Fenofibrate Induced Renal Toxicity and Paradoxical Low HDLC- A Boon or Bane? : A Review

ABSTRACT

Fenofibrate is the most common drug prescribed to treat atherogenic dyslipidaemia. The nephrotoxicity of fenofibrate, as characterised by the increased Serum Creatinine (SCr) and reduced estimated glomerular filtration rate (eGFR), though reported in literature, it's clinical awareness, and it's implications, seem to be low. Also reported is the paradoxical Low level of High-density lipoprotein cholesterol (HDLC) during fenofibrate therapy, as against the the expected rise, as an isolated event and, in conjunction with the raised SCr. Perhaps such association occurred, in a small subset of cases of fenofibrate induced nephrotoxicity or it may be due to lack of awareness about the association or the association being overlooked, might be the reasons for the paucity of reporting the same, in the literature. The The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, and the Action to Control Cardiovascular Risk in Diabetes (ACCORD Lipid Study), it is confirmed that, the SCr levels decreased, eGFR improved and HDLC levels are raised on cessation of the the fenofibrate therapy. The cause and effect is, thus proved. The CKD, triglyceredemia and the low HDLC. each of the three, are know individual risk factors for cardiovascular disease (CVD). It would be the concern of any body, treating atherogenic dislipidema, as to whether to expose the patient to the risks of possible renal damage and the risks of low HDLC, in treating hypertriglyceridemia ,with fenofibrate. It is imperative that these concerns, if any, be resolved. Awareness of fenofibrate causing the raised Scr and reduced eGFR, is essential for avoiding wrong diagnosis and treatment of an iotrogenic cause. Apart from the dark side of phenofibrate therapy, umpteen number of benefits of fenofibrate therapy are reported. Intriguingly, the greatest benefits are seen in those who experienced the severe adverse effects mentioned above. Hence is the justification for the dilemma expressed in the tittle. A brief review of all the issues concerned, including the present status of the fenofibrate therapy, is being reviewed in this article.

Keywords: Creatinine; fenofibrate; nephrotoxicity; triglycerides; estimated glomerular filtration rate; HDL cholesterol .

1. INTRODUCTION

Fenofibrate is a drug used to treat hypertriglyceridemia and atherogenic dyslipidaemia [1]. it reduces serum TG levels and increases serum HDL cholesterol levels [2,3].These effects are even quantified, fenofibrate elevates HDL cholesterol by 10%–25% and reduces TGs by 20%–50%, [4,5]. Fenofibrate and other fibrates have long been known to elevate SCr levels [6-10]. FIELD [11]. and ACCORD Lipid, [12]. trials have shown an early, sustained rise in SCr with fenofibrate in patients with Type 2 diabetes. The controlled Clinical trials by N Boeders C Knoop, M Antoine et al. [13].; J Lipscombe, GF Lewis, D Cattran et al. [14]. JL Ritter, S Nabulsi and S Paul, [15]. Paul Sand Mohan [16]. CR McQuade, J Griego, J Anderson et al. [17].; confirmed the fenofibrate induced rise in SCr and reduced eGFR. Attridge RL, Linn WD, L Ryan et al. Evaluated the incidence and risk factors for development of fenofibrate-associated nephrotoxicity [18]. C Hottelart, F Rose et al suggested that, Fenofibrate increases creatininemia by increasing metabolic production of creatinine [19]., and also confirmed the raise in SCr and reduced eGFR following fenofibrate therapy . Most of the above trials had pts who had some CVS morbidity or varying degrees of renal insufficiency. In 2004, Angeles and colleagues published a case series of three renal transplant recipients who developed fenofibrate-associated nephrotoxicity. Ansquer JC, Dalton RN, Causse E et al.(2008), in a 6-week randomized crossover trial in healthy people, noted increased creatinine level also, in those with normal renal function, taking fenofibrate [20].The trial by S Kim, K Ko , S Park , DR Lee(2017), was conducted on healthy volunteers in the primary health care setup. It was shown that the fibrates induce increase in SCr and reduced eGFR [21]. In a

prospective study by Hottalerr and colleagues, raised SCr and lowered eGFR were observed but no change in amino-hippurate sodium, inulin, and urine creatinine concentrations. In the above studies a raise of SCr of 0.2 /0.3 mg /dl over the base line reading is taken as significant.The renal toxicity appeared from few weeks to few months of starting fenofibrate.

2. DISCUSSION

Bonds et al. [22]. characterised the profile of the patients with fenofibrate-associated increase in S.creatinine.They were more likely to be;

- Older persons.
- Male sex.
- Long standing diabetics.
- Baseline history of cardiovascular disease (CVD),
- Higher serum TG levels.
- higher systolic blood pressure.
- Lower baseline levels of SCr and LDL cholesterol.

The patients with the above profile are the Patients who showed more responsive to fenofibrate treatment.

The discussion is centred on the plus side and dark side of fenofibrate therapy.

2.1 The Dark Side of Fibrates

2.1.1 Increased SCr and decreased eGFR

That the fenofibrate treatment increases the S.Cr levels and reduces the eGFR is is an established fact now supported by the number of studies and trials referred to in the introduction. The questions of concern are, whether these findings increase the risk of CVD ? Do the changes worsen the kidney function in the long run ? Investigations into these issues, ruleout any long term renal or CVD risks. Surprisingly , beneficial effects on long term use of phenofibrate, offering renoprotection and cardio protection was noted.

- The fenofibrate doesn't cause structural damage is supported by the following facts.
- The reversibility of fenofibrate induced SCr and paradoxical low HDLC
- After cessation of fenofibrate therapy ,the reversal of the above findings has been confirmed the FFIELD study and. ACCORD Study and also by all the studies and trials cited above, including the case reported by the author. In almost all cases the return to pre-treatment levels of SCr and eGFR had been noted.
- The inulin clearance test, the gold standard for renal function was normal precludes any structural renal damage [23,24].
- Para amino hippuric acid (PAH) clearance test, which measures the renal plasma flow it was also reported normal [25].
- The urine analysis iwas found to be normal
- There was no deterioration of albuminuria. DIAS study [26,27].
- There was no added risk of progression to ESRD [28,29].

The raised SCr, normally is taken as a measurable marker of the underlying renal disease, in clinical practice. But in case of fenofibrate, other than kidney destruction, appear to be operating. The possible mechanisms of the same are summarized below. Since there is no structural damage to kidney, even on prolonged treatment with fenofibrate, it is questionable to call this adverse effect, as "nephrotoxicity "and should be labelled as a reversible side effect of fenofibrate.

This increase in SCr associated with fenofibrate has been of uncertain significance [30,31]. Still, in CKD, appropriate dose reduction is advised and complete stoppage when GFR falls below 30 ml /mt/ 1.73 M2.

2.1.2 Mechanisms suggested for decreased eGFR

- Hemodynamic changes, consequent to the inhibition of generation of vasodilatory prostaglandins , leading to reduced intra- glomerular filtration pressure (GFR) and consequent low GFR [32,33].
- Competitive inhibition of the proximal tubular secretion of creatinine by a metabolite of fenofibrate [34,35]. Increase in urinary creatinine, is a fact against this hypothesis.
- Increased endogenous production of creatinine [36].
- There may be cross-reactivity be-.tween fenofibrate or its metabolites and the assay used to measure creatinine [37].
- Being an agonist of PPAR Alfa, it may inhibit the expression of the enzyme concerned potassium- chloride transporter protein [38].
- In FIELD study, plasma creatine phosphokinase rose 2.4% in those on fenofibrate versus 0.5% in those on

placebo (p = 0.06 for difference suggesting ncreased turnover of muscle creatine due to finofibrate.

- Decreased renal plasma was suggested, but the normal PAH clearance precludes this possibility **.**

2.2 The Paradoxical Low HDLC during Fenofibrate Therapy

G Magee, PC Sharpe reported paradoxical decrease in HDLC with fenofibrate in 50%of 96 pts in the study conducted by them [39]. Peter E. Linz, C Laura Lovato et al (2014), found paradoxical decrease in HDLC with fenofibrate therapy [40]. CV Venero, PDThompson, Fernandez AB reported Reduced HDLC.

In patients receiving rosiglitazone and fenofibrate [41]. Fenofibrate induced low HDLC was reported by Giuliana Mombelli,Franco Pazzucconi, Alighiero Bondioli Anna Maria Zanaboni,Sabrina Gaito, Laura Calabresi, R Cesare. Sirtori et al considered the phenomena, a rarity [42]. Iatrogenic severe epression of High-Density Lipoprotein Cholesterol by fenofibrate was reported by D.Mymin, HH Dembinski, et al, MH Friesen. et al. [43]. They even advised to consider fenofibrate when very low levels of HDLC are encountered. Among ACCORD Lipid Trial participants, the occurrence of extremely low HDL-C ever during study follow-up was 106% higher among those randomized to fenofibrate (10.1% fenofibrate vs. 4.9% placebo, P< 0.001).

Though fenofibrate is known to increase the low levels of HDLC, In what percentage of cases this is observed, is not clear nor why fenofibrate does not improve the low HDLC levels/ or even decreases paradoxically, the HDLC, in at least a subset of cases, treated with fenofibrate.The mechanism underlining the paradoxical low HDLC is not clear, though though several possible mechanisms are suggested for low JDLC other than the fenofibrate induced nephhrotoxicity. and whether the renal effects and lipid effect stem from a single mechanism, if not how their interlinking could be explained, is still not very clear. This author explained the mechanism of inverse relationship between SCr and HDLC in the background of CKD and DM2, in a previously published article [78]. The crucial step is found to be the failure of hydrolysis of CP in the Sl MtC of the myocyte by the CK enzyme. Sedentary lifestyle was the invoked as being responsible for the failure of hydrolysis of CrP, into creatine and ATP , supplying immediate energy, needed for Intermittent moderate muscular exercise. The same hypothesis holds good here also except that possible inhibition of the CK in sl Mtc takes the place of sedentary lifestyle invoked easier, to explain the failure of CPK enzyme mediated reaction in the sl MtC. The proposed hypothesis is brief towards the end of the article briefly and for details readers may refer to the previous article by the author referred to above.

2.3 The Plus Side of Fenofibrate Treatment

2.3.1 Slowing of atherogenesis

The combination of high triglycerides and low HDLC, known as atherogenic dyslipidaemia, is characteristic of DM 2.The TG- rich, very low density lipoprotein (VLDL) particle's accumulation in the kidney, is a risk factor of diabetic renal injury [43]. Patients with elevated TGs and low high-density lipoprotein are at particularly high risk of CVD [44]. Fenofibrate is effective in lowering the elevated concentrations of TG-rich lipoproteins ie.VLDL and VLDL remnants and low levels of HDL cholesterol [45]. This is achieved by decreasing apo C-III levels and increasing the apoC-II: apoC-III ratio.This promotes enhanced lipoprotein lipase-mediated catabolism ofTG-rich VLD [46]. The clearance of VLDL, by the LDL receptor, is mediated by apo B, apo C-III, by inhibiting apoB ,decreases the duration of stay of VLDL, in the blood [47]. Fenofibrate decreases small dense LDL particles in favor of large, more buoyant LDL particles, which are less susceptible to oxidation and less 'atherogenic' [48,49].

2.3.2 Cardiac protection

Fenofibrate therapy in those with pre-existing moderately impaired eGFR, produced the greatest estimated absolute reduction in CVD risk, despite the greatest early plasma creatinine rise [50]. There was no loss of CVD benefit among those with the greatest creatinine rise compared with others. In fact, the greatest absolute CVD benefit was seen in this group (p-value for interaction = 0.5) [51]. PPAR-α stimulation may contribute to the reduction in atherosclerosis progression and lessening of cardiovascular events [52].

The primary outcome was coronary events, which fenofibrate did not significantly reduce (hazard ratio, PPAR-α stimulation may contribute

to the reduction in atherosclerosis progression and lessening of cardiovascular events [53].

in one of the trials, patients with the greatest fenofibrate-associated creatinine rise appeared to derive the greatest cardiovascular benefi [54].

eGFR and microalbuminuria are independent risk factors for CVD, and fenofibrate by preserving eGFR and delaying microalbiminuria may reduce the CVS risk [55].

2.3.3 Anti-thrombotic effects of fenofibrate

- Fenofibrate decreases plasma levels of Lp(a) by 7% to 23% [56,57]. a risk factor for atherosclerosis and related diseases, such as coronary heart disease and stroke.
- Reduces fibrinogen, [58]. and reduces tendency to thrombosis .
- Decreases tissue factor (TF) expression in human monocytes and macrophages [59,60].
- upregulates the expression of thrombomodulin (an anticoagulant protein) as shown from studies using carotid atheroma biopsies [61].
- Decreases the High levels of plasminogen activator inhibitor-1 (PAI-1), an inhibitor of plasma fibrinolytic activity [62,63].

2.3.4 The mechanism of cardio vascular protection due to fibrates

- Reduction of vascular inflammation [64,65].
- Decreased recruitment of blood cells into blood vessel walls that initiates arterial plaque formation [66].
- Inhibition of activation of VSC [67].
- Lowering of CRP [68,69].
- In addition, the anti-thrombotic effects of fenofibrate (described bow)also contribute.

2.3.5 Reno protective effects

Reno protective effects could be related to direct actions that reduce renal fat accumulation, lipotoxicity, renal inflammation and oxidative stress .This reno protective effects could be related to direct actions that reduce renal fat accumulation, lipotoxicity, renal inflammation and oxidative stress [70].

2.3.6 Effect on albuminuria

- effective treatment of hypertriglyceridemia could slow the progression of urinary albumin excretion [71].
- The DIAS trial found that fenofibrate significantly reduced the progression of albuminuria, particularly from normal albumin excretion to mmicroalbuminuria [72].
- The FIELD study found that,Overall, 2.6% more patients on fenofibrate than placebo group regressed or did not progres**s (**p < 0.001).
- The ACCORD Lipid Study showed, Fenofibrate reduced the development of both micro albuminuria (fenofibrate: 38.2 vs placebo: 41.6%; p = 0.01) and macro albuminuria.
- fenofibrate use in a mouse model of type 2 diabetes was linked with reduction in albuminuria, as well as histopathological improvements, e.g. reduced glomerular hypertrophy and reduced mesangial expansion [73].

2.3.7 Preservation of GFR

- Preservation of GFR that is revealed only when fenofibrate is withdrawn. Therefore, the increase in creatinine is definitely reversible and appears to be a separate process from the underlying renal preservation, which is 'masked' during active treatment.
- In ACCORD Lipid trial , patients who experienced little or no rise in SCr immediately after initiating therapy were more likely to derive eGFR preservation from long-term fenofibrate therapy, while those with a ≥20% initial creatinine rise had long-term effects similar to placebo.
- n FIELD, when patients with a ≥12% initial creatinine rise were compared with those with a <12% rise, despite those with the smaller rise having an independently significantand greater preservation of eGFR .

2.3.8 Hypertensive nephrosclerosis

Fenofibrate is reported to be useful in hypertensive nephrosclerosis by virtue of it's anti inflammatory and antioxidant properties [74].

2.3.9 End-stage renal disease

- In FIELD study, there was no significant difference between groups in the number of patients that needed dialysis at any time after randomization, with numerically fewer events among those receiving active treatment (21 vs 16 in the placebo and fenofibrate groups, respectively).
- A similar pattern was seen in the ACCORD Lipid trial, with no difference in

development of the end-stage renal disease (placebo: 77 patients; fenofibrate: 75 patients).

- Both FIELD, and ACCORD Studies, confirmed the reversibility of the nephrotoxicity due fenofibrate, indicating that there is no structural damage in the kidneys, in the long run, both in those with normal kidney function and also in those with. mild to moderate renal pathology. However, the use of phenofibrate is contraindicated in persons with eGFR less than 30 ml/ mt/ 1 73 sq meters of BSA.

2.3.10 Retinopathy

- Fenofibrate is known to increase the levels of circulating Apo lipoprotein A-I, which has recently been shown to be an independent protective factor for diabetic retinopathy development. Fenofibrate may also be important in regulating intra-retinal lipid metabolism and reducing lipid deposition and lipotoxicity.
- Two large randomized clinical trials, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) studies, demonstrated the benefit of oral fenofibrate in the treatment of patients with type 2 diabetes and diabetic retinopathy (DR), including reduced disease progression and need for laser treatment for diabetic macular oedema and proliferative diabetic retinopathy [75].
- It has been found to reduce the need for laser photocoagulation therapy in patient with diabetic retinopathy and to reduce the risk of microvascular amputations [76,77].

2.3.11 Gout

- Fenofibrate Lowers the levels of serum uric acid, facilitate an increase in uric acid excretion to the point where it might have therapeutic effects on gout [78].
- This increased urinary excretion of uric acid seems most likely through the inhibition of urate transporter 1 by fenofibric acid, a fenofibrate metabolite [79].

2.4 The Mechanism of Phenofibrate Induced Nephrotoxicity and Paradoxical Low HDLC

Author's hypothesis

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Preferably, a single mechanism should explain the above twin observations. There is no such mechanism suggested to explain both these observationsoccuring together. . In fulfilment of this, the present hypothesis is proposed. Of all the mechanisms for increased SCr considered above, the increased endogenous production of SCr, is supported by the author. This proposed hypothesis is an extension of the previously published hypothesis of this author, linking the inverse relationship between the raised s cr and low HDLC in the backdrop of DM2 and CKD [80].

The hypothesis is dealt with in 2 steps , which are interconnected.

1. Molecular Mechanism of increased SCr due to fenofibrate
2. Molecular Mechanism of HDLC, coupled to above.

1. Molecular mechanism of fenofibrate induced increase in SCr.

- Crucial to the hypothesis to be proposed, is the enzyme, Creatin phospho Kinase, (CPK) which catalyses a reversible reaction, (equations 1 & 2) as shown below

Creatine + ATP ---------- CRP (1) (Forward reaction) enzymatic synthesis of Cr

CrP ---------- Cr + ATP (2) (Backward reaction) enzymatic hydrolysis of CrP

- In the forward direction Creatine Phosphate (CrP) is synthesized from Cr in the Ubiquitous mitochondria (uMtc). In the reverse direction, the CrP synthesized by the uMtc, and transported into the M line Sarcolemmal mitochondria (sl Mtc), it is hydrolysed, to creatine and ATP.
- This hydrolysis of CrP has 2 important effects. The ATP released. is used as a 'immediately replenishable, 'buffer energy', need for muscular contraction as in exercise Secondly , the creatine released is transported into the uMtc, by a process called 'Creatine Shuttle' for resynthesis of CrP.
- The creatine is initially synthesized in the liver and other tissues, by the sequential action of the 2 enzymes- the Adenine guanosine aminotransferase (AGAT) and Guanine alanine methyl transferase (GAMT,), and is transported into the uMtc, by creatine transporter (CrT) . From the Creatine is synthesized CrP by the CPK enzyme. Creatine in the UMtc,

Subsequently is replenished by the " creatine shuttle" (Vide above).

- The step, catalysed by AGAT, is the rate limiting step. Also, this enzyme as well as the creatine transporter, are under the feedback inhibition by the creatine level present in the UMtc. Since the creatine shuttle intermittently supplies the creatine to uMtc, The enzymatic synthesis is suspended by the feedback inhibition but restarts if, in case the creatine shuttle stops, due to failure of CPK to hydrolyse CrP, in the sl Mtc. This is the crucial step for the present hypothesis.
- Now it is to be shown, how the inhibition of hydrolysis of CPK, results in increased endogenous synthesis of creatinine, resulting in increased SCr levels
- Suppose, the hydrolysis of CrP by CPK is prevented, (the probable causes of which are discussed , vide infra), the Creatine shuttle stops, and the UMtC doesn't get it's quota of the substrate, the creatine, for the resynthesis of CrP. The feedback inhibition on the AGAT and CrT is lifted (due to absent Cr in the UMtc), and the enzymatic synthesis of creatine starts once again. The CrP, transported into the sl MtC, since, it is no longer hydrolysed, by the inhibited CPK, the creatine shuttle stops continuously. The CrP synthesized by phosphorylating the enzymatically synthesized Creatine , is transported into sl MtC , but the same is not hydrolysed into creatine and ATP as CPK in the the sl Mtc is non functional.
- The CrP, being a high energy molecule, is unstable and spontaneously decomposes when it's concentration increase beyond a critical leveling, into the more thermodynamically, stable product ,the creatine, along with the release of free energy. (Equation 3)
- 3). CrP ---------- Cr. + [Free Energy] ....(3) Spontaneous decomposition of CrP. The spontaneous decomposition of the CrP, is normally kept in check by the normal CrP : Cr ratio of 60:40 , which is disturbed as seen above .
- The difference between the enzymatic decomposition of CrP by CPK and the spontaneous non- enzymatic decomposition, is that, the former releases the ATP to support muscle contractions and also makes available the creatine to be transported to UMtc for re- synthesis of CrP, by Creatin Shuttle, but not in the case of the spontaneous decomposition of CrP. The creatine released in the cytosol of the myocyte, by the spontaneous decomposition of the CrP, is not available for creatine shuttle, due to it's Compartmentation and the Free Energy doesn't support muscle contraction.
- The Second Law of Thermodynamics states that, for a chemical reaction to be spontaneous, there must be an increase in entropy. It is known fact that, if the free energy of he reactants is greater than that of the products, the entropy will increase (equation 4).

$$\Delta G = \Delta H - T\Delta S, \quad (4)$$

(ΔG = Gibb's Free energy, ΔH = Change in enthalpy ΔS = Change in enthalpy)

- while the spontaneity of the reaction is decided by the high entropy of the CrP, the direction of the reaction is decided by the Gibbs Free energy (ΔG), (equation 4) which is negative(- 43 .1 KJ/ mol) for the CrP , and hence the reaction proceeds to right (resulting in the formation of the products mentioned above, but in the reverse direction i.e.formation of CrP, from the products does not occur.
- The creatine so formed, is compartmentalized in cytosol with no communication with other compartments i.e. MtC and blood, as already stated.
- The increase in the cytosolic creatine, disturbs the equilibrium between the CrP and Cr in the cell, (the normal ratio being 60:40) , which regulates the production of Cr.
- The excess creatine, so formed diffuses out, of the cell, into the blood, to bring back the disturbed equilibrium between the CrP and Cr, in the cell.
- As the creatine enters the blood, it is metabolized into Creatinine, a metabolic waste product of creatine. This explains, how the creatine level of blood is.increased, as seen under conditions when rP hydrolysis and consequently the Creatine Shuttle is stoped. What possibly causes under physiological conditions and due to iatrogenic causes ,as een below.

2.5 The Cause of Failure of Hydrolysis of CrP

1. Under normal physiological conditions

The author, in the previous article, Sedentary life style(as defined as any waking behaviour

characterised by an energy expenditure ≤1.5 metabolic equivalents, such as television viewing time with little scope for Intermittent moderate excercise, is assigned the cause of non hydrolysis of CrP, as the buffer energy is called into action only during exercise. This is supported by the fact that exercise decreases the raised Cr.

2. The iatrogenic cause as in case of fenofibrate .

In this case it is hypothesized that fenofibrate by it known effect of myofibril damage, causes the disruption of the M line sl mitochondria in which the CPK enzyme is located , as supported by a small increase in the blood CPK enzyme levels , during fenofibrate therapy .The disruption of CPK fails to hydrolyse the CP into Cr and ATP which leads to the subsequent steps that leads to increased SCr levels .

3. Molecular mechanism of the Fenofibrate induced Low HDLC coupled to Increased S. creatinine:

Though several causes are described for the occurrence of the low HDLC (as reviewed in the previous article by this author) .The cause in case of iatrogenic induced low HDL due to fenofibrate , as coupled to increased Scr, is not being explained in the literature . Glaysher J, Van Heyningen C et al reported low HDLCunder combined treatment of statin with fenofibrate and suggested that PPAR alfa stimulation, through XLR receptor [81]. C Foucher, L. Brugere, JC Ansquer, tried to correlate the elevation of Homocysteine, which is also elevated along with SCr by fenofibrate, but could not find a common mechanism vis a vis kidney function [82]. The hypothesis proposed above, by the author could be extended to explain the low HDLC coupled to the increased SCr, by invoking competition for ATP between the CPK and active transporters that oversee the efflux of the excess, unutilised cholesterol by the cell, into the HDL, in the first step of reverse cholesterol transport (RCT).

Under normal physiological conditions, the competition between ABC1 / AGC 1 transporters that effect the influx of the cholesterol that is in excess to the cell's needs, into the HDL and the CPK enzyme, is Intermittent, occurring only during the synthesis of CrP, being ATP dependent, (endothermic reaction), but not during the hydrolysis of CrP, (an exothermic reaction). Hence, the competition for ATP, between both the processes occurs Intermittently in the time interval between the two cycles of make and break of the CrP, during which the transporters of cholesterol efflux, utilise the ATP [83,84]. But under the condition, where the CPK is inhibited / disrupted, (presumably due to an iatrogenic cause, like fenofibrate) and hydrolysis of the CrP is prevented, it results in suspending of the creatine reshuttle, and consequently, the enzymatic synthesis of of creatine and its subsequent phosphorylation, by CPK occurs in the uMtc. The CrP that is transported subsequently to the sl Mtc, only increases the level of CrP as it fails to be hydrolysed. This leads to the enzymatic CrP synthesis in UMtc, continuously, without break. resulting in the continuous consumption of the ATP, at at the expense of the quota due for the ABC1/ ABG 1 transporters. Consequently, affects the efflux of cholesterol into HDL, resulting inthe low HDLC levels in the blood.

3. CONCLUSION

The main objectives of this article are creating awareness of the possibility of occurrence of fenofibrate induced nephrotoxicity , as otherwise the cause of the deteriorated kidney function might be misinterpreted.. The second objective is, to raise the question, whether, it is beneficial to continue fenofibrate, in the subset of patients, showing the paradoxical Low HDLC The article also suggests to consider , fenofibrate as a cause of low HDLC when no other cause of the same is discernible. The review reaffirms the reversible nature of the increased SCr and low eGFR caused by fenofibrate therapy and their innocuous nature, as no actual structural damage is done to the kidneys. The Paradoxical, low HDLC , seen during the fenofibrate treatment is, perhaps seen only in a subset of fenofibrate induced nephrotoxicity cases, as no special focus is seen, either in the FIELD study or ACCORD study. The size and prevalence of this subset, remains to be determined by the future research. The reason is that, the beneficial effects of lowering the hypertriglyceridemia, by the fenofibrate, might be counteracted by the risks associated with the low HDLC, which by itself, is a known individual risk factor for CVD. This could perhaps be one of the reasons for the insignificant role in achieving the primary objective of prevention of CVD by the fenofibrate, ie prevention of heart attacks and Cardiovascular deaths, despite it's acknowledged role in successful achievement of the secondary CVD objectives like reducing hospitalizations, reduced interventions etc. While the increased SCr and reduced eGFR, during fenofibrate therapy, are inconsequential because they don't cause any structural damage of the kidney (another known

risk factor for CVD, same cannot be said of the paradoxical Low HDLC, whose risk of CVD is real, unless rectified. Hence, the usefulness or otherwise of instituting fenofibrate therapy in the subset of patients with paradoxical low HDLC, with the nephrotoxicity, need to be assessed by further research.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Backes JM, Gibson CA, Ruisinger JF, Moriarty PM. Fibrates: What have we learned in the past 40 years. Pharmacotherapy. 2007;27:412–424. [PubMed] [Google Scholar]
2. Shah A, Rader DJ, Millar JS. The effect of PPAR-alpha agonism on apolipoprotein metabolism in humans. Atherosclerosis. 2010;210:35–40. [PubMed] [Google Scholar]
3. Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, et al. Effect of fibrates on lipid profiles and cardiovascular outcomes: A systematic review. Am J Med. 2009;122:962.e1–962.e8. [PubMed] [Google Scholar]
4. Jacobson TA, Miller M, Schaefer EJ. Hypertriglyceridemia and cardiovascular risk reduction. Clin Ther. 2007;29:763–777. [PubMed] [Google Scholar]
5. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: Its etiology, effects and treatment. CMAJ. 2007;176:1113–1120. [PMC free article] [PubMed] [Google Scholar]
6. Rossner S, Oro L. Fenofibrate therapy of hyperlipoproteinaemia: A dose-response study and a comparison with clofibrate. Atherosclerosis. 1981;38:273–282. [PubMed] [Google Scholar]
7. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. Lancet. 2005;366:1849–1861. [PubMed] [Google Scholar]
8. Ginsberg HN, Elam MB, Lovato LC, Crouse JR, 3rd, Leiter LA, et al. (ACCORD Study Group.). Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–1574. [PMC free article] [PubMed] [Google Scholar
9. Lageder H. Comparative double-blind investigation of bezafibrate and clofibrate in patients with primary hyperlipoproteinaemia. Wien Klin Wochenschr. 1980;92:95–101. [PubMed [Google Scholar]
10. Dick TB, Marples J, Ledermann HM, Whittington J. Comparative study of once and 3-times daily regimens of bezafibrate in patients with primary hyperlipoproteinaemia. Curr Med Res Opin. 1981;7:489–502. [PubMed] [Google Scholar]
11. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. Lancet. 2005;366:1849–1861. [PubMed] [Google Scholar]
12. ACCORD Study Group. Ginsberg HN, Elam MB, Lovato LC, Crouse JR, 3rd, Leiter LA, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–1574. [PMC free article] [PubMed] [Google Scholar]
13. Broeders N, Knoop C, Antoine M et al. Fibrate-induced increase in blood urea and creatinine: Is gemfibrozil the only in-nocuous agent? Nephrol Dial Transplant. 2000;15:1993-9.
14. Lipscombe J, Lewis GF, Cattran D, et al. Deterioration in renal function associ- ated with fibrate therapy. Clin Nephrol. 2001;55:39-44.
15. Ritter JL, Nabulsi S. Fenofibrate-induced elevation in serum creatinine. Pharmaco-therapy. 2001;21:1145-9.
16. Paul S, Mohan V. Fenofibrate can increase serum creatinine levels in renal insufficiency. J Assoc Physicians India. 2006;54:337. Letter.
17. McQuade CR, Griego J, Anderson J, et al. Elevated serum creatinine levels associated with fenofibrate therapy. Am J Health-Syst Pharm.
18. Attridge RL, Linn WD, Ryan L et al. Evaluation of the incidence and risk factors for development of fenofibrate- associated nephrotoxicity. J Clin Lipidol. 2012;6:19-26.

19. Hottelart C, El Esper N, Rose F, et al. Fenofibrate increases creatininemia by increasing metabolic production of creatinine. Nephron. 2002;92:536-41. .
20. Ansquer JC, Dalton RN, CaussEffect of fenofibrate on kidney function: A 6-week randomized crossover trial in healthy people. Am J Kidney Dis. 2008;51:904-13
21. Ritter JL, Nabulsi S. Fenofibrate-induced elevation in serum creatinine. Pharmacotherapy. 2001; 21:1145-9.22. Bonds DE, Craven TE, Buse J et al. Fenofibrate-associated changes in renal function and relationship to clinical outcomes among individuals with Type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) experience. Diabetologia. 2012;55:1641–1650.
22. Ansquer J-C, Dalton RN, Causse E, Crimet D, Malicot KL, Foucher C. Effect of fenofibrate on kidney function: A 6-week randomized crossover trial in healthy people. Am J Kidney Dis. 2008;51:904–913.
23. Forsblom C, Hiukka A, Leinonen E, Sundvall J, Groop PH, Taskinen M-R. Effects of long-term fenofibrate treatment on markers of renal function in type 2 diabetes: FIELD Helsinki Substudy. Diab Care. 2010;33:215–220.
24. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation. 1998;98:2088–2093.
25. Ansquer JC, Foucher C, Rattier S, Taskinen MR, Steiner G. Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in Type 2 diabetes: Results from the Diabetes Atherosclerosis Intervention Study (DAIS). Am. J. Kidney Dis. 2005; 45:485–493.
26. Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in Type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet. 2001;357:905–910.
27. The FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD Study): randomised controlled trial. Lancet. 2005;366:1849–1861.
28. The Accord Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–157430.
Hottelart C, El Esper N, Rose F, Achard JM, Fournier A. Fenofibrate increases creatinemia by increasing metabolic production of creatinine. Nephron. 2002;92:536–541.
29. Hottelart C, El Esper N, Rose F, Achard JM, Fournier A. Fenofibrate increases creatinemia by increasing metabolic production of creatinine. Nephron. 2002; 92:536–541. [Google Scholar]
30. Balakumar P, Kadian S, Mahadevan N. Are PPAR alpha agonists a rational therapeutic strategy for preventing abnormalities of the diabetic kidney? Pharmacol. Res. 2012;65:430–436.
31. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41.
[Google Scholar
32. Broeders N, Knoop C, Antoine M, et al. Fibrate-induced increase in blood urea and creatinine: Is gemfibrozil the only innocuous agent? Nephrol Dial Transplant. 2000;15:1993-9.
33. Shahinfar S, Dickson T, Zhang Z, Keane WF, Brenner BM, for the renaal Investigators. Baseline predictors of end-stage renal disease risk in patients with Type 2 diabetes and nephropathy: new lessons from the RENAAL Study. Kidney Int. 2005;67:S48–S51.
34. Paul S, Mohan V. Fenofibrate can increase serum creatinine levels in renal insufficiency. J Assoc Physicians India. 2006; 54:337. Letter.
35. Ritter JL, Nabulsi S. Fenofibrate-induced elevation in serum creatinine. Pharmacotherapy. 2001;21:1145-9.
36. Lipscombe J, Lewis GF, Cattran D, et al. Deterioration in renal function associ-ated with fibrate therapy. Clin Nephrol. 2001; 55:39-44.
37. Hottelart C, El Esper N, Rose F, et al. Fenofibrate increases creatininemia by increasing metabolic production of creatinine. Nephron. 2002;92:536-41.
38. Forsblom C, Sundvall J, Hiukka A, et al. Effects of long-term fenofibrate treat-ment on markers of renal function in type 2 diabetes: the FIELD Helsinki sub-study. Diabetes Care. 2010;33:215-20.
39. Ansquer JC, Dalton RN, Causse E, et al. Effect of fenofibrate on kidney function: A 6-week randomized crossover trial in

healthy people. Am J Kidney Dis. 2008; 51:904-13.

40. McQuade CR, Griego J, Anderson J et al. Elevated serum creatinine levels associated with fenofibrate therapy. Am J Health-Syst Pharm. 2008;65:138-41.
41. D, Dembinski T, Friesen MH. Iatrogenic severe depression of high-density lipoprotein cholesterol. J Clin Pharmacol. 2009;49:865–871 [PubMed] [Google Scholar]
42. Peter E. Linz, Laura C. Lovato, Marshall B. Elam paradoxical reduction in HDL-C with fenofibrate and thiazolidinedione therapy in type 2 diabetes: The accord lipid trial. Diabetes Care. 2014;37(3):686–693.
Published online 2014 Feb 11.
DOI: 10.2337/dc13-0790
43. Venero CV, Thompson PD, Fernandez AB. Reduced high-density lipoprotein cholesterol in patients receiving rosiglitazone and fenofibrate. Am J Med. 2008;121:e3–e4
[PubMed] [Google Scholar]
44. Giuliana Mombelli, Franco Pazzucconi, Alighiero Bondioli, et al Paradoxical decrease in high-density lipoprotein cholesterol with fenofibrate: A quite rare phenomenon indeed .cardiovascular therapeutics. 2010;28(3):153-60.
DOI: 10.1111/j.1755-5922.2009.00121.
45. Mymin D, Dembinski T, HH M, et al. The Journal of Clinical Pharmacology. 2013; 49(7):865-871.
Available:https://doi.org/10.1177/0091270009335766
46. McBride P. Triglycerides and risk for coronary artery disease. Curr Atheroscler Rep. 2008;10(5):386-90.
DOI: 10.1007/s11883-008-0060-9. PMID: 18706279.
47. Staels B, Dallongeville J, Auwerx J, Schoonjans K, Leitersdorf E, Fruchart JC. Mechanism of action of fibrates on lipid and lipoprotein metabolism. Circulation. 1998;98:2088–2093.
48. Agouridis AP, Kostapanos MS, Tsimihodimos V, et al. Effect of rosuvastatin monotherapy or in combination with fenofibrate or omega-3 fatty acids on lipoprotein subfraction profile in patients with mixed dyslipidaemia and metabolic syndrome. Int. J. Clin. Pract. 2012;66:843–853.
49. Jong MC, Hofker MH, Havekes LM. Role of apoCs in lipoprotein metabolism:functional differences between apoC1, apoC2, and apoC3. Arterioscler. Thromb. Vasc. Biol. 1999;19:472–484.
50. Shah A, Rader DJ, Millar JS. The effect of PPAR-alpha agonism on apolipoprotein metabolism in humans. Atherosclerosis. 2010;210:35–40.
[PubMed] [Google Scholar]
51. Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, et al. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. Am J Med. 2009;12* Review of the possible mechanisms of PPAR-α activation in the treatment of diabetic kidney disease.
52. Ting RD, Keech AC, Drury PL, et al. Benefits and safety of long-term fenofibrate therapy in people with Type 2 diabetes and renal impairment: the FIELD Study. Diabetes Care. 2012;35:218–225.
53. Davis T, Ting R, Best J et al. Effects of fenofibrate on renal function in patients with Type 2 diabetes mellitus: The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetologia. 2011;54:280–290.
* Clinical paper of a large randomized controlled trial examining the renal effects of fenofibrate in Type 2 diabeting RD, Keech AC, Drury PL et al. Benefits and safety of long-term fenofibrate therapy in people with Type 2 diabetes and renal impairment: the FIELD Study.
54. Agouridis AP, Kostapanos MS, Tsimihodimos V et al. Effect of rosuvastatin monotherapy or in combination with fenofibrate or omega-3 fatty acids on lipoprotein subfraction profile in patients with mixed dyslipidaemia and metabolic syndrome. Int. J. Clin. Pract. 2012;66:843–853.
55. Shahinfar S, Dickson T, Zhang Z, Keane WF, Brenner BM, for the RENAAL Investigators. Baseline predictors of end-stage renal disease risk in patients with Type 2 diabetes and nephropathy: New lessons from the RENAAL Study. Kidney Int. 2005;67:S48–S51.
56. Ru-Dee Ting; Anthony Keech Fenofibrate and Renal Disease Clinical Effects in Diabetes Clin Lipidology. 2013;8(6):669-680 14.Keating GM, Croom KF. Fenofibrate: a review of its use in primary dyslipidaemia, the metabolic syndrome and Type 2 diabetes mellitus. Drugs. 2007;67:121–153.
57. Yokoyama H, Oishi M, Kawai K, Sone H. Japan diabetes clinical data management study group. Reduced GFR and microalbuminuria are independently

associated with prevalent cardiovascular disease in Type 2 diabetes: JDDM study 1 Diabet Med. 2008;25(12): 1426-32.
DOI: 10.1111/j.1464-5491.2008.02592.x. PMID: 19046241.

58. Adkins J C, Faulds D,"Micronised fenofibrate: a review of its pharmacodynamic properties and clinical efficacy in the management of dyslipidaemia", Drugs. 1997;54:615-633.8.
59. Farnier M, Bonnefous F, Debbas N, Irvine A, "Comparative efficacy and safety of micronized fenofibrate and simvastatin in patients with primary type IIa or IIb hyperlipidemia", Archives of Internal Medicine (1994);154: pp. 441-449..cardiovascular Pharmacology. 1996;27:563 570. Crossref| PubMed
60. Hottelart C, El Esper N, Rose F, et al. Fenofibrate increases creatininemia by increasing metabolic production of cre-atinine. Nephron. 2002;92:536-41.
61. Neve BP, Corseaux D, Chinetti G, et al. PPARalpha agonists inhibit tissue factor [expression in human monocytes and macrophages. Circulation. 2001;6;103(2): 207–212. [PubMed] [Google Scholar]
62. Marx N, Mackman N, Schonbeck U, et al. PPARalpha activators inhibit tissue factor expression and activity in human monocytes. Circulation. 2001;103(2):213–219. [PubMed] [Google Scholar]
63. Mangan S, Clancy P, Golledge J. Modulation of endothelial cell thrombomodulin by PPAR ligands--variation according to environment. Thromb Res. 2008;121(6):827–834. [PMC free article] [PubMed] [Google Scholar]
64. Okopien B, Cwalina L, Lebek M, et al. Effects of fibrates on plasma prothrombotic activity in patients with type IIb dyslipidemia. Int J Clin Pharmacol Ther. 2001;39(12):551–
557. [PubMed] [Google Scholar
Kostapanos MS, Florentin M, Elisaf MS. Fenofibrate and the kidney: An overview. Eur. J. Clin. Invest. 2013;43:522–531.
65. Pineda Torra I, Gervois P, Staels B. Peroxisome proliferator-activated receptor alpha in metabolic disease, inflammation, atherosclerosis and aging. Current Opinion In Lipidology 1999;10:151-159
66. Poynter ME, Daynes RA. Peroxisome proliferator-activated receptor alpha activation modulates cellular redox status, represses nuclear factor-kappaB signaling, and reduces inflammatory cytokine production in aging. Journal of Biological Chemistry. 1998;273:32,833-32,841.
67. Delerive P, De Bosscher K, Besnard S, Vanden Berghe W, Peters JM, Gonzalez FJ, Fruchart J-C, Tedgui A, Haegeman G, Staels B. Peroxisome proliferator-activated receptor alpha negatively regulates the vascular inflammatory gene response by negative crosstalk with transcription factors NF-kappa B and AP-1. J. Biol. Chem. 1999;274:32,048-32,054.
68. Marx N, Sukhova G K, Collins T, Libby P, Plutzky J. PPARalpha activators inhibit cytokine-induced vascular cell adhesion molecule-1 expression in human endothelial cells. Circulation 1999;99: 3,125-3,1131.l.
69. Staels B, Koenig W, Habib A, Merval R, Lebret M,Torra I P, Delerive P, Fadel A, Chinetti G, Fruchart J C, Najib J, Maclouf J,Tedgui A. Activation of human aortic smooth-muscle cells is inhibited by PPARalpha but not by PPARgamma activators", Nature. 1998;393:790-793.
70. Jonkers IJ, Mohrschladt MF, Westendorp RG, van der Laarse A, Smelt AH. Severe hypertriglyceridemia with insulin resistance is associated with systemic inflammation: reversal with bezafibrate therapy in a randomized controlled trial. Am. J. Med. 2002;112:275-280.
71. Despres JP, Lemieux I, Pascot A, Almeras N, Dumont M, Nadeau A, Bergeron J. Prud'homme D,"Gemfibrozil reduces plasma C-reactive protein levels in abdominally obese men with the atherogenic dyslipidemia of the metabolic syndrome. Arteriosclerosis, Thrombosis & Vascular Biology. 2003;23: 702-703.
72. Shah A, Rader DJ, Millar JS. The effect of PPAR-alpha agonism on apolipoprotein metabolism in humans. Atherosclerosis. 2010;210:35–40.
[PubMed] [Google Scholar]
73. Abourbih S, Filion KB, Joseph L, Schiffrin EL, Rinfret S, Poirier P, et al. Effect of fibrates on lipid profiles and cardiovascular outcomes: a systematic review. Am J Med. 2009;122:962.e1–962.e8.
[PubMed] [Google Scholar
74. Diabetes Atherosclerosis intervention study investigators. Effect of fenofibrate on progression of coronary-artery disease in Type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet. 2001;357: 905–910.

;

75. Park CW, Zhang Y, Zhang X, et al. PPARalpha agonist fenofibrate improves diabetic nephropathy in db/db mice. Kidney Int. 2006;69:1511–1517.
76. Kostapanos MS, Florentin M, Elisaf MS. Fenofibrate and the kidney: An overview. Eur. J. Clin. Invest. 2013;43:522–531.
77. Lipscombe J, Lewis GF, Cattran D, Bargman JM. Deterioration in renal function associated with fibrate therapy. Clin. Nephrol. 2001;55:39–44.
78. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.

    [PubMed] [Google Scholar]
79. McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, et al. Diagnosing insulin resistance in the general population. Diabetes Care. 2001; 24:460–4. [PubMed] [Google Scholar]
80. Feher MD, Hepburn AL, Hogarth MB, Ball SG, Kaye SA. Fenofibrate enhances urate reduction in men treated with allopurinol for hyperuricaemia and gout. Rheumatology. 2003;42:321-325.
81. Uetake D, Ohno I, Ichida K, et al. Effect of fenofibrate on uric acid metabolism and urate transporter 1. Intern Med. 2010;49(2):89–94. [PubMed] [Google Scholar5.

    Chen H, Sullivan G, Yue LQ, Katz A, Quon MJ. QUICKI is a useful index of insulin sensitivity in subjects with hypertension. Am J Physiol Endocrinol Metab. 2003;284:E804–12. [PubMed] [Google Scholar]
82. Prasad ASV. An investigation into the molecular mechanism of inverse relationship between *S. Creatinine* and HDL-C in CKD. Asian Journal of Research in Nephrology. 2022;5(2):30-39.

    Available:https://journalajrn.com/index.php/AJRN/article/view/4
83. Glaysher J, Van Heyningen C. Paradoxical decrease in high density lipoprotein-cholesterol associated with statin and fenofibrate combination therapy. The British Journal of Diabetes & Vascular Disease. 2007;7(6):295-7.
84. Foucher C, Brugere L, Ansquer JC. Fenofibrate, homocysteine and renal function. Current Vascular Pharmacology. 2010;8(5):589-603.

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