

Investigating the effect of Fenofibrate on biomarkers of vascular inflammation in L-NAME induced hypertensive rats

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Abstract

This study aims to evaluate the impact of fenofibrate on the levels of (IL-6, hsCRP, Lp-PLA2, sCD40L, and cystatin C) in hypertensive rats. Twenty-four rats were divided into two groups each of twelve. The first group served as the normotensive group, while the second group was regarded as the hypertensive group. Each group was further divided into two subgroups (control and treated). The control subgroups only received a placebo and the treated subgroups were given fenofibrate 30 mg/kg daily orally by gastric gavage for 4 weeks. The level of hsCRP, IL6, and Lp-PLA2 significantly increased, but sCD40L and cystatin C levels were not changed in hypertensive rats. Fenofibrate has significantly reduced the levels of hsCRP and Lp-LPA2 in hypertensive rats while IL6 and sCD40s have not been changed in both groups. In conclusion, Fenofibrate has revealed a pleiotropic anti-inflammatory effect by reducing the level of hsCRP and Lp-LPA2 in hypertensive rats.

Keywords

Fenofibrate, hypertension, inflammatory biomarkers

Introduction

Dyslipidemia is an established risk factor for cardiovascular disease (CVD) over the decades most therapies have been directed towards lowering LDL cholesterol primarily by statins for reducing cardiovascular diseases. (Ross et al. 1999; Stone et al. 2013) However, in spite of a good reduction in LDL cholesterol with a high dose of statin, a residual risk for cardiovascular events persists (Mora et al. 2012). Several studies have shown associations of hypertriglyceridemia and low HDL levels with cardiovascular diseases (Sarwar et al. 2007; Aberra et al. 2020) hence, therapies targeting hypertriglyceridemia and low HDL cholesterol could decrease the residual risk of CVD.

Fibrates have been used for the treatment of dyslipidemia for a long time. They reduce the level of triglyceride-rich lipoproteins and increase high-density lipoprotein cholesterol (HDL-C) levels (These drugs mainly exert their actions via the activation of specific nuclear receptors called peroxisome proliferator-activated receptors α (PPAR α) (Oh et al. 2020). Many evidences have shown that fibrates treatment reduced CV events (either alone or in combination with statins) in patients with type 2 diabetes or metabolic syndrome through reducing atherogenic dyslipidemia (Scott et al. 2009; Okopień et al. 2017; Zhu et al. 2020). Some other studies indicated that fibrates protect against CVD by modulation of inflammatory and cardiovascular risk biomarkers (Chinetti-Gbaguidi et al. 2005). These effects are called “pleiotropy”. Fenofibrate a member

of fibric acid derivative, in addition to its lowering effects on triglyceride and increasing HDL levels, exerts pleiotropic effects in form of endothelium protection by increasing the expression of endothelial NO synthase (eNOS), reducing oxidative stress, and modulating inflammation through inhibition of pro-inflammatory cytokines (Koh et al. 2005; Tsimihodimos et al. 2005).

Hypertension is one of the five important conditions included in a metabolic syndrome that are regarded as risk factors for cardiovascular disease (Franklin 2006). Different mechanisms are contributed in the pathophysiology of hypertension, however, in the last two decades, the role of inflammation in its development becomes more obvious (Dinh 2014; Patrick et al. 2021). Many circulating inflammatory markers have been detected to increase in patients with essential hypertension including hsCRP, IL6, and Lp-PLA2 (Barbaro and Harrison 2019; Hidru et al. 2019).

Metabolic syndrome (MetS) is characterized by many risk factors (arterial hypertension, atherogenic dyslipidemia (high TG and low HDL levels)), obesity, and disturbed glucose metabolism), which ultimately may lead to atherosclerosis and type 2 diabetes mellitus (Vávrová et al. 2013). Several clinical and experimental studies have demonstrated the effect of fenofibrate on different inflammatory markers including hsCRP, IL6, TNF- α , Lp-PLA2, CystatinC ICAM-1, and sCD40L in subjects with different components for metabolic syndrome (Rosenson 2008; Ghani et al. 2013; Noureldein et al. 2015). However, the level of most of these markers has not been reported in subjects with hypertension. This experimental study aims to estimate the concentration of these inflammatory biomarkers in hypertensive rats and to show how fenofibrate affects their levels.

Methods and experimental design

In this study, the experiment was conducted on male albino rats weighing 220–350 grams. Rats were kept in Polypropylene cages (2 animals/cage) with stainless steel wire cover and chopped bedding, in the animal house of Hawler Medical University, College of Medicine. The rats were put under controlled room temperature (20–25 °C) and a 12-hour light/dark cycle was set. They were fed rodent food rich in nutrients and they had free access to tap water.

Twenty-four male Wister rats were divided into two groups, the normotensive and hypertensive group, with twelve rats in each group. Both groups were also divided into two subgroups each of 6 rats. The normotensive subgroups included the control (negative control) and treated subgroup (treated with fenofibrate 30 mg/kg). However, the hypertensive subgroups involved hypertensive (positive control) and treated subgroups. All rat groups were fed a standard diet for one week before starting the experiment as an acclimatization period for adaptation (Fig. 1).

Induction of hypertension was done by giving N ω -nitro-L-arginine (L-NAME, Tocris Bioscience) 40 mg/kg/day by gastric gavage, for 3 weeks (Aziz and Dizaye 2019). Fenofibrate (Lipanthyl, 200 mg micronized

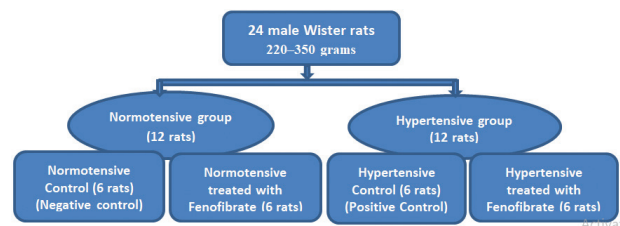


Figure 1. Diagram shows the study design.

capsule, Abbott, France) was administered daily at a dose of 30 mg/kg by gastric gavage for 4 weeks. The drugs were dissolved in the distilled water (Dizaye and Ahmed 2019).

Blood pressure (systolic, diastolic, and mean blood pressure) and heart rate were measured using a noninvasive CODA monitor (Tail-cuff method). A specialized cage was used to restrain the rats in it. They were maintained in this restraining cage for at least 20 minutes before each blood pressure recording. For each rat, at least 5 readings of blood pressure and heart rate were recorded. Blood pressure and heart rate have been documented for all groups at the beginning of the study and were re-measured at the end of the treatment.

The animals were anesthetized with an intraperitoneal injection of Xylazine 5 mg/kg and Ketamine 35 mg/kg (Dizaye and Qadir 2014). Blood samples were taken out through cardiac puncture, on the last day of treatment, for each group. ELISA rat kits (Enzyme-Linked Immunosorbent Assay) were used for serological tests and the levels of the following biomarkers (hsCRP, IL-6, Lp-LPA2, sCD40L, and cystatin C) have been measured.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) Version 20.0 for Windows. The data were expressed as mean \pm SE. Comparisons between groups were done using the Tukey test and student t-test. A P-value of 0.05 or less was considered statistically significant.

Results

No significant change in systolic, diastolic, mean blood pressure, and heart rate were observed in normotensive rats when they were treated with fenofibrate (30 mg/kg) for 4 weeks (Table 1)

In the hypertensive rat group, L-NAME significantly ($P < 0.05$) increased the systolic, diastolic, and mean blood pressure, while the heart rate was significantly decreased when they were compared to the control group (negative control) However, when the hypertensive rats were treated with fenofibrate, no changes in the blood pressure and heart rate were reported (Table 2).

The level of inflammatory markers hsCRP, IL6, and Lp-PLA2 significantly raised in hypertensive rats when they were compared to the normotensive control group. Fenofibrate significantly reduced the level of hsCRP and Lp-PLA2 in hypertensive rats (Figs 2 and 3) but not in normotensive

Table 1. Effect of fenofibrate (30 mg/kg) on blood pressure and heart rate in normotensive rats (n = 6).

Parameters	Normotensive Control	Normotensive rats treated with Fenofibrate
Systolic blood pressure (mmHg)	120.00±11.26	106.16±10.94
Diastolic blood pressure (mmHg)	87.16±12.15	75.83±10.14
Mean blood pressure (mmHg)	97.5±11.67	85.83±10.04
Heart Rate Beat/Minute	354.83±36.04	340.33±17.67

Table 2. Effect of Fenofibrate (30 mg/kg) on blood pressure and heart rate in L-NAME induced Hypertensive rats.

Blood pressure and Heart rate	Normotensive Control	Hypertensive Control	Hypertensive rats treated with Fenofibrate
Systolic blood pressure (mmHg)	113.0±2.33 a	155.1±2.02 b	166.00±4.58 b
Diastolic blood pressure (mmHg)	84.1±3.27 a	117.1±2.70 b	126.33±6.24 b
Mean blood pressure (mmHg)	95.5±2.48 a	129.6±2.29 b	138.33±5.02 b
Heart rate (Beat/min)	380.3±5.44 b	334.0±6.02 a	341.1±5.10 a

Mean values ± S.E.M. are presented.

-The same letters mean there is no significant difference

-The different letters mean there is a significant difference at P > 0.05

In comparison to the control group, cystatin C level in hypertensive rats did not show any significant change. Additionally, in both hypertensive and normotensive rats, fenofibrate non-significantly increased cystatin C levels (Table 3).

Table 3. Effect of fenofibrate (30 mg/kg) on inflammatory biomarkers in Hypertensive and normotensive rats.

Biomarkers	Normotensive Control	Hypertensive Control	Hypertensive treated with Fenofibrate	Normotensive treated with Fenofibrate
hsCRP (ng/ml)	0.991±0.053 a	1.215±0.038 b	1.043±0.014 a	0.944±0.050 a
IL6 (ng/ml)	5.49±0.24 a	6.40±0.09 b	6.25±0.12 b	5.92±0.06 a
Lp-PLA2 (ng/ml)	11.19±0.35 a	12.70±0.29 b	11.490±0.068 a	11.470±0.265 a
sCD40L (ng/ml)	7.97±0.15 a	8.49±0.29 a	7.49±0.36 a	8.43±0.25 a
Cystatin C (ng/ml)	8.05±0.28 ab	7.47±0.16 ab	8.28±0.13 a	8.42±0.31 b

Mean values ± S.E.M. are presented.

-The same letters mean there is no significant difference

-The different letters mean there is a significant difference at P < 0.05

rats. Furthermore, it could not change the level of IL6 in both normotensive and hypertensive groups (Table 3).

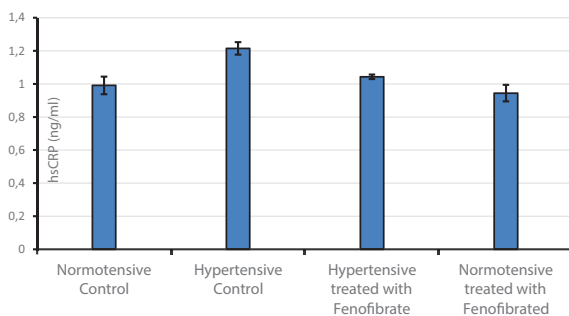


Figure 2. Effect of fenofibrate (30 mg/kg) on hsCRP levels in Hypertensive and normotensive rats.

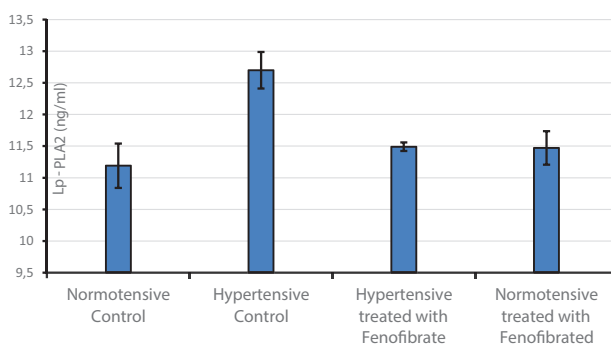


Figure 3. Effect of fenofibrate (30 mg/kg) on Lp-PLA2 levels in Hypertensive and normotensive rats.

No change in the level of sCD40L was observed in hypertensive rats when they were compared to the control group. Moreover, fenofibrate did not affect its level in both normotensive and hypertensive rats.

Discussion

L-NAME (L-NG-Nitro arginine methyl ester) could significantly (P < 0.05) increase the systolic, diastolic, and mean blood pressure in hypertensive rats when they were compared to the control group. L-NAME is a non-selective antagonist of nitric oxide synthase (NOS). It's a common method used for inducing experimental hypertension (Kopinová et al. 2012; Pechanova et al. 2020). Induction of hypertension by inhibiting nitric oxide synthase (NOS) activity with L-NAME is associated with profound vasoconstriction, activation of the sympathetic nervous system, and RAAS (Renin Angiotensin Aldosterone System), oxidative stress, kidney damage, and structural alterations of the vascular wall (Lerman et al. 2019).

In the present study, fenofibrate did not produce any significant decrease in the systolic, diastolic, mean blood pressure, and heart rate in the normotensive rat group. In agreement with this, a clinical study done by Walker et al. (2012) showed that treatment of normotensive and normolipidemic patients with fenofibrate could not significantly lower systolic and diastolic blood pressure (SBP and DBP) in spite of the improvement in the vascular endothelial function.

Additionally, in the current experimental study fenofibrate could not change systolic, diastolic, mean blood pressure or heart rate in hypertensive rat groups. There are multiple mechanisms involved in regulating the blood pressure such as the sympathetic nervous system, renin-angiotensin-aldosterone system, endothelial function plus sodium and water retention (Delacroix et al. 2014), the endothelial dysfunction is not the only mechanism through which blood pressure may increase, and this may explain the inability of fenofibrate in reducing the blood pressure. A limited number of clinical and experimental researches have studied the effect of fenofibrate on blood pressure and there is inconsistency concerning its effect on arterial blood pressure (BP). In a randomized, double-blind, placebo-

bo-controlled, cross-over trial study fenofibrate could significantly reduce blood pressure in hypertriglyceridemic hypertensive patients (Koh et al. 2006). In another study, Gilbert et al. (2013) showed that fenofibrate reduced blood pressure, heart rate and renal vasoconstriction in salt-sensitive volunteers, but not in salt-resistant volunteers.

In hypertensive rats the inflammatory markers hsCRP, IL6 and Lp-PLA2 significantly increased when they were compared to the control group. This supports the evidences which suggest that the inflammation process and oxidative stress have a role in the development of hypertension (Dinh et al. 2014; Guler et al. 2021). The Association of inflammation and hypertension has been focused on in many studies which revealed a clear relationship between inflammatory markers (IL6 and hsCRP) and high blood pressure (Yu et al. 2018; Tanase et al. 2019). A recent meta-analysis demonstrated that a higher level of IL-6 and CRP increase the risk of hypertension (Jayedi et al. 2019). Many inflammatory markers are elevated in hypertension however C-reactive protein is elevated even before the onset of overt hypertension which can predict the development of hypertension (Sesso et al. 2003). Furthermore, elevated levels of Lp-PLA2 are indicative of vascular inflammation associated with the formation of plaque within the arteries (Cojocar et al. 2010). Therefore quantitative estimation of Lp-PLA2 is regarded as a valuable predictor for vascular disease, especially hypertension and hypertension with metabolic syndrome (Van 2016; Diaconu et al. 2021). These results indicate the role of inflammation as an underlying mechanism in the pathogenesis of hypertension.

The level of both sCD40L and Cystatin C was not increased in hypertensive rats in the current study. The sCD40L (a prothrombotic and proinflammatory cytokine) is delivered into the circulation mainly by activated platelets that indicate plaque destabilization and rupture (Antoniades et al. 2009). The elevated level of sCD40L has been demonstrated in hypertensive patients (Guzel et al. 2019). However, in line with the present study, Sonmez et al. (2005) indicated that there was no association between high blood pressure and sCD40L in newly diagnosed hypertensive patients. Furthermore, another study revealed that increased concentrations of sCD40L were measured in patients with severe end-organ damage but not in hypertensives with no or mild organ damage (Yuan et al. 2010).

Serum cystatin C compared with serum creatinine is a more reliable marker for clinical decision making which may reveal even mild kidney dysfunction (Salminen et al. 2016). A raised serum concentration of cystatin C serves as an independent risk factor for target-organ damages and cardiovascular events in patients with essential hypertension (Han et al. 2016). Renal damage is a consequence of the long-term effect of hypertension or the degree of elevation of blood pressure on the renal vasculature (Bidani and Griffin 2004). In this study, the level of cystatin C did not change in hypertensive rats. This could be explained by that, the time which the kidneys were exposed to high blood pressure in this experiment was not enough to produce any damage, that's why the level of Cystatin C was not elevated.

In the present study, fenofibrate could significantly lower the level of both hsCRP and Lp-PLA2 in the hypertensive group but not in normotensive rats. Fenofibrate is a PPAR α agonist that reduces TG, increases HDL-C levels, and reduces the risk of major cardiovascular events in patients with metabolic syndrome and atherogenic dyslipidemia (Katsiki et al. 2013). Fenofibrate is very effective in primary and secondary prevention of CVD, through its pleiotropic anti-inflammatory effects by downregulating the expression of genes encoding inflammatory cytokines and acute phase response proteins (Chinetti-Gbaguidi et al. 2005). Some experimental and clinical studies have investigated the role of fibrates (PPAR α agonists) in modulating inflammatory response, and decreasing (hsCRP, IL6, Lp-PLA2) markers of inflammation in different subject groups (Belfort et al. 2010; Bragt and Mensink 2012; Sun et al. 2015). Furthermore, no changes have been seen in the level of IL6 and sCD40L biomarkers in both groups. No research or data has been detected to evaluate the effect of fenofibrate on these biomarkers in hypertensive subjects.

Additionally, in both hypertensive and normotensive groups fenofibrate increased the level of cystatin C non-significantly. It's well-known that cystatin C is a better marker than serum creatinine for assessing kidney function (Murty et al. 2013). Several clinical studies have reported that fenofibrate increases the concentration of serum creatinine and causes a decline in the glomerular filtration rate (Ansquer et al. 2008; Kostapanos et al. 2013). Sahebkar et al (2018) in a meta-analysis of clinical trials showed that therapy with fenofibrate raises the circulating cystatin C levels, and this supports the results in this study.

Conclusions

In the present study, Fenofibrate significantly decreased the level of hsCRP and Lp-PLA2 in hypertensive rats. However, it could not reduce other inflammatory markers (IL6, sCD40L) in hypertensive and normotensive rats. The levels of inflammatory markers (hsCRP, IL6, and Lp-PLA2) have been increased in hypertensive rats and the level of sCD40L and Cystatin C did not change. Fenofibrate could not affect the blood pressure and heart rate in both normotensive and hypertensive groups.

Abbreviations

MetS: Metabolic syndrome; PPAR α : Peroxisome Proliferator-Activated Receptors α ; CV: Cardiovascular; CVD: Cardiovascular disease; RAAS: Renin Angiotensin Aldosterone System; ELISA: Enzyme-Linked Immunosorbent Assay; hsCRP: high sensitivity C reactive protein; ICAM-1: Intercellular adhesion molecules-1; IL-6: Interleukin 6; TNF- α : Tumor necrosis factor- α ; LDL-C: low-density lipoprotein cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; BP: Blood pressure;

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; L-NAME: Nitro-L-arginine methyl ester; Lp-PLA2: Lipoprotein-associated phospholipase A2; NO: Nitric oxide; NOS: Nitric oxide synthase; eNOS: endothelial Nitric oxide synthase; sCD40L: Soluble CD40 ligand.

Ethics approval

This work has been approved by the ethics committee in the College of Medicine /Hawler Medical University with the approval number Meeting code: 5 paper code 7.

Throughout this research work all procedures were performed in accordance with the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines.

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Availability of data and materials

The datasets used and/or analyzed for the current study are available from the corresponding author on reasonable request.

Authors' contributions

KD-Conceptualization, data analysis, manuscript revision, and supervision;

BOB-Literature review, manuscript writing, data acquisition, and data interpretation. All authors revised the article critically for important intellectual content and approved the final version of the manuscript.

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