Fenofibrate-induced renal dysfunction, yes or no?

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In the treatment process of hypertriglyceridemia and diabetic nephropathy in type 2 diabetes, fenofibrate (FEN) is a well-known medication. FEN is from fibrate class drugs that using orally; however, as a side effect, it is associated with serum creatinine level increasing. The aim of this review was to determine the real effect of FEN therapy on renal functions based on both experimental and clinical studies. For this review, using the keywords of "fenofibrate" and "renal" and "function," a variety of sources of information banks, including PubMed, Google Scholar, and Scopus, were used, and the published articles were considered and interpreted. Followed by searching in databases, 45 articles were collected. After screening these articles, based on the study source, they were devided into two parts: 23 articles on animal experiments and 22 articles clinical experiments. Based on this information, it seems that the protective mechanism of FEN is related to vascular endothelial functions. The increased creatinine by FEN is related to different sensitivities to FEN effects caused by a polymorphism in different patients. In patients with normal renal function, follow-up of serum creatinine would be necessary after FEN, but the discontinuation of FEN is not recommended. In addition, in diabetic patients with hypertriglyceridemia, FEN treatment would be suggested for protecting the kidney from diabetes-induced renal injury.

Key words: Creatinine, fenofibrate, renal dysfunction

INTRODUCTION

Fenofibrate (FEN) is one of the well-known medications for the treatment of hypercholesterolemia in type 2 diabetes.[1] FEN, a synthetic derivate of fibric acid, is an activator of peroxisome proliferator-activated receptor-α (PPAR-α) and has potential therapeutic effects on hypertriglyceridemia and dyslipidemia.[2] Activation of this receptor leads to lipolysis and reduces the serum level of triglycerides by increasing the activity of lipoprotein lipase.[2] FEN decreases triglyceride and low-density lipoprotein levels and raises high-density lipoprotein (HDL) levels of about 5%–20%.[3] Furthermore, FEN has protective effects on cardiovascular functions in diabetic patients, so it used diabetes type 2 or metabolic syndrome patients.[4] Despite its positive effects on lowering blood lipid levels, rare side effects such as pancreatitis, raised serum creatinine (Cr) levels, and kidney injury were observed.[1] In addition, the controversial results have been reported regarding FEN and increasing serum Cr and renal function in clinical studies and animal experiments. The aim of this article is to review the literature published on the relationship between FEN administration and renal function in clinical and animal experiments.

METHODS

Here, in this study, we searched these three keywords "fenofibrate," "renal," and "function" in three databases: PubMed, Google Scholar, and Scopus. After screening the title and abstracts of published articles, we collected all data that were consistent with the purpose of this review.

Followed by searching in databases such as PubMed, Google Scholar, and Scopus with "fenofibrate" and

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"renal" and "function" keywords, we collected 45 articles related to FEN treatment and renal function. After screening these articles, based on the study source, they were divided into two parts: 23 articles on animal experiments and 22 articles clinical experiments. For experimental studies, the articles were divided into three sections of "high-fat diet (HFD) model and obese animals," "diabetic animal models," and "other conditions in animal studies," based on the animal model.

Fenofibrate in experimental studies

Fenofibrate and renal function in obesity in animal models

FEN has been used in the animal model to determine its positive effects and to obtain information related to its side effects. The 4-week effect of FEN on renal eicosanoid synthesis and endothelial function in obese male Zucker rats (OZRs) indicated that FEN decreased the plasma levels of insulin, triglyceride, and total cholesterol, and the protein expression of CYP2C11 and CYP2C23 was downregulated, and afferent arteriolar responses to of acetylcholine was increased.[5] The protective effects of FEN as a lipid-lowering agent on renal function in a model of HFD and hypertension rats reduced mean arterial pressure, renal vascular resistance, and sodium retention and increased renal blood flow (RBF).[6] The proposed mechanism was related to the drug-induced expression of CYP2C and CYP2J enzymes in the kidney cortex and medulla, which were followed by the increase of epoxidation of arachidonic acid and the production of epoxyeicosatrienoic acids (EETs).[6] In addition, it is reported that renal lipotoxicity, hypertension, and insulin resistance were associated with a reduction of expression and activity of PPARα, in HFD male adult rats model treated with FEN, and the protective effect of the drug on kidney was associated with reducing stress oxidative and lipoapoptosis in the renal cells via PPARa–FoxO3a– PGC-1a pathway.[7] The renoprotective effect of FEN on 5-week-old male mice with HFD also was investigated, and the results showed that 12-week treatment of FEN attenuated lipotoxicity induced glomerular and tubulointerstitial injuries.[8] Recently, Sohn *et al*. reported that 12 weeks HFD mice induced insulin resistance and kidney injury followed by posttreatment of FEN for 8 weeks activated renal AMP-activated protein kinase, upregulated fatty acid oxidation enzymes and antioxidants, and initiated autophagy.[9] Collectively, the protective effects of FEN in hemodynamics controlling and renal function parameters in obesity condition or HFD may be proposed by different mechanisms in different models of experimental animals. However, the animal models have limitations that may not exactly correspond to what our body really is.

Fenofibrate and renal function in diabetic animal models

Diabetes mellitus is a global dilemma that has a more complicated side effect in people's lives. The use of FEN to reduce the serum lipids is very important in such a situation. However, the fear of taking undesirable kidney effects has always been a concern. The 8-week treatment of FEN in diabetic male rats performed a protective effect on kidney functions and delay in the progression of diabetic nephropathy, and the FEN therapy decreased the expression and activity of plasminogen activator inhibitor-1 (PAI-1).[10] A model of 26-week-old male Zucker diabetic fatty rats was subjected to treat with 6 weeks of FEN, and although the systolic blood pressure was normalized, other indicators such as glomerular size were ameliorated.[11] FEN also was kidney protective in diabetic animals to prevent diabetic nephropathy, while it decreased the expression of renal cyclooxygenase-2 and reduced the prostaglandins releasing to protect the kidney against tissue damage.[12] Balakumar *et al*. demonstrated that FEN therapy increased the serum levels of nitric oxide (NO) metabolites (nitrite/nitrate) levels; decreased stress oxidative, serum Cr, and blood urea nitrogen (BUN) levels; reduced proteinuria; improved kidney function; and prevented nephropathy and vascular endothelial dysfunction in streptozotocin (STZ)-induced diabetics rats models.[13] It is suggested that the renoprotective mechanisms of FEN are related to prevent uric acid elevation and lipid profile improvement.[14] In addition, 4-week treatment of FEN after STZ administration prevented diabetic nephropathy in rats, while 8-week treatment of FEN after STZ administration did not have any nephroprotective effect, which reveals that low-dose FEN treatment does not have a protective effect on the progression of nephropathy.[15]

Usually, diabetic nephropathy is associated with renal lipid accumulation, and in such conditions in male db/db mice, the 8–12 weeks of FEN therapy prevents renal cell apoptosis, decreases lipid accumulation and oxidative stress, and improves renal lipotoxicity and hemoglobin A1c levels by activating PPARα, which protects the kidney against diabetic nephropathy.[16] The positive effects of FEN on insulin resistance, hyperglycemia, glomerular lesions, and albuminuria were also documented.[17] In the other researches, the protective effects of 12-week FEN therapy in diabetic male rats promote renal functions, and the therapy performs renoprotective effects against diabetic nephropathy.[17,18] The results of these studies have also shown that FEN decreased albuminuria, serum level of Cr, and urea and normalized kidney weight while it increased Cr clearance (ClCr) and ameliorated hypertrophy and kidney fibrosis.[18,19] Finally, Yaribeygi *et al*. reported that 8 weeks of FEN therapy has a renoprotective effect in diabetic male Wistar rats by improving ClCr and protein excretion and decreasing serum levels of BUN and Cr via decreasing expression of nicotinamide adenine dinucleotide phosphate oxidase type 4, interleukin-18 (IL-18), and protein p53.[20]

Fenofibrate and other conditions

It is reported that 2 weeks of FEN therapy (300 mg/kg/day) had not any direct nephrotoxic effect and did not cause glomerular filtration rate (GFR) or RBF reductions.[21] It is known that doxorubicin (DOX) induces kidney injury; however FEN pretreatment (7 days before DOX injection) efficiently decreased proteinuria and reduced podocyte foot process elimination.[22]

The methotrexate-induced nephrotoxicity in male rats was protected by 15 days of FEN therapy by reducing stress oxidative, renal cell apoptosis, serum Cr, and urea levels.[23] Similarly, the renoprotective effects of low doses of FEN alone or in combination with pioglitazone in cisplatin-induced nephrotoxicity animal model were observed via inflammatory marker reduction.[24] The FEN also performed an antioxidant effect on hypertensive rats with mild renal dysfunction, and it reduced hypertension-associated nephrotoxicity via the reduction of cellular inflammation and oxidative stress and the prevention of proteinuria, glomerulosclerosis, and tubular fibrosis.[25] The renal ischemia-reperfusion injury in male C57BL/6 mice also was protected by pretreatment of FEN, which reduced the serum levels of BUN and Cr and expression levels of tumor necrosis factor, IL-8, and IL-6.[26] Finally, the renal function biomarkers (decrease of albuminuria and increase in ClCr) were improved by 6 months of FEN therapy in age-related renal dysfunction of 8-month-old male animals while histological changes such as glomerulosclerosis and tubular interstitial fibrosis also were improved by ameliorated oxidative stress and mitochondrial dysfunction.[27]

Fenofibrate in clinical studies
Fenofibrate and renal function

The need to prescribe FEN, on the one hand, and its side effects, on the other hand, is a common concern in the clinic. Usually, the FEN side effects such as Cr increasing are always accompanied by a medical concern for a physician. Therefore, research on the side effects of FEN always has been of interest. Generally, the FEN-associated nephrotoxicity occurred in more than 50% of kidney-transplant patients; while some of them experienced permanent renal dysfunction, the adverse effect of FEN in nontransplantation patients is reversible with FEN discontinuation.[28] In addition, FEN treatment can raise the serum levels of Cr and urea, and it decreases GFR while no significant relationship between these renal changes and preexisting of renal dysfunction or kidney transplantation is existed.[28] It is mentioned that FEN increases the daily production of Cr, and therefore, renal function follow-up is not necessary because, in hyperlipidemic patients with normal renal function or mild-to-moderate renal failure, FEN therapy (200 mg/day or 200 mg/2 days) increased serum levels of Cr and the elevated Cr is not related to GFR or ClCr.[29] On the contrary, in normal subjects, a 6-week FEN therapy (160-mg/d) was accompanied by an increase of serum Cr level, decrease of ClCr, and no change of GFR.[30]

In a cohort study by Ying *et al.* in a set of population patients aged 66 years old or older with other chronic diseases, the FEN group was more possible to be hospitalized for an increase of serum Cr level compared with ezetimibe drug (a medication used high blood cholesterol and other lipid abnormalities treatment), and it seems that there was not any detectable effect of FEN on renal function, so the increase of serum Cr can be caused by increased Cr production or prostaglandin production disorder.[31] The incidence of nephrotoxicity also was studied in 428 male patients who were undertaken 6-month therapy with FEN, and it was observed that the serum levels of Cr increased >0.3 mg/dl and GFR decreased to 24 ml/min/1.73 m² in 25% of patients while 20% of them did not have any renal dysfunction or diabetes.[32] The result of this study demonstrated that the risk of nephrotoxicity increased when high dose of FEN or concomitant use of FEN with calcium channel blockers (CCBs) was used,[32] and interestingly, in 70% of patients, the serum levels of Cr returned back to normal value without discontinuing medication, and in 30% of patients, the serum levels of Cr have steadily increased, but it returned to a normal baseline value after discontinuation of FEN.[32] Similar results were reported and confirmed by others.[33,34] Some different case studies related to FEN administration and the side effect are summarized in Table 1. Finally, the FEN therapy improves triglyceride metabolism and uric acid level and increases serum level of HDL in patients with hypertriglyceridemia and/or hyperuricemia and suggested that improvement in hyperuricemia is associated with a reduction of albuminuria.[40]

Fenofibrate and renal dysfunction in diabetes

The administration of FEN in patients with type 2 diabetes and hyperlipidemia is abundant in the clinic; however, the clinisions are concerns about its side effects in the renal system.

In Ansquer *et al.*'s study, 314 patients (77 women and 237 men) with type 2 diabetes and mild-tomoderate hyperlipidemia but without renal dysfunction were subjected to FEN therapy, and it was reported that FEN can improve the progression of microalbuminuria and renal disease, and this renoprotective effect of FEN is independent of blood pressure, smoking, and baseline glycemic control.[41] In addition, at the first 3 months, FEN improved vascular endothelial function in patients with normal albuminuria, and the protective effect of FEN is related to the improvement of vascular function.[41] However, the side effects of FEN in a case of a 45-year-old female patient with

Table 1: Some cases of studies related to fenofibrate administration and its side effect

Patient information	FEN dose and duration of therapy	FEN therapy effect
Female patient without diabetes, hypothyroidism, or kidney dysfunction	250 mg/day for 1 month	Acute renal failure due to rhabdomyolysis[35]
Two patients with acute renal failure and severe rhabdomyolysis who were under cotreatment of statin and FEN	Case 1: 200 mg/day for 2 months Case 2: 200 mg/day for 1 month	↑BUN, ↑Cr muscle signs, hemoglobinuria, and oliguria[36]
12 mid-aged patients	267 mg/day for 3 months	↑Cr, ↑ cystatin C (as Cr independent marker for kidney function)[37]
Male patient with HIV infections, hypertension, chronic hepatitis C, and hyperlipidemia	160 mg/day for 6 weeks	↓GFR, ↑Cr (due to renal disease history or concomitant drugs) By discontinuation of FEN, the serum level of Cr gradually returned to normal baseline[38]
Male patient with FJHN	160 mg/day for 1 month	↑Cr, no muscle pain or changes in urinary properties and any sign of rhabdomyolysis. After 3 months of discontinuing the FEN, serum creatinine decreased to baseline levels[34]
Female patient with diabetes type 2, hypertension, and hypertriglyceridemia	200 mg/day for 3 weeks	Muscle pain, chronic fatigue, rhabdomyolysis, acute renal failure, urine flow decreasing, and dark brown urine colour[39]

FEN=Fenofibrate; FJHN=Familial juvenile hyperuricemic nephropathy; GFR=Glomerular filtration rate; BUN=Blood urea nitrogen, ↑: Increase, ↓: Ddecrease

diabetes type 2, hypertension, and hypertriglyceridemia included muscle pain, chronic fatigue, rhabdomyolysis, acute renal failure, decreased urine flow, and dark brown urine color.[39] The research in the large sample size patients also was verified the renoprotective effect of FEN. A study on 9795 patients with diabetes type 2 aged 50–75-year-olds revealed that FEN therapy increased serum Cr level in the 1st week, but this elevation was reversible without any renal injury, and long-term FEN therapy reduced albuminuria progression and renal dysfunction.[42] Further, the long-term FEN therapy (taking 200 mg FEN daily for 5 years) in 4895 type 2 diabetes patients with moderate renal impairment demonstrated that FEN could reduce cardiovascular disorder (hazard ratio 0.89 in comparison with placebo) while GFR and end-stage renal disease were not different between FEN and placebo group, and FEN had not any side effect in the patient with moderate renal impairment.[43]

Other study demonstrated that the serum level of Cr in 48% of FEN-treated diabetic patients raised >20%. Most of these patients were male and old, with cardiovascular disease, and they used angiotensin-converting enzymes 1 (ACEI) or diuretics accompanied by FEN.[44] Mostly, FEN therapy is associated with Cr and HDL levels increasing, and triglyceride level and blood pressure decreasing. Hence, it can be concluded that these patients are more sensitive to FEN, and this sensitivity is probably associated with PPAR-α genes polymorphism in different people. On the other hand, there is no significant relationship between serum Cr elevation and renal and cardiovascular disease. In addition, there is no long-time adverse effect associated with FEN-associated Cr elevation. Hence, this study suggested that FEN effects act through the same pathway as ACEIs, and although it increases serum Cr level, it has a renoprotective effect.[45]

The effect of FEN also was considered in 170 patients with diabetes type 2 , and FEN therapy decreases CrCl and estimated GFR (eGFR), decreases blood pressure, and increases cysteine C level, but no effect was observed on albumin excretion rate and progression of albuminuria.[44] Accordingly, it is suggested that FEN inhibits renal Cr excretion and increases the release of Cr from muscles. Therefore, serum Cr levels would be increased, and FEN has no renoprotective effects on diabetes type 2 patients.[44]

Finally, the reversibility of FEN-induced kidney dysfunction in 321 diabetic patients indicated that after 3 months of FEN therapy, the serum Cr and cystatin C levels increased, and GFR decreased. However 6–8 weeks (51 days off-drug) after discontinuation of FEN, the above parameters returned to the baseline.[46]

DISCUSSION

FEN is a common medicine drug for the treatment of hypertriglyceridemia and hyperlipidemia. However, as a side effect, it is associated with serum Cr level increasing, but the relationship between increased serum Cr and renal function in clinical and experimental articles is not well clear.

On the basis of experimental studies, FEN therapy not only does not have any adverse effect on the renal function, but also it has renoprotective effects in different conditions such as obesity and hyperlipidemia, hypertension, diabetes, drug-induced nephrotoxicity, and aging.[6,7,13,18,23,25,27] There are many suggestions for the protective mechanisms of FEN, but the most likely mechanisms are as follows. First, the inhibition of inflammatory pathways by reducing the release of prostaglandin,[12] increasing the release of

endothelial NO,[18] inducing the expression of CYP2C and CYP2J enzymes[6] in the cortex and medulla, elevating the production of epoxyeicosatrienoic acids (EETs), and decreasing CYP2C11 and CYP2C23 as inflammatory enzymes.[6] Previous studies demonstrated that EETs keep the sodium balance and vasodilation in the kidney.[47] Second, based on previous studies, the activation of PPAR-α renal receptors decrease oxidative stress levels, so FEN as an agonist of these receptors has renoprotective effects.[7,16,23,24] Hou *et al.* reported that FEN as a PPAR-α agonist has antioxidant effects in hypertensive rats and decreases oxidative stress levels via the inhibition of mitogen-activated protein kinases.[25] In addition, two other protective mechanisms are proposed on diabetic models as follows. First, decreasing the expression and activity of PAI-1,[10] and second, decreasing the expression of transforming growth factor-β1.[19] It is reported that both factors are useful in tissue injury and hypertrophy.[48,49] The notable point in diabetic model studies is that all of them continue the hyperglycemic condition for more than 7 weeks due to the fact that the protocol revealed the renal injury associated with diabetes. Therefore, 1-week hyperglycemia protocols may not suggest for the evaluation of FEN effects on renal function.

On the basis of the clinical studies, it seems that FEN-associated Cr elevation is not a long-term adverse effect, and it is reversible. In addition, the results revealed that there is no significant relationship between serum Cr increasing and renal dysfunction;[30,45] however, renal injury is likely due to patients' histories, such as previous renal disease, kidney transplantation, and renal injury associated with diabetes; high dose of FEN; and concomitant medicines such as ACEIs, CCBs, and diuretics. Different results also have been achieved in different studies. One of these studies showed that cysteine C levels increased with serum Cr levels and renal function affected by FEN therapy, but it is reversible, so they suggested that the hypothesis based on increasing the production of Cr in muscle tissues would be rejected. Nonetheless, there is no more evidence for this claim.[37] As the results in two case studies on female patients with or without diabetes type 2 indicated that acute renal failure and rhabdomyolysis caused by FEN treatment, and since all animal experiments have been studied on male gender, we proposed that the notable point is the effects of gender on the serum Cr elevation because countable results for female are not available. On the other hand, in diabetic patients, it can be concluded that FEN therapy has renoprotective effects and prevents the progression of microalbuminuria. The suggested protective mechanism is that FEN improves vascular endothelial functions[41] The increase of level by FEN is related to different sensitivities to FEN effects caused by a polymorphism in different patients..[45] Furthermore, many studies suggested that the

serum Cr elevated levels are associated with increasing the production of Cr from muscles.[29,44]

CONCLUSION

If patients had a history of renal dysfunction, or if rhabdomyolysis symptoms appeared with raise of serum Cr level, discontinuation of FEN will be suggested. However, in patients with normal renal function, follow-up of serum Cr would be necessary, but discontinuation of FEN does not recommend. Furthermore, we suggest that further studies and follow-up are needed in female patients. In addition, in diabetic patients with hypertriglyceridemia, FEN treatment would be suggested for protecting the kidney from diabetes-induced renal injury.

Conflicts of interest
There are no conflicts of interest.

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