients and methods: A prospective cohort study over 6 months with a total of 80 patients on fibrates divided into 2 groups, 40 of which received statins, and the other 40 continued on fibrates. All patients were subjected to full history, clinical examination, and complete baseline labs. The KFTs including serum creatinine and eGFR were measured at 0, 1, 2, and 6-months intervals and lipid profile at 0,3,6 months serially in both groups.

Results: Out of the baseline values of KFTs, the statin group showed a significant decrease in all kidney function values including mean serum creatinine by (0.9mg/dL, P=0.001) and an increase in eGFR (8.9 mL/min/1.73 m2, P<0.001). Whilst in patients who continued to receive fibrates the KFTs continued to rise as serum creatinine showed a significant increase in their mean serum Cr levels (by 0.9 mg/dL or 20%, P=0.001), and a significant decrease in their mean eGFR values (by 8.2 mL/min/1.73 m2 or 20.55%, P<0.001). On the other hand, total and LDL Cholesterol were significantly lower in the statin group at all follow-up intervals. Also, triglycerides were significantly higher in the Statin group at the end of month-6 from baseline.

Conclusion: In our study fibrates administration showed a short-term state of renal insufficiency. The long-term effects of fibrates versus variable renal derangement are yet to be identified.

Keywords: Chronic kidney disease, fibrates, Lipid profile.

INTRODUCTION

Fenofibrates are used to cure dyslipidemia, they are often administered regardless of the chronic nephropathies, as well as in transplanted patients [1, 2].

Fibrates were not previously known to affect renal function tests. Updated research pointed towards renal function derangement [1]. The underlying mechanism is still, however, unclear. Changes in GFR, creatinine excretion within the kidney tubules, altered renal hemodynamics, and changes in the production of creatinine by skeletal muscle have all been hypothesized [3-5].

Fenofibrate's safety in patients with renal insufficiency is an issue because it may increase plasma creatinine. Furthermore, guidelines regarding fenofibrate dosing in renal impairment vary internationally. We investigated fenofibrate's effects on cardiovascular and on advanced CKD, according to eGFR [6].

AIM OF THE WORK

To evaluate the potential benefits of fenofibrate versus renal injury.

PATIENTS AND METHODS

Our prospective cohort study over 6 months was conducted on 98 patients, 14 of them did not meet the inclusion criteria and 4 refused to participate in the study which left a total of 80 patients on which the randomized control study was performed. All of them were maintained on fenofibrate by their cardiologists and came to our nephrology out-patient clinics (OPC) at Ain Shams University Hospitals and Ain Shams Specialized Hospitals to follow up their kidney function tests.

Inclusion Criteria:
1. All CKD patients with ischemic heart disease.
2. All stages of CKD following in nephrology and cardiology clinics.

Exclusion Criteria:
1. Other causes of impaired kidney functions like contrast nephropathy,
2. Recent intake of diuretics or evidence of hypovolemia.
3. Recent intake of ACEIs or ARBs, NSAIDs, UTI.

Then patients were randomized into two groups:
Group I: Shifted to statins instead of fenofibrate.
Group II: Maintained on the same dose of fenofibrate.

All patients were subjected to full history, clinical examination, and Kidney function tests, including serum creatinine, urea, K+, uric acid, eGFRwith Cockcroft Gold formula at 0 (baseline) 1, 2, and 6 months. Complete lipid profile at 0 (baseline) 3 and 6 months.

Ethical approval:
All procedures performed in the study were following the ethical standards of the Ain-Shams University hospital research committee (Ethics committee reference number 000017585) and with the

**ethical standards laid down in the 1964 Declaration of Helsinki.**

Oral consent for participation was taken from all patients, local ethics committee ruled that no formal ethics approval was required in this study as it is not a clinical trial.

Statistical methods:

Sample Size: Up to our knowledge till the beginning of our research no previous data were published on a similar topic; it is an exploratory study, so we will include 40 cases in each group. The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. Inferential analyses were done for quantitative variables using the Shapiro-Wilk test for normality testing, independent t-test in cases of two independent groups with normally distributed data, and repeated measure ANOVA (RM ANOVA) test for more than two times with normally distributed data with post hoc Dennett test to find a relation with baseline. In qualitative data, inferential analyses for independent variables were done using the Chi-square test for differences between proportions and Fisher's Exact test for variables with small expected numbers. The level of significance was taken at P- value < 0.050 is significant, otherwise is non-significant.

RESULTS
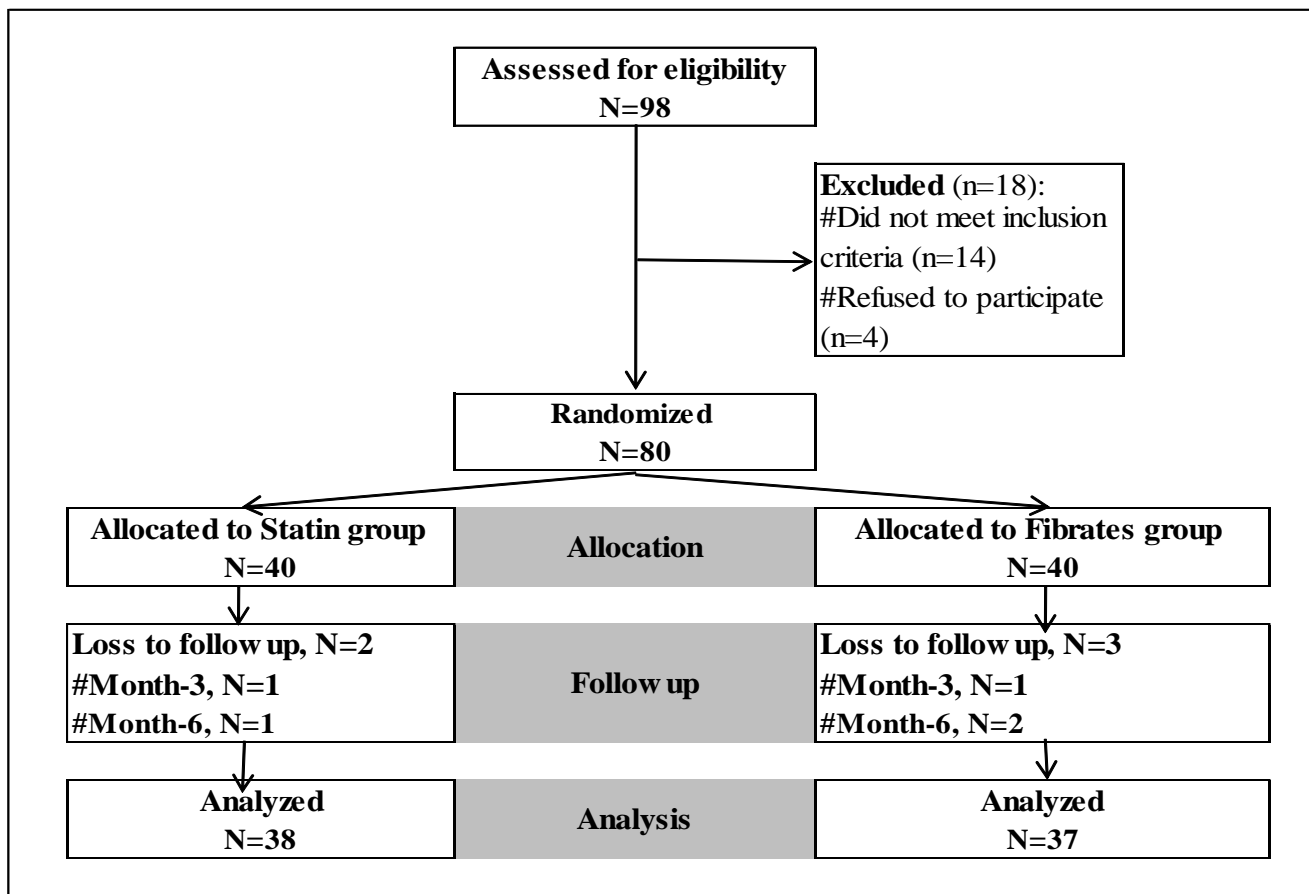
Figure (1): Flow chart of the studied patients.

The 80 patients with impaired renal functions at baseline were all subjected to full history and clinical examination and full labs including Kidney function tests including serum creatinine, urea, uric acid, K+, eGFR, complete lipid profile, serially over 6 months.

Demographics: there were 48 males versus 32 females, 47 of them were diabetic, 33 of them were hyperuricemic; the most common comorbidity in both groups with 57.5% and 60 % respectively. The most common cause of underlying CKD was diabetic nephropathy. The mean duration for CKD was 3.7+/- 1.3 and 3.2 +/- 0.9 years respectively. Durations on fibrate therapy were 1.9+/- 0.6 months and 2.2+/- 0.7 months respectively. Doses of fibrates in the studied groups ranged from 160 to 300mg as seen in **Table** 1.

Patients were randomized to two groups 40 on fibrates and the other 40 patients were shifted to statins.

Table (1): Comparison of demographic and clinical characteristics between patients' groups.

Variables		Statins	Fibrates	P-value
Age (years)		54.6±10.7	56.7±10.7	^0.389
BMI (kg/m^2)		32.5±2.3	33.1±3.0	^0.305
Sex	Male	23 (57.5%)	25 (62.5%)	#0.648
	Female	17 (42.5%)	15 (37.5%)	
Comorbidities	DM	23 (57.5%)	24 (60.0%)	#0.820
	IHD	22 (55.0%)	23 (57.5%)	#0.822
	Hyperuricemia	17 (42.5%)	16 (40.0%)	#0.820
	HTN	15 (37.5%)	17 (42.5%)	#0.648
Etiology	DM	23 (57.5%)	24 (60.0%)	§0.822
	HTN	10 (25.0%)	12 (30.0%)	
	NSAIDs	3 (7.5%)	2 (5.0%)	
	Others	4 (10.0%)	2 (5.0%)	
Duration of CKD (year)		3.7±1.3	3.2±0.9	^0.103
Duration of Fibrates (months)		1.9±0.6	2.2±0.7	^0.107
Dose of Fibrate (mg)		212.5±68.6	230.0±70.9	^0.265

^Independent t-test. # Chi-square test. §Fisher's Exact test. *Significant

Table (1) shows no significant difference between the studied groups regarding baseline demographic and clinical characteristics. In our study, the two groups of patients were subjected to lipid profile estimation serially over 6 months at 0 months (baseline) and 3 months and 6 months.

Table (2): Comparison of Lipid profile among the studied groups over the study period.

Variables	Times	Statins	Fibrates	^P-value (groups)
Serum cholesterol (mg/dL)	Baseline	218.2±29.9	224.7±30.4	0.343
	Month-3	210.0±29.8	222.7±26.7	**<0.001**
	Month-6	180.4±23.4	226.5±28.8	**<0.001**
	#P-value (times)	**<0.001**	0.240	
Serum triglycerides (mg/dL)	Baseline	229.5±40.6	234.8±36.9	0.545
	Month-3	234.0±27.7	235.2±34.3	0.865
	Month-6	251.7±22.2	235.8±39.3	**0.034**
	#P-value (times)	**<0.001**	0.889	
Serum LDL (mg/dL)	Baseline	115.2±11.1	118.3±11.3	0.219
	Month-3	107.4±11.0	118.7±12.7	**<0.001**
	Month-6	89.7±11.0	118.5±11.6	**<0.001**
	#P-value (times)	**<0.001**	0.582	
Serum HDL (mg/dL)	Baseline	36.3±3.9	35.2±3.9	0.226
	Month-3	36.9±4.1	34.8±4.5	**0.022**
	Month-6	39.1±4.8	35.0±3.8	**<0.001**
	#P-value (times)	**<0.001**	0.329	

^Independent t-test. #RMANOVA. *Significantly different from baseline based on Dennett test.
LDL=low density lipoproteins, HDL=high density lipoproteins.

Table (2) and figures (2a), (2b), (2c) show no significant difference between the studied groups regarding baseline lipid profile. The lipid profile throughout the follow-ups did not significantly change in the Fibrates group. HDL and Triglycerides (TG) significantly increased in the statin group throughout the follow-ups, but the differences were statistically significant, higher than basal, at month-6 only. Cholesterol and LDL significantly decreased in the statin group throughout the follow-ups, the differences were statistically significant, lower than basal, beginning from month-3. Cholesterol and LDL were significantly lower in the statin group at all follow-ups. Triglycerides and HDL were significantly higher in the statin group at month-6 only, compared to the fibrate group.
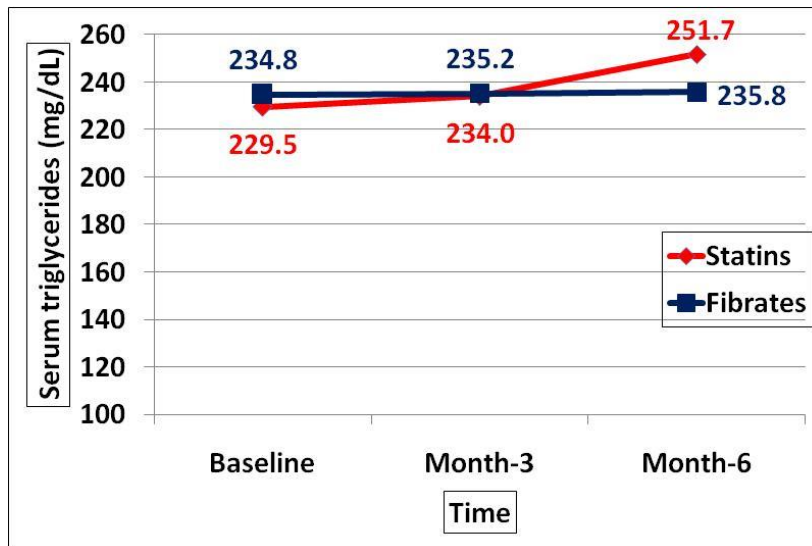
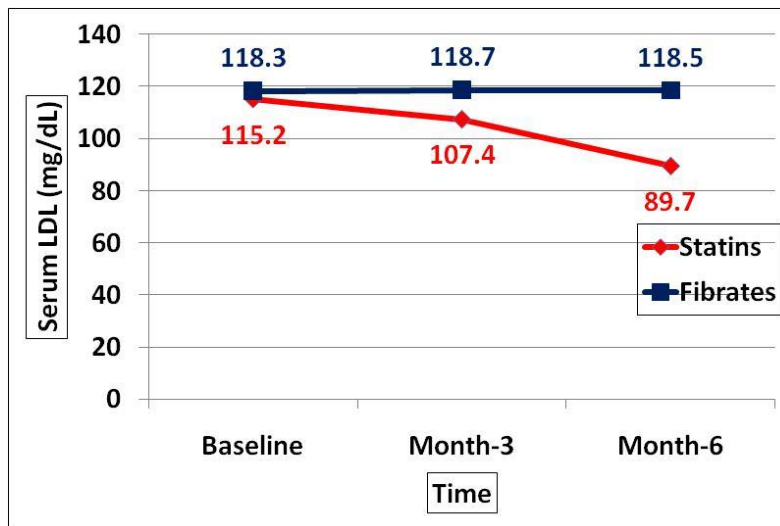**Figure (2a):** Comparison of serum triglycerides among the studied groups over the study period.

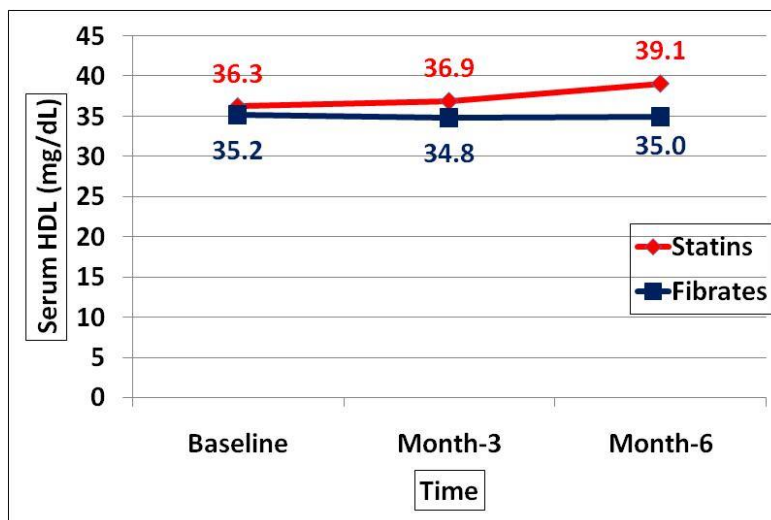**Figure (2b):** Comparison of serum LDL among the studied groups over the study period.

Figure (2c): Comparison of serum HDL among the studied groups over the study period.

All patients in the two studied groups were subjected to full Kidney function tests including creatinine, Urea, K+, Uric acid, eGFR before, one, two, and 6 months of, the study (Table 3).

Table (3): Difference in kidney function tests among the studied groups.

Variables	Times	Statins	Fibrates	^P-value (groups)
Serum creatinine (mg/dL)	Baseline	3.3±0.2	3.6±0.2	0.354
	Month-1	2.4±0.1*	3.7±0.1	**<0.001**
	Month-2	2.1±0.1*	4.0±1.1	**<0.001**
	Month-6	1.5±0.2*	4.5±1.0*	**<0.001**
	#P-value (times)	**<0.001**	**<0.001**	
Serum urea (mg/dL)	Baseline	126.3±32.4	132.9±35.2	0.389
	Month-1	106.0±28.5*	137.4±21.1	**<0.001**
	Month-2	98.4±15.0*	143.5±21.2	**<0.001**
	Month-6	89.8±18.4*	157.4±19.1*	**<0.001**
	#P-value (times)	**<0.001**	**<0.001**	
Serum uric acid (mg/dL)	Baseline	8.2±1.0	8.3±1.0	0.717
	Month-1	7.5±1.0*	8.4±1.0	**<0.001**
	Month-2	7.4±1.1*	8.6±1.1	**<0.001**
	Month-6	7.1±1.1*	8.9±1.1*	**<0.001**
	#P-value (times)	**<0.001**	**<0.001**	
Serum K (meq/L)	Baseline	4.6±0.4	4.7±0.4	0.279
	Month-1	4.4±0.4*	4.8±0.4	**0.004**
	Month-2	4.3±0.4*	4.9±0.4	**<0.001**
	Month-6	4.3±0.4*	5.0±0.3*	**<0.001**
	#P-value (times)	**0.005**	**0.011**	
eGFR (mL/minute)	Baseline	42.9±10.4	39.9±7.5	0.232
	Month-1	49.1±11.8*	37.5±8.8	**<0.001**
	Month-2	47.0±11.1*	36.0±7.4	**<0.001**
	Month-6	51.8±10.8*	31.7±7.3*	**<0.001**
	#P-value (times)	**<0.001***	**<0.001***	
CPK(Total)	Baseline	**125.0**±4.0	**116.0**±3.0	>0.05
	Month 3	**117.0**±5.3	**112.0**±8.6	0.21
	#P-value (times)	**<0.001**	**<0.001**	

^Independent t-test. #RMANOVA. *Significantly different from baseline based on Dunnett's test.
S K=serum potassium, eGFR= estimated GFR, CPK= creatine phosphokinase.

Table (3) and figures (3a), (3b), (3c), show no significant difference between the studied groups regarding baseline renal functions. Serum creatinine, urea, uric acid, and K significantly decreased in the Statin group throughout the follow-ups, the differences were statistically significantly lower than basal beginning from month-1.GFR significantly increased in the statin group throughout the follow-ups, the differences were statistically significantly higher than basal beginning from month-1. Serum creatinine, urea, uric acid, and K were significantly lower in the statin group at all follow-ups. GFR was significantly higher in the statin group at all follow-ups. There was no significant difference between both groups as regards to CPK total values.
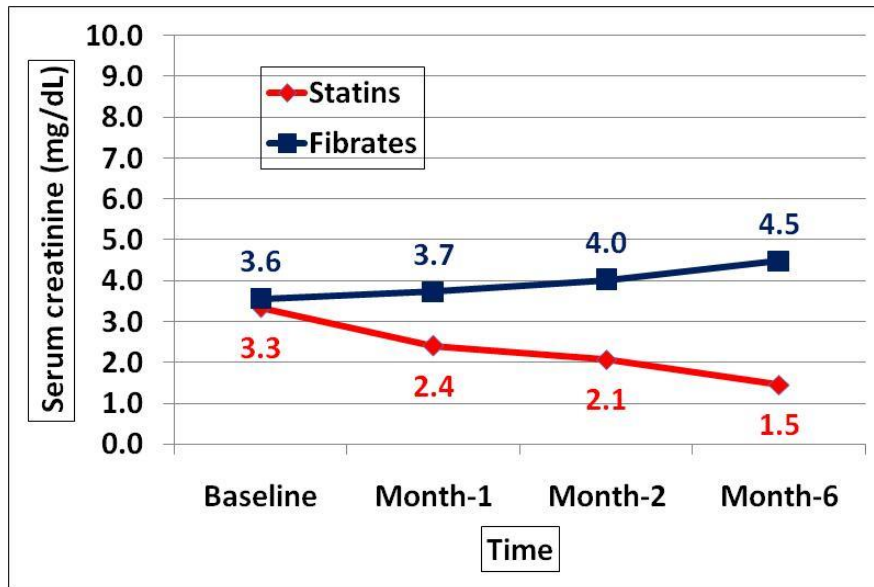
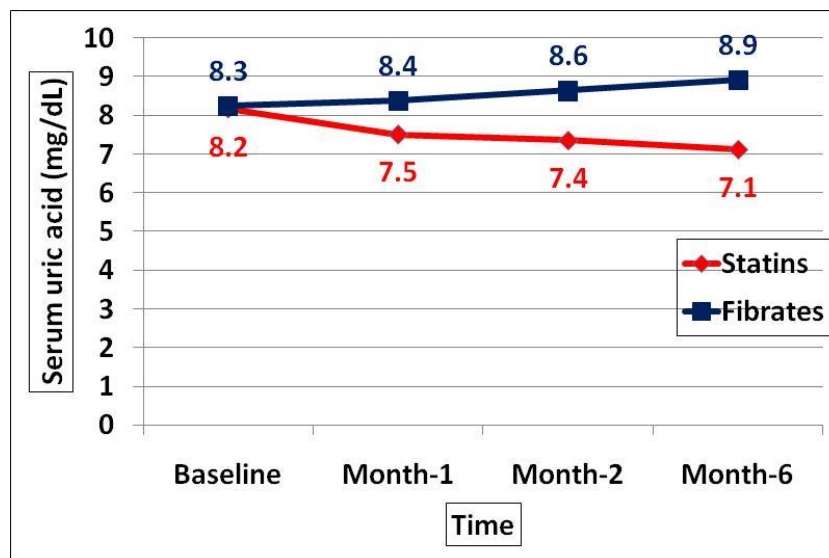**Figure (3a):** Serum creatinine among the studied groups.

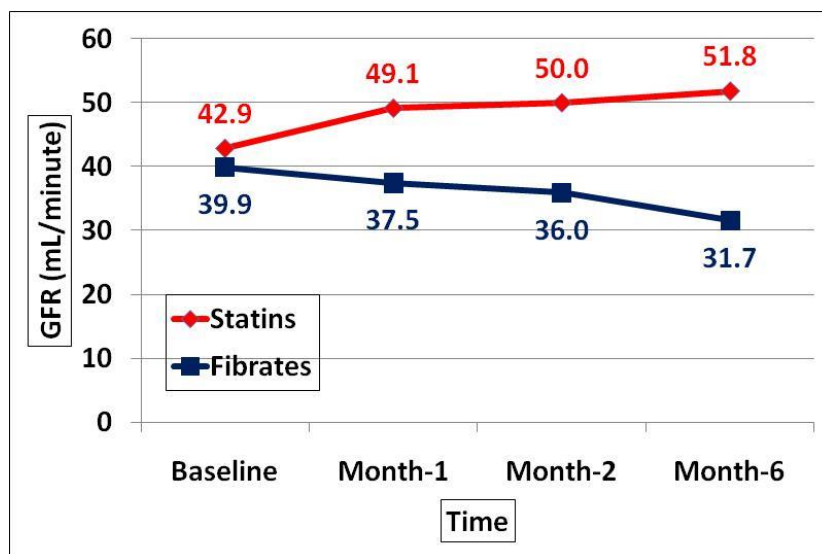**Figure (3b):** Serum uric acid among the studied groups.

Figure (3c): Serum GFR among the studied groups.

DISCUSSION

The relation of fibrates to the kidney function tests including the eGFR has been only recently raised as some studies have noted a rise in episodes of acute kidney injury in patients on fibrates [7].

Earlier studies disregarded the injurious effect of fenofibrate on the kidney function values and focused on the importance of fibrates in decreasing lipid profile and its relative cardiovascular disease (CVD) risk without pointing towards the drawbacks of a raised renal profile and a decreased eGFR on the general prognosis of CKD [6, 8, 9].

Although confirming the decline of eGFR with fibrates was supported by **Ting et al.** [6] they concluded the pleiotropic effect of fibrates on diabetic vasculopathy and decreased damage induced by TG on renal microvasculature.

The way by which fenofibrates harm the kidney has been addressed in previous studies, but no firm conclusion has been reached [10–11]. They may increase the metabolic production of creatinine [12], or alter renal blood flow, via a peroxisome proliferator-activated receptor-alpha-mediated decrease in the renal synthesis of vasodilatory prostaglandins [10]. It may induce muscle damage [12].

All patients in the present study were referred from the cardiology clinic and all of them were on fibrates. Half of them were assigned to shift to statins and the other half to continue on fibrates for 6 months. All patients were subjected to full history, clinical examination, and Kidney function tests, including serum creatinine, urea, K+, uric acid, eGFR with Cockcroft Gold formula at 0 (baseline) 1, 2, and 6 months. Complete lipid profile at 0 (baseline) 3 and 6 months.

It was shown that kidney function tests significantly improved in the statin group throughout the follow-ups, the differences were statistically significantly lower than basal beginning from the first month. They were also significantly lower in the statin group at all follow-ups compared to the fibrate group. There was no significant difference between both groups as regards the CPK total values at baseline & after 3 months.

Kim et al. [13] compared fibrates to statins as per serum creatinine levels. In the fibrates group, serum creatinine significantly increased from 1.12±0.14 mg/dL before treatment to 1.22±0.16 mg/dL after12 months of fenofibrate treatment (P=0.001). In contrast, the serum Cr level, in the control group (on statins), was unchanged (1.12±0.13 mg/dL versus 1.11±0.12 mg/dL, P=0.57).

Our study has investigated the withdrawal effects over 6 months of fenofibrate treatment in patients previously receiving fenofibrates taken for hypertriglyceridemia versus continuing the treatment in the other group. These patients are frequently seen in the primary care settings and showed a significant increase in their mean serum Cr levels (by 0.9 mg/dL or 20%, P=0.001), and a significant decrease in their mean eGFR values (by 8.2 mL/min·1.73 m2 or 20.55%, P<0.001) following treatment with fenofibrates. On the other side,

the serum Cr level of the patients decreased after shifting to statin therapy serially over6 months (from 3.3±1.0 mg/dL to1.5±0.8mg/dL P=0.001 at 6 months from baseline)and an increase in GFR (8.9 mL/min·1.73 m2, P<0.001) (Table 3).

Our results agree with that of **Bonds et al.** [14] who found a rapid rise in serum creatinine upon starting fenofibrates, but in contrast to other papers stated that long term fenofibrates exerting drug-induced nephrotoxicity which is of uncertain significance and surprisingly should not be contraindicated in moderate renal impairment [6].

As regards the rise of serum creatinine level on continuing fenofibrate use in our study was consistent with those of previous studies [3, 7, 11, 14, 15] but in contrast to that of **Ting et al.** [6] who seems to constantly nullify the long term effects despite proven in other studies; as in post-transplant patients with a permanent rise in renal values[3] and those who had to discontinue fibrates due to their proven deleterious effects on serum creatinine and eGFR without reciprocal cardiovascular risk from discontinuing fibrates, over the 6-12 months study periods previously done [13].

The results of **Broeders et al.** [3] showed nephrotoxicity after taking fibrates; this study defined nephrotoxicity as a serum Cr level increase of ≥0.2 mg/dL. These results showed that the mean serum creatinine level increased by 40% on fibrates, which caused 24 of the studied 27 patients to discontinue the treatment, and the serum creatinine levels reverted to pre-treatment values in 18 of the 24 patients who discontinued fibrates. In the present study, a serum creatinine increase ≥ of 0.9mg/dL over initial levels was observed in the patients' group who received fenofibrates.

Broeders et al. [3] described renal function returning to normal after fibrate discontinuation, however, the transplant patients' creatinine levels have been permanently elevated. The present study described a decline of serum creatinine levels after shifting to statins (Table 3, Figure 3a).

Meanwhile, **Forsblom et al.** [11] indicated that serum creatinine and other kidney function tests increased in response to fenofibrates administration and they suggested no extracardiac protection benefit from fenofibrates as the level of TG has been questioned as to being atherogenic or harmful to the cardiac myocytes.

In the present study, lipid profile throughout the follow-ups did not significantly change in the fibrates group but **Ikewaki et al.** [16]; stated that fenofibrate may be an especially appropriate therapy to reduce CVD risk in the setting of renal impairment because it raises apolipoprotein A1 and HDL cholesterol levels and influences HDL particle size.

LDL levels did not significantly change with fibrates in the FIELD study as cited by **Moutzouri et al.** [17] and this was also supported in our study with no change in LDL levels throughout our 6 months' trial period in the fibrate group. **Krittayaphong et al.** [18]

proved the efficacy of statins in reducing LDL in both of his groups of target LDL <70 or <100 respectively. LDL was significantly lower in our study more with statins than with fibrates, in all follow-ups; (89.7±11.0 vs. 118.5±11.6 at 6 months) which highlighted the cardioprotective effect of statins more than fibrates.

A cross-sectional study indicated that the use of statin monotherapy can reduce TG levels up to 40%, significantly supporting the preferred shift to statins rather than fibrates, that demonstrated a clear rise in KFTs despite a gentle decrease in TG [9].

Triglycerides were significantly higher in the statin group at month-6 only, inconsistently with **Giusseppe et al.** [19] who stated the ability of statins to reduce TG levels, this was not detected in our study perhaps attributed to the previous use of fibrates on our patients. The rise of TG in our statin group was not concomitant with any clinical impact although it showed a statistically significant increase (P=0.034).

In addition to the rapid improvement of renal profile on fenofibrate withdrawal (statin group), no genuine damage on CVS was reported by a slight elevation in serum TG during our six months' study. Also, none of the subjects in the present study complained of muscle aches or demonstrated an increase in CPK total above the reference interval denoting that impaired kidney functions are related to muscle damage induced by fibrates.

The deleterious effect of fibrates may be temporary whereas more studies are required to denote the long-term effect of fibrates compared to our short-term six-months study.

CONCLUSION

Routine use of fibrates is not advised in patients with borderline kidney function tests due to the deleterious effect on the renal profile and even if fibrates are employed, it is necessary to monitor patient renal functions regularly during fibrates treatment.
Additionally, the cardiovascular risk is negligible on omitting fibrates despite a mild to moderate increase of serum triglycerides.
Furthermore, it would be expedient to conduct a large-scale clinical trial to determine which patients are at the highest risk for fibrate-induced renal dysfunction, as well as determining the pathogenesis &reversibility of this effect, particularly after long-term fibrate administration which might consider a revision of the guidelines altogether for giving fibrates, given the detected renal risk.

ACKNOWLEDGMENTS

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