Improvement in Kidney Function after Discontinuation of Fenofibrate in Outpatient Nephrology Consultation for Chronic Kidney Disease

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Abstract

Background: It has been noted in observational and interventional studies that individuals exposed to fenofibrate can exhibit a rise in serum creatinine (sCr) concentration. However, it is not known to what extent this phenomenon impacts kidney function in patients who are referred to a nephrology clinic for consultation for chronic kidney disease (CKD). Methods: We conducted a prospective observational study of patients referred to our nephrology clinic for a new evaluation of a rise in sCr or worsening CKD and who were on fenofibrate therapy. We examined the effect of discontinuation of fenofibrate on kidney function, change in sCr, and estimated glomerular filtration (eGFR) at 3, 6, and 12 months. Results: A total of 22 patients (59% women, 86% White, 59% with type 2 diabetes, and 18% with peripheral arterial disease) were captured over 2.5 years. Median sCr at the time of fenofibrate discontinuation was 1.9 (1.1–3.3) mg/dL and eGFR, 32 (17–57) mL/min; proteinuria was absent in 17 (77%). Upon discontinuation of fenofibrate, median sCr decreased to 1.5 (0.9–2.4), 1.4 (1.0–2.5), and 1.4 (1.0–2.3) mg/dL at 3, 6, and 12 months, respectively (p < 0.05); whereas median eGFR increased to 44 (27–71), 45 (23–71), and 42 (21–71) mL/min, respectively (p < 0.05). A ≥30% rise in eGFR was observed in 59% of the patients at 3 months, and it persisted in 45% and 50% of patients at 6 and 12 months, respectively. Conclusion: Discontinuation of fenofibrate in patients referred for CKD evaluation can result in sustained reduction in sCr in about half of the patients and for up to 1 year. There is a need to raise awareness among primary practitioners about this phenomenon. Recognition of fenofibrate as a cause of rise in sCr could reduce unnecessary nephrology consultation and resource utilization.

Introduction

Patients with chronic kidney disease (CKD) are at risk of coronary artery disease, dyslipidemias, and sudden cardiac death [1]. Lipid-lowering therapies are appropriately justified in patients with CKD in an attempt to reduce atherosclerotic heart disease and coronary vascular events. Fenofibrate is an anti-lipidemic agent approved by the Food and Drug Administration (FDA), has been increasingly used
over the past 2 decades for the treatment of dyslipidemia [2, 3]. Fenofibrate activates proliferator-activated receptor alpha, causes alterations in lipid metabolism, reduces triglyceride levels by 20–50%, and increases high-density lipoprotein levels by 10–25% [4]. Given their wide range benefits, fenofibrate is commonly used by primary care physicians across the spectrum of CKD with and without statins for the treatment of hypertriglyceridemia [5, 6].

The phenomenon of increase in serum creatinine (sCr) associated with fenofibrate has been described in multiple prospective and retrospective studies [7–17]. Whether hypercreatininemia is secondary to alterations in creatinine metabolism or tubular handling or reflects a true impairment in kidney function remains a question of debate. Proposed factors associated with risk of so-called fenofibrate-associated nephrotoxicity include the presence of underlying CKD, male gender, age, long-standing history of diabetes mellitus, higher dose of fenofibrate, and concurrent administration of diuretics [18, 19].

A common reason for nephrology consultation in the outpatient setting is a rise in sCr concentration. Despite repeated studies showing a reversible increase in sCr and decrease in estimated glomerular filtration rate (eGFR) with the use of fenofibrate, there is lack of awareness of this phenomenon among primary care physicians. As a result, patients are often referred to a nephrology clinic for consultation when a rise in sCr is observed, following institution of oral therapy with fenofibrate due to the fact that those events (rise in sCr and fenofibrate exposure) are not recognized as being connected to each other. In this study, we sought to describe the trajectories of sCr and eGFR values over a period of 1 year following discontinuation of fenofibrate in an outpatient nephrology clinic. We hypothesized that discontinuation of fenofibrate will result in partial or complete resolution of the rise in sCr that had prompted the consultation to nephrology in majority of the cases.

### Methods

We conducted a prospective observational study at our outpatient nephrology clinic at the Ochsner Medical Center for a period of 2.5 years. The study was approved by an Institutional Review Board (IRB) and was conducted in accordance with the Declaration of Helsinki. The information collected was deidentified, and confidential management of the data in accordance with the requirements of the Health Insurance Portability and Accountability Act was maintained. We searched electronic medical records to collect data of adult patients receiving oral fenofibrate (5 patients were on 135 mg per day, 5 on 145 mg, 5 on 160 mg, 3 on increasing doses of 160–200 mg, 2 on 54–160 mg, 1 on 48 mg, and 1 on 67 mg) for 1–24 months who were referred for a new consultation due to: 1) ≥20% rise in sCr from a baseline value or 2) sCr ≥1.4 mg/dL for those without baseline value of sCr and underwent discontinuation.
of fenofibrate. We excluded patients with recent acute kidney injury, CKD stage 5, kidney transplantation, or concomitant use of trimethoprim-sulfamethoxazole. Out of 22 patients in the study, 20 were on ACEi/ARB (90%), 16/22 on statins (73%), 12/22 on calcium channel blocker (55%), and 5/22 on diuretics (23%). When no other potential cause for a recent rise in sCr or development of CKD was identified at time of consultation, fenofibrate was discontinued with the expectation that such intervention should restore kidney function back to baseline. Patients were subsequently followed with clinical and laboratory data obtained at 3, 6, and 12 months, respectively, during 1 year of follow-up. The primary outcome was change in sCr and eGFR (CKD-EPI formula) over time.

**Statistical Analysis**

Continuous variables were compared by the t-test. Categorical variables were compared by the Fischer χ² test. A p value <0.05 was considered statistically significant. All calculations were performed with GraphPad Prism 7 (San Diego, CA, USA).

**Results**

A total of 22 patients (59% women, 86% White, 59% type 2 diabetes, 18% peripheral arterial disease, 14% non-alcoholic steatohepatitis) were captured over 2.5 years and included in the study (Table 1). The median sCr and eGFR before the start of fenofibrate therapy were 1.3 (0.9–2.3) mg/dL and 48 (27–77) mL/min, respectively, and only 2 patients with CKD stage 4 (eGFR <30 mL/min). The median sCr at the time of fenofibrate discontinuation was 1.9 (1.1–3.3) mg/dL, and the median eGFR was 31.5 (17–57) mL/min. Proteinuria (urine protein-to-creatinine ratio >0.2 g/g or dipstick ≥1+) was absent in 17 (77%) patients. Upon cessation of fenofibrate, the median value of sCr decreased to 1.45 (0.9–2.4), 1.35 (1.0–2.5),
and 1.35 (1.0–2.3) mg/dL at 3, 6, and 12 months, respectively ($p = 0.009, 0.03$, and 0.004, respectively) (Fig. 1a, b); whereas median eGFR increased to 44 (27–71), 45 (23–71), and 41.5 (21–71) mL/min, $p = 0.005, 0.01$, 0.002, respectively (Fig. 1c, d). The median relative change in eGFR was +28.5% (0 to +83), +21.9% (–13 to +100), and +30.9% (0 to +145) at months 3, 6, and 12, respectively. A ≥30% rise in eGFR was observed in 59% of patients at 3 months, and it persisted in 45% and 50% of patients at 6 and 12 months, respectively.

At the start of the study, the distribution of patients by CKD stage (Fig. 2) was 36.4%, 50%, and 13.6% in stage 4, 3b, and 3a, respectively. By 6 months, CKD stage 4 had decreased to 22.7%, while CKD stage 3a increased to 45.5%. By 12 months, CKD stage 4 had further decreased to 13.6%, CKD stage 3b included 45.5%, CKD stage 3a comprised 22.7%, and CKD stage 2 accounted for 18.2% of patients. Thus, the proportion of patients who by 12 months were categorized into CKD stage 2 from a previously more advanced stage (3–4) increased significantly ($p = 0.038$).

For the subset of patients with no increase in eGFR ≥30% after discontinuation of fenofibrate, median starting sCr and eGFR were 1.6 mg/dL and 48 mL/min as compared to 1.3 mg/dL and 55 mL/min in patients who had improvement in renal function after fenofibrate discontinuation with nonsignificant “p” values of 0.64 and 0.6, respectively. The total duration of therapy ranged between 1 and 24 months. Additionally, our study population did not manifest significant proteinuria. The median urine protein-to-creatinine ratio in study population was 0.1 g/g and did not differ among patients who had improvement in eGFR as compared to those did not. The common concomitant pathologies included diabetes mellitus, hypertension, metabolic syndrome, and ischemic nephropathy, which did not differ among two groups.

Median triglyceride values at baseline and at 3, 6, and 12 months were 215, 263, 244, and 257 mg/dL, respectively. The triglyceride level increased by >2-fold in 5 patients during follow-up, whereas it remained within the same range in 17 patients (only 3 required gemfibrozil to control serum triglycerides). Three patients were restarted fenofibrate at the end of the study. In all 3 cases, it resulted in an increase in sCr values of similar magnitude compared to what was observed upon fenofibrate cessation.

**Discussion**

In our small cohort, we observed a consistent reduction in sCr concentration following discontinuation of fenofibrate. These changes were durable as evidenced by persistence of the changes in kidney function parameters up to 12 months after the initial discontinuation of fenofibrate. This observation aligns with previous reports describing common increases in sCr in patients treated with fenofibrate. Although this phenomenon is fairly well described in the medical literature, the practice pattern of referrals to a nephrology clinic when an increase in sCr is observed in association with exposure to fenofibrate denotes limited education on this topic among primary care providers.

Not surprisingly, our cohort included a majority with diagnosis of type 2 diabetes mellitus since dyslipidemia is a common comorbidity among individuals with diabetes mellitus and CKD. Interestingly, overt proteinuria was uncommon in our cohort. On the other hand, peripheral arterial disease and nonalcoholic steatohepatitis were among the most common comorbidities. Thus, we speculate that patients with chronic renovascular disease might be particularly vulnerable to exhibit a rise in sCr following exposure to fenofibrate.

Considering the benefits of fenofibrate and their usage across the spectrum of CKD, we need to emphasize that fenofibrate should be used with caution in patients with severe renal impairment, defined as eGFR <30 mL/min per 1.73 m², and the dose of fenofibrate should not exceed 100 mg standard or 67 mg micronized once daily among those with eGFR between 30 and 59 mL/min per 1.73 m². Furthermore, fenofibrate may be discontinued if during follow-up, the eGFR decreases persistently to <30 mL/min per 1.73 m². Notably, in our study, the subset of patient with CKD stage 4 was small at the beginning of the study.

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![Fig. 2. Changes in CKD stage following discontinuation of fenofibrate. Relative distribution of patients by CKD stage at the start of study (time zero) at 3, 6, and 12 months later.](image-url)
The exact mechanism of rise in sCr in patients secondary to fenofibrate therapy is not completely understood. Few studies suggest that a true impairment in kidney function is caused by fenofibrate due to decrease in renal blood flow which is ensued by a reduction in renal synthesis of vasodilatory prostaglandins via proliferator-activated receptor alpha activation [9, 13, 16, 20]. In addition, there are reports of biopsy-proven acute tubular injury in patients exposed to fenofibrate [21]. However, in a prospective study of fenofibrate use among patients with moderate CKD, renal blood flow (by para-aminohippurate) and GFR (by inulin clearance) did not change despite increase in sCr, indicating that rise in sCr could be from another cause, such as increased endogenous production of creatinine, and not from a true decline in kidney function [12, 22]. Unlike that study, another report described increase in serum cystatin C parallel to increases in sCr, thus supporting the contention for a true GFR reduction [23]. Alternatively, Ansquer et al. [7] proposed that decreased tubular secretion of creatinine could account for the elevated sCr levels. Altogether, it is hard to reconcile all existing data to be able to conclude what is the primary mechanism of fenofibrate-induced rise in sCr. Nevertheless, it is reassuring that the large randomized controlled trial Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) demonstrated that patients with CKD who received fenofibrate had a reduction in cardiovascular events compared to those who received placebo and without an increase in end-stage kidney disease events [24]. Therefore, while rise in sCr may be worrisome at first, it is not associated with impaired kidney outcomes. Furthermore, experimental data suggested various renoprotective effects of fenofibrates against several types of nephropathy for limiting proteinuria, which is an independent risk factor for both CV events and CKD [25, 26]. Importantly, there could be cases of true AKI due to fenofibrate, and caution is advised to monitor patients on fenofibrate and individualize decisions based on optimal risk:benefit ratio.

Plasma lipid levels were consistently followed in our cohort, and a 2-fold increase in triglyceride levels were observed only in 5 (23%) patients during follow-up, while none of the remaining patients had >2-fold increase in triglyceride levels after fenofibrate discontinuation. Thus, some patients with CKD with dyslipidemias may be managed with nonfenofibrate-based lipid-lowering therapies. However, if persistent hyperlipidemia demands the use of fenofibrate, a rise in sCr after fenofibrate initiation should be expected. Recognition of fenofibrate as a cause of rise in sCr could reduce nephrology consultations and appropriate resource utilization.

Our study has limitations. First, changes in sCr and eGFR were based on single measurements of sCr at each time point. It is known that an average of 3 measurements is likely to offer a more accurate estimate of kidney function. However, 1 measurement reflects routine clinical practice. Although the temporal association between the change in sCr and the discontinuation of fenofibrate coupled with preceding literature supporting the phenomenon strongly argues in favor of causality, we cannot definitively ascertain that the rise in sCr was definitely caused by fenofibrate or that the improvement in sCr was caused by its discontinuation. In the absence of a control group, we only report the association. In addition, kidney biopsies were not performed to assess for kidney parenchymal injury attributable to fenofibrate.

Conclusion

Our study suggests that discontinuation of fenofibrate in patients referred for CKD evaluation can result in sustained reduction in sCr. There is a need to raise awareness among primary practitioners about this phenomenon that prompts unneeded consultation to nephrology. Recognition of fenofibrate as a cause of rise in sCr could reduce premature nephrology consultations and resource utilization. Knowing that fenofibrate may offer cardiovascular protection in patients with CKD, without increasing the risk for end-stage kidney disease, we do not advocate for systematic discontinuation of fenofibrate in this patient population. However, temporary discontinuation could be considered in order to eliminate a confounding variable during evaluation of an unexplained rise in sCr or new-onset CKD.

Statement of Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki, with approval of Institutional Review Board of Ochsner Medical Center and with waiver of informed consent by Institutional Review Board of Ochsner Medical Center. No approval number is available. The study was approved in January 2018.

Conflict of Interest Statement

J.C.Q. Velez has participated in advisory board/consulting engagements with Mallinckrodt Pharmaceuticals, Bayer, and Trevere Therapeutics and has been a member of a Speaker Bureau for Otsuka Pharmaceuticals. Preliminary results of this study were
Fenofibrate Discontinuation in CKD

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Author Contributions

J.C.Q Velez: conceptualization, data curation, investigation, methodology, formal analysis, software, supervision, validation, and writing – review and editing. C. Hernandez-Arroyo: data curation, investigation, writing – original draft, and writing – review and editing. Swetha Kanduri: writing – original draft and writing – review and editing. R. Justinianno: data curation, investigation, and writing – review and editing. Pedro J. Martinez-Pitre: data curation and writing – response to reviewers. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual’s own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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