

## POSSIBLE CARDIOVASCULAR PROTECTIVE EFFECT OF SOME PPAR ACTIVATORS IN EXPERIMENTALLY-INDUCED HYPERTENSIVE MODEL IN RATS

**OMAYMA KHORSHID<sup>\*1</sup>, EBTISSAM ABDEL- GHAFFAR <sup>1</sup>, AMAL MISHRIKI <sup>1</sup>, AMR GALAL<sup>1</sup> AND AMAL HAREEDY <sup>2</sup>**

Departments of Pharmacology <sup>1</sup>and Pathology <sup>2</sup>, Faculty of Medicine, Cairo University, Egypt, Email: dr\_ekhorshid@hotmail.com

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### **ABSTRACT**

PPARs initially believed to regulate genes involved in lipid and glucose metabolism. Recently, both PPAR $\alpha$  and PPAR $\gamma$  were suggested to play an important role in protection against cardiovascular diseases. The present study tested the possible cardiovascular protective effect of combined low doses of PPAR $\alpha$  (Fenofibrate) and PPAR $\gamma$  (Rosiglitazone) activators. 42 albino rats were classified into different groups. Rats received oral Fenofibrate and Rosiglitazone individually and in combination of each other in low doses (30 & 2 mg/kg/day respectively) and in full doses (100 & 5mg/kg/day respectively) using the Deoxycorticosterone acetate (DOCA)-salt model for induction of hypertension in uninephrectomized rats. The effects on blood pressure, biochemical and histopathological changes were studied. Rosiglitazone and Fenofibrate significantly reduced the systolic blood pressure. Fenofibrate protected against cardiac hypertrophy while Rosiglitazone prevented aortic media hypertrophy. The combined low doses of Fenofibrate and Rosiglitazone were found to have significant cardiovascular protective effects similar to that achieved by combined full doses of both drugs and higher than that achieved by the full dose of each drug individually. The significant cardiovascular protective effects of the combined low doses of Fenofibrate and Rosiglitazone were manifested by lowering of the systolic blood pressure, decrease myocardial and aortic media thickness with low risk ratio in lipid profile.

**Keywords:** PPAR, blood pressure, Rosiglitazone, Fenofibrate.

### **INTRODUCTION**

Hypertension is a major risk factor in the development of atherosclerosis and cardiovascular disease and frequently occurs together with disorders of carbohydrate and lipid metabolism as part of the metabolic syndrome [1].

Peroxisome proliferator activator receptors (PPARs) belong to the nuclear hormone receptor superfamily of ligand-activated transcription factors. PPARs initially believed to regulate genes involved in lipid and glucose metabolism only. However both PPAR $\alpha$  and PPAR $\gamma$  were found to be expressed in the endothelial cells and vascular smooth muscle cells, suggesting their vascular protective effects [2].

Both PPAR $\alpha$  and PPAR $\gamma$  activators in therapeutic doses have side effects. The present work was designed to study the possible cardiovascular protective effect of combined low doses of PPAR $\alpha$  (fenofibrate) and PPAR $\gamma$  (Rosiglitazone) activators in DOCA-salt induced hypertensive model in rats.

### **MATERIALS AND METHODS**

#### **Drugs**

Rosiglitazone & Fenofibrate powder (*Fluka Company, Switzerland*) dissolved in distilled water. Deoxycorticosterone acetate (DOCA) powder (*Sigma Chemical Company, USA*) dissolved in olive oil.

#### **Kits**

Sodium, Potassium, Cholesterol, LDL, HDL, Aspartate aminotransferas & Alanine aminotransferase (*Chronolab, Spain*). Glucose (*Spinreact Company, Spain*).

#### **Animals**

Laboratory bred adult male albino rats weighing between 150-180 grams, were used. They were maintained under standard laboratory conditions at 25°C, normal photoperiod (12 hours dark/12 hours light) and standard rat chow diet. The study was conducted in accordance with Cairo University animal research guidelines. The study approval was granted by Cairo university ethics review board.

#### **Induction of hypertension in rats**

Uninephrectomized rats were injected twice weekly with 20mg/kg S.C. deoxycorticosterone acetate (DOCA) in olive oil for 4 weeks. Drinking water was replaced with a 1% NaCl solution [3].

#### **Experimental Design**

The present study was conducted on 42 rats. The rats were divided into the following groups (each containing 6 rats):

##### **Group I:** (control group)

The rats received saline (0.9%) injection S.C. (1-2 ml) twice weekly and tap water to drink for 4 weeks.

##### **Group II :** (vehicle group)

The rats received olive oil injection S.C. (1-2 ml) twice weekly and tap water to drink for 4 weeks.

##### **Group III :** (DOCA-salt group)

Uninephrectomized rats received DOCA in a dose of 20 mg/kg S.C. (1-2 ml) twice weekly for 4 weeks and 1% NaCl to drink [3].

##### **Group IV:** DOCA-salt + rosiglitazone (DOCA-salt + Rosi.)

The uninephrectomized rats received DOCA-salt as mentioned in group III. Simultaneously, PPAR- $\gamma$  activator rosiglitazone in a dose of 5mg/kg/day orally (entragastric by gastric tube) was given for 4 weeks [4].

##### **Group V:** DOCA-salt + fenofibrate (DOCA-salt + Feno.)

The uninephrectomized rats received DOCA-salt as mentioned in group III. Simultaneously, PPAR- $\alpha$  activator fenofibrate in a dose of 100mg/kg/day orally (entragastric by gastric tube) was given for 4 weeks [4].

##### **Group VI:** DOCA-salt + rosiglitazone 1+fenofibrate 1 (DOCA-salt + Rosi.1+Feno.1)

The uninephrectomized rats received DOCA-salt as mentioned in group III. Simultaneously, combined low doses of PPAR- $\gamma$  (rosiglitazone) and PPAR- $\alpha$  (fenofibrate) activators were given orally (entragastric by gastric tube) in doses of 2mg/kg/day and 30mg/kg/day respectively for 4 weeks [5].

##### **Group VII:** DOCA-salt + rosiglitazone 2+fenofibrate 2(DOCA-salt + Rosi.2+Feno.2)

The uninephrectomized rats received DOCA-salt as mentioned in group III. Simultaneously, combined PPAR- $\gamma$  (rosiglitazone) and PPAR- $\alpha$  (fenofibrate) activators were given orally (entragastric by gastric tube) in doses of 5mg/kg/day & 100mg/kg/day respectively for 4 weeks [3].

#### **Measurements**

##### **Blood pressure measurement**

Blood pressure of the rats in all groups were measured and recorded before the start of medication and twice weekly for the next 4 weeks.

Blood pressure was recorded using the tail-cuff method (rat tail blood pressure recorder - Ugo Basile S.r.l. Biological Research Apparatus)

#### Heart/Body Weight Ratio

After scarifying animals in all groups, Heart/Body weight ratio (mg/g) was calculated.

#### Biochemical analysis

Blood sample for biochemical analysis were withdrawn before the start of medication for rats in all groups, and at the end of medication period for each group.

#### The biochemical parameters include

1. Serum electrolytes level: Na<sup>+</sup>, K<sup>+</sup>
2. Serum glucose level.
3. Lipid profile: serum level of cholesterol, LDL, HDL
4. Liver enzymes: ALT and AST

#### Histopathological study

At the end of the experimental period for all groups, all animals were decapitated and the hearts and arteries were isolated. The isolated aorta separated from adjacent tissues and placed in 10% formalin. Sections of aorta were cut at a thickness of 5-6 µm and stained with haematoxylin-basic fuchsin-picric acid stain [6]. The weight of the heart was measured in milligrams. The left ventricle was incised longitudinally then the thickness of myocardium is measured in millimeters using vernier calliper. Using Olympus BX40 microscope connected to computer system using "Leica Qwin 500" software, images for aorta and left ventricle sections were obtained. The "interactive measurements" were used to calculate thickness of aortic media (for each animal (slide) five readings were obtained).

**Table 1: The systolic arterial blood pressures (mmHg) at the end of the 4<sup>th</sup> week in all groups**

Groups	1st wk	2nd wk	3rd wk	4th wk
I    Control	101 ±2.4	101 ±1.4	100.8 ±1.7	100.2 ±2.5
II   Vehicle	100 ±1.4	101 ±2.6	102 ±1.9	101 ±1.2
III   DOCA	101 ±2.4	137 ±3.9 #	159 ±7.5 #	208 ±1.4 #
IV   DOCA+Rosi (5mg/kg)	100.8 ±1.7	133.8 ±2.6	154.8 ±4.5	172 ±0.9 *
V   DOCA+Feno (100mg/kg)	101 ±1.4	138.4 ±4.7	158.4 ±2.8	188 ±3.4 *
VI   DOCA+Rosi1+Feno1 (2mg/kg & 30mg/kg)	100.2 ±2.5	132.5 ±2.7 *	149 ±1.4 *‡	162.7 ±2.7 *‡ §
VII   DOCA+Rosi2+Feno2 (5mg/kg &100mg/kg)	99 ±2.8	134.4 ±3.6	150.2 ±0.8 *	173 ±5.1 *

N.B: Data are summarized using mean ± SD (n=6),

# Significant in comparison to Control Group (P<0.05)

\* Significant as compared to DOCA Group (P<0.05)

‡ Significant as compared to DOCA+ Rosi. Group (P<0.05)

§ Significant as compared to DOCA+Rosi.2+Feno.2 Group (P<0.05)

Vehicle = Olive oil (S.C injection)

DOCA = deoxycorticosterone acetate (S.C injection), Rosi= Rosiglitazone, Feno= Fenofibrate.

#### Results of biochemical analysis (Table 2)

No significant changes were observed between Group (I) and (II) (Control and Vehicle groups) in all biochemical parameters measured. In comparison to control group, group III (DOCA-salt group) at the end of the 4<sup>th</sup> week, showed a significant increase in the serum level of Sodium, glucose and AST while a significant reduction in the serum level of Potassium was observed. The lipid profile analysis revealed no significant change in the Cholesterol, LDL and HDL serum levels. In comparison to group III (DOCA-salt group), group IV (DOCA-salt + Rosi) at the end of the 4<sup>th</sup> week, showed a significant decrease in Sodium and AST serum level. Serum glucose level showed insignificant decrease, while the lipid profile showed significant elevation of Cholesterol and HDL serum levels with no significant change in LDL levels.

In group V (DOCA + Feno), serum Potassium level was significantly increased while there was no significant difference in the serum level of Sodium and glucose as compared to DOCA-salt group.

#### Statistical analysis

Computer software package SPSS 15.0 was used in the analysis. For quantitative variables, mean (as a measure of central tendency), standard deviation (as measures of variability) were presented. Frequency and percentages were presented for qualitative variables. ANOVA test, Independent T-test, One-way and Post-Hoc test were used to estimate differences in quantitative variables. P Value < 0.05 is significant.

#### RESULTS

##### Blood pressure measurement

DOCA injection in the uninephrectomized rats results in gradual significant increase in the systolic blood pressure in the 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> week as compared to the Control and Vehicle groups (Group I and II respectively). Administration of Rosiglitazone or fenofibrate (Group IV & V respectively) results in significant decrease in the systolic blood pressure in the 4<sup>th</sup> week as compared to DOCA-salt group. Significant decrease in systolic blood pressure was observed in the 3<sup>rd</sup> and 4<sup>th</sup> weeks of administration of combined full doses of rosiglitazone and fenofibrate (Group VII) as compared to DOCA-salt group. Significant decrease in the systolic blood pressure was observed in the 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> weeks of administration of combined low doses of rosiglitazone and fenofibrate (Group VI) in relation to DOCA-salt group.

By comparing the results of systolic blood pressure in Group (VI) with those in Group (VII) there was a significant decrease of systolic blood pressure in the 4<sup>th</sup> week. By comparing the results of systolic blood pressure in Group (VI) with those in Group (IV) a significant decrease in the systolic blood pressure was found in the 3<sup>rd</sup> and 4<sup>th</sup> weeks.

N.B: Data are summarized using mean ± SD (n=6),

# Significant in comparison to Control Group (P<0.05)

\* Significant as compared to DOCA Group (P<0.05)

‡ Significant as compared to DOCA+ Rosi. Group (P<0.05)

§ Significant as compared to DOCA+Rosi.2+Feno.2 Group (P<0.05)

Vehicle = Olive oil (S.C injection)

DOCA = deoxycorticosterone acetate (S.C injection), Rosi= Rosiglitazone, Feno= Fenofibrate.

Significant decrease in serum Cholesterol, LDL and ALT level was observed in comparison to DOCA-salt group.

The serum electrolytes of Group VI (DOCA + Rosi.1+Feno.1) at the end of the 4<sup>th</sup> week revealed highly significant decrease in Sodium and a significant increase in Potassium level as compared to DOCA-salt group. No significant change in the serum Glucose level was observed, while the lipid profile showed significant elevation in HDL and Cholesterol level, and no significant change in the level of LDL as compared to DOCA-salt group. The liver enzyme, AST showed a highly significant decrease less than one fold (normalized), as compared to DOCA-salt group. Comparing group (VI) with group (V) revealed significant decrease in the serum level of Sodium, Potassium and AST, while in the lipid profile Cholesterol, LDL and HDL level showed a significant increase. (Table 2)

In Group VII (DOCA + Rosi.2+Feno.2) significant decrease in the

serum level of Sodium and significant increase in the Potassium were found compared to DOCA-salt group. No significant difference in serum Glucose level, while the lipid profile showed significant elevation in HDL and cholesterol as compared to DOCA-salt group. The liver enzymes, ALT and AST showed significant decrease less than one fold (nearly back to normal level), as compared to DOCA-

salt group. Comparing biochemical changes in this group (VII) and group (V) revealed significant decrease in serum level of Sodium and Potassium. In lipid profile, Cholesterol, LDL and HDL levels showed a significant increase while the liver enzyme AST showed significant decrease.

**Table 2: The biochemical parameters at the end of the 4<sup>th</sup> week in all groups**

S.no	Groups	Na mEq/ml	K mEq/ml	GL mg/dl	Chol. mg/dl	LDL mg/dl	HDL mg/dl	ALT IU/ml	AST IU/ml
I	Control	146.3±1	4.8 ±4.3	132.7±5.2	72.1±4.1	28.2±4.3	31.2±4.4	9.7±1	34.3±2.7
II	Vehicle	144 ±2	4.7 ±3.2	136 ±2.4	72.2±3.2	29.4±3.2	31.5±3.3	9.5±2	31.4±2.3
III	DOCA	151.2±1.2#	4.3±0.24#	144±2.8#	71.2±2.6	32.2±17.7	35.8±10.8	11±1.3	42.8±0.6#
IV	DOCA+Rosi.(5mg/kg)	145.8±1.3*	4.3±0.22	141.2±4.4	79±2.4*	27.2±6.2	55.8±7.6*	12±2.3	34.2±5.6*
V	DOCA+Feno.(100mg/kg)	150.2±0.98	5.3±0.28*	141.2±5.8	62.3±1.6*	20±6.6*	34±6.7	9.3±0.5*	43±2.0
VI	DOCA+ Rosi1+Feno1 (2mg/kg & 30mg/kg)	144±1.5*§	4.7±0.15*§	141.7±5.4	76±4.4*§	29.7±4.4§	53.8±7.5*§	12±0.52	29.8±1.6*§
VII	DOCA+ Rosi2+Feno2 (5mg/kg &100mg/kg)	143±1.1*§	4.7±0.42*§	140.8±5.3	76.2±4.4*§	27.7±1.5§	47.7±2.3*§	9.7±0.52*	25.4±1.1*§

**N.B:** Data are summarized using mean ±SD (n=6)

Significant (P<0.05)

# Significant in comparison to Control Group

§ Significant as compared to DOCA+ Feno. Group

\* Significant as compared to DOCA Group

**N.B:** GL = serum glucose, Chol. = serum cholesterol, Vehicle = Olive oil (S.C injection)  
DOCA = deoxycorticosterone acetate (S.C injection), Rosi= Rosiglitazone, Feno= Fenofibrate.

#### The Histopathological study results (Table 3, Figures 1- 8)

DOCA injection in the uninephrectomized rats (Group III) (DOCA-salt group) resulted in significant increase in the myocardial thickness (45.9%), heart/body weight ratio (56%) and thickness of

Aortic media (71.2%) in comparison to the control and Vehicle group (Table 3, Fig. 1&2). Also, the microscopic examination of left ventricular sections showed marked myocardial hypertrophy with proliferation of myocytes in comparison to the control and Vehicle group. (Fig. 3&4)

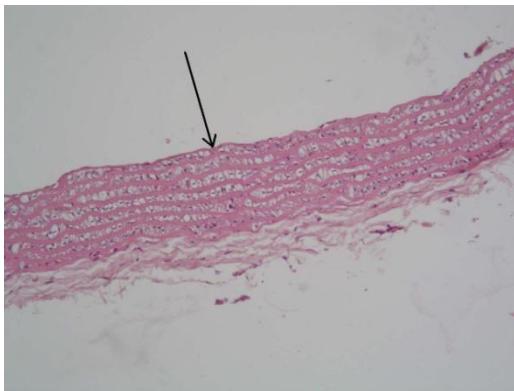


Figure 1: Section showing normal Aorta in control group (x200)

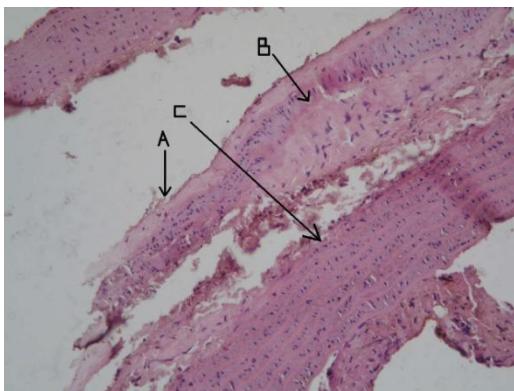
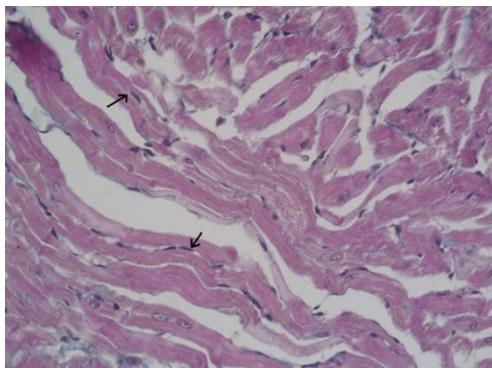


Figure 2: Section in Aorta in DOCA-salt group (x200)

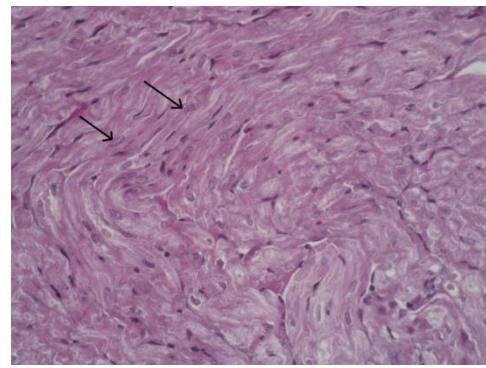
(A)The intima showed disruption and cellular infiltration

(B)subintimal increase in connective tissue with atheromatous plaque

(C) The media showed marked hypertrophy and thickening with proliferation of myocytes.



**Figure 3:** Cross section showing normal myocardium in *control group* (x400)



**Figure 4:** Cross section in myocardium in *DOCA-salt group* (x400)

The myocardium showed marked hypertrophy and thickening with proliferation of myocytes.

**Table 3:** The myocardial thickness (millimeters), heart/body weight ratio (mg/g) and aortic media thickening (micrometer) at the end of the 4<sup>th</sup> week in all groups.

Groups	Myocardial thickness (mm)	Heart/body weight ratio (mg/gm)	Aortic media thickness (μm)
I Control	3.7±0.26	2.5±0.26	95.98±2.46
II Vehicle	3.5±0.36	2.4±0.6	93.26±3.63
III DOCA	5.4 ±0.5#	3.9 ±0.28#	163.37 ±5.64#
IV DOCA+Rosi (5mg/kg)	5.3 ±0.52	3.8 ±0.28	106.5 ±6.51*
V DOCA+Feno (100mg/kg)	4.7 ±0.6*	2.9 ±0.23*	121.87±6.84*
VI DOCA+Rosi1+Feno1 (2mg/kg & 30mg/kg)	4.9 ±0.38*§	2.8 ±0.11*§	108.13 ±5.68*‡
VII DOCA+Rosi2+Feno2 (5mg/kg & 100mg/kg)	4.8 ±0.27*§	2.8 ±0.27*§	107.54 ±6.78*‡

NB: Data are summarized using mean ± SD (n=6)

# Significant in comparison to Control Group (P<0.05)

\* Significant as compared to DOCA Group (P<0.05)

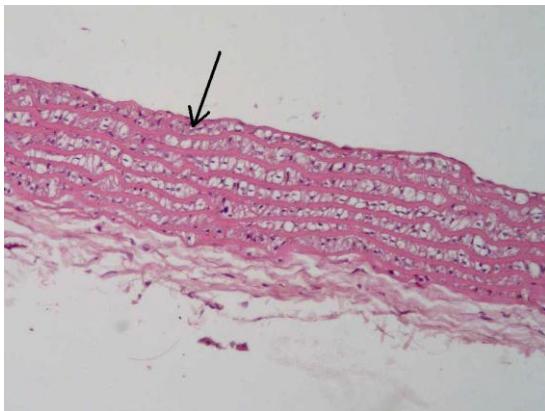
§ Significant as compared to DOCA+ Rosi. Group (P<0.05)

‡ Significant as compared to DOCA+ Feno. group (P<0.05)

Vehicle = Olive oil (S.C injection)

DOCA = deoxycorticosterone acetate (S.C injection), Rosi= Rosiglitazone, Feno= Fenofibrate.

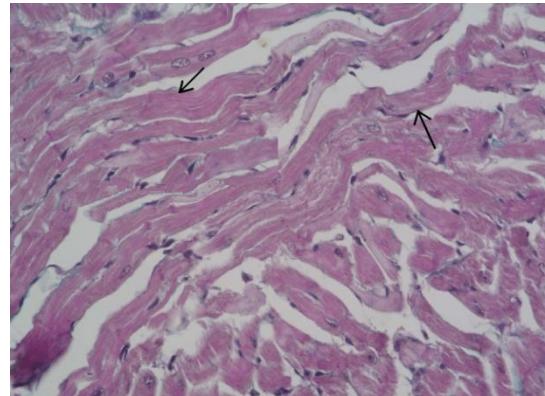
By comparing the results of the myocardial thickness and heart/body weight ratio after rosiglitazone administration in Group IV with those of Group III (DOCA-salt group), there were no significant difference between both groups (Table 3). However, a significant decrease in the Aortic media thickness was detected by 34.8% reduction than that in Group III (table 3, Fig. 5).



**Figure 5:** Section in Aorta in *DOCA+Rosi group* (x200)

Intact intima, the media showed mild hypertrophy and thickening with no proliferation of myocytes

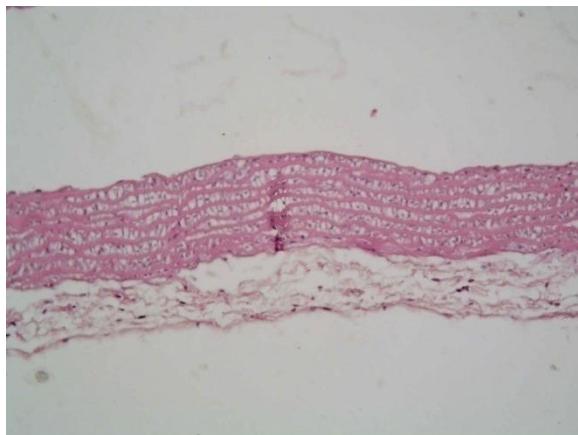
Fenofibrate administration (Group V) resulted in significant decrease in the myocardial thickness (12.3%) and heart/body weight ratio (25.6%) as compared to Group III (table 3). Microscopic examination showed mild myocardial hypertrophy (Fig. 6). Also, the thickness of Aortic media showed significant decrease as compared to Group III (table 3).



**Figure 6:** Cross section in myocardium in *DOCA+Feno group* (x400)

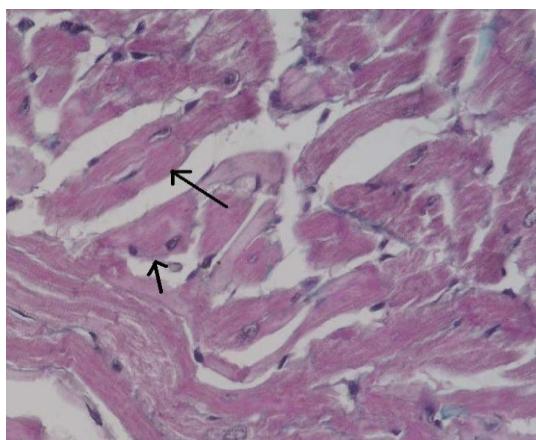
The myocardium showed mild hypertrophy and thickening with no proliferation of myocytes

Administration of combined low doses (Group VI) or full doses (Group VII) of rosiglitazone and fenofibrate resulted in significant decrease in the myocardial thickening, heart/body weight ratio and thickness of Aortic media as compared to DOCA-salt group (Table 3, Fig. 7). Also, the microscopic examination of left ventricular sections showed mild myocardial hypertrophy (Fig. 8). There was no significant difference between groups (VI) & (VII) in the histopathological results.



**Figure 7: Section in Aorta in DOCA+ Rosi1+Feno1 group (x200)**

**Intact intima the media showed mild hypertrophy and thickening with no proliferation of myocytes.**



**Figure 8: Cross section in myocardium in DOCA+ Rosi 1+Feno1 group (x400)**

**The myocardium showed mild hypertrophy and thickening with no proliferation of myocytes.**

It is to be mentioned that there was significant decrease in the myocardial thickness and heart/body weight ratio in Groups VI & VII in comparison to group IV. Also, Groups VI & VII showed significant decrease in the thickness of Aortic media in comparison to group V. (Table 3)

## DISCUSSION

In the present study, DOCA injection in the uninephrectomized rats results in gradual significant increase in the systolic blood pressure and the maximum reading is recorded in the 4<sup>th</sup> week. The administration of rosiglitazone in full dose causes significant lowering of systolic blood pressure. Also fenofibrate administration leads to significant lowering of blood pressure, but less than that manifested by rosiglitazone. The studies of Schiffrin et al. [7], Efrati et al. [8] Balsi et al. [9] and Koh et al. [10] were in agreement with these results. In contrary of the results of fenofibrate on the blood pressure, previous studies reported either no effect [11] or further elevation of blood pressure [12] in mice by concomitant treatment with fenofibrate.

Rosiglitazone showed significant vascular protective effect on blood vessels in the present work as manifested by significant decrease in the aortic media thickness compared to DOCA-salt group. The vasculoprotective effect of rosiglitazone was also showed in the studies of Wang et al. [13] Roszer and Ricote [14]. This vascular protective effect of rosiglitazone may contribute to its ability to lower the blood pressure. A number of mechanisms were suggested to explain the anti-hypertensive effect of rosiglitazone. Anti-inflammatory and anti-proliferative mechanism was suggested by Diep et al. [2]. The contribution of Endothelin-1 (ET-1) in the development of high blood pressure and vascular growth in DOCA-salt rats was demonstrated and it was reported that both PPAR activators abolished the increase of preproET-1 mRNA content in the mesenteric vasculature of DOCA-salt rats [7]. In the study of Ryan et al. [15] done on mouse model of lifelong hypertension caused by overexpression of both human rennin and human angiotensinogen transgenes (R+A+ model), they suggested that rosiglitazone may directly regulate vessel tone and thus contribute to the improved blood pressure in the R+A+ model. Moreover, Roszer and Ricote [14] mentioned that PPAR $\gamma$  activation is suggested to reduce angiotensinogen synthesis, impeding rennin-angiotensin-aldosterone system activation; this can ameliorate hypertension in obese diabetic patients.

PPAR-independent mechanism could play a role in the antihypertensive effect of PPAR activator. Nakamura et al. [16] reported that in addition to potential genomic effects of rosiglitazone in the regulation of vascular tone and blood pressure there have been reports of PPAR-independent effects of the thiazolidinediones (TZD) class of drugs that are thought to be due to activation or inhibition of ion channel activity. More specifically, ETO et al. [17] demonstrated in isolated vascular smooth muscle that rosiglitazone attenuated inward calcium currents and enhanced calcium-activated potassium currents. The net effect would cause cellular hyperpolarization and, therefore, relaxation of the vessel.

Inspite of its significant vasculoprotective effect, rosiglitazone have no role as a cardioprotective and this is manifested in the present work by the myocardial thickness, heart/body weight ratio and the histopathological cardiac myocytes proliferation which were almost equal to the results of DOCA-salt group. Left ventricular hypertrophy and cardiac dysfunction was reported as an unfavorable effect of rosiglitazone in previous studies. [18, 9]

The mechanism for the cardiac hypertrophy induced by rosiglitazone was suggested to be either through PPAR- $\gamma$  receptor activation or PPAR- $\gamma$  independent effects. The work of Son et al. [19] reported that Over-expression of PPAR- $\gamma$  in the heart resulted in cardiac dysfunction. On the other hand Duan et al. [20] suggested that the cardiac hypertrophy caused by rosiglitazone in mice does not completely require PPAR- $\gamma$  in cardiomyocytes, as rosiglitazone induced cardiac hypertrophy in CM-PGKO mice (a cardiomyocyte-specific PPAR- $\gamma$  knockout mouse model).

On the other hand, a more obvious cardio-protective role for fenofibrate in comparison to rosiglitazone was observed in the present work and manifested by significant decrease in the myocardial thickness, heart/body weight ratio and significant reduction in myocytes proliferation in the histopathological results as compared to DOCA-salt group. These results were in agreement with the results of Liang et al., [21] and Irukayama-Tomobe et al., [22] studies on the effect of fenofibrate treatment on ventricular hypertrophy.

Many mechanisms of cardioprotective effect of fenofibrate were suggested in different studies. Inhibition of ET-1 promoter activity, preproET-1 mRNA expression, and hypertrophy in ET-1-stimulated cardiomyocytes [22]. LeBrasseur et al., [11] showed that the cardioprotective effect of fenofibrate could be attributed to its suppression of aldosterone-mediated increase in myocyte matrix metalloproteinase activity and extracellular signal-regulated kinase phosphorylation which may contribute to ventricular remodeling and left ventricular hypertrophy by impairing the integrity of the interstitial matrix. Duhaney et al., [23] using both *in vivo* (wild-type and PPAR  $\alpha$ -deficient mice) and *in vitro* studies (cultured adult rat cardiomyocytes), reported that fenofibrate exerts beneficial effects

on chronic, progressive cardiac remodeling and hypertrophy by PPAR  $\alpha$ -independent actions.

Both vasculoprotective and cardioprotective effects of PPAR $\gamma$  and PPAR $\alpha$  (respectively), explain the rationale of using the combination of rosiglitazone and fenofibrate in the present study. The combined rosiglitazone and fenofibrate administration in full dose in this study results in reduction of systolic blood pressure; decrease in cardiac hypertrophy and decrease aortic media thickness.

It is to be mentioned that several potent dual PPAR-alpha/gamma agonists (glitazars) have been clinically developed and it was expected that these agents could modulate cardiovascular risk by improving endothelial reactivity, reducing blood pressure, and improving lipid profiles. However, the emergence of different types of toxic effects in clinical trials has resulted in their failure to progress beyond phase III development, they may have also too much PPAR  $\alpha$  activity, which might be carcinogenic<sup>[24]</sup>.

Trying to avoid the known blood volume expansion present with rosiglitazone and its recent side effects appeared on the myocardium in full therapeutic dose, the effect of combined low doses of rosiglitazone and fenofibrate was studied in the present work. The results revealed more significant decrease in blood pressure than that resulted from combined full dose of the two drugs with a good protective effect on vascular media and myocardial thickness as compared to DOCA-salt group. In addition, the combined low doses of rosiglitazone and fenofibrate restored the normal sodium and potassium serum levels, preserved the normal lipid profile with no change in liver enzymes.

Ciuceis et al.,<sup>[5]</sup> study on combined low doses of rosiglitazone and fenofibrate, concluded that the beneficial effects of dual PPAR- $\alpha$  and PPAR- $\gamma$  activation were obtained with a small but significant reduction of angiotensin II-induced blood pressure increase. In addition, cardiac hypertrophy, was prevented only when 2mg/kg/day dose of rosiglitazone was coadministered with the PPAR $\alpha$  activator fenofibrate. Also, the combination of fenofibrate and rosiglitazone reduced the Media/Lumen ratio of resistance arteries whereas no effects were observed when either drug was given individually.

From the present study, it is concluded that the dual activation of PPAR- $\gamma$  and PPAR- $\alpha$  may be potentially beneficial in prevention of hypertension-induced cardiovascular damage. Using a combination of low doses of each activator, might result in a reduced side effect profile.

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**Conflict of Interest:** None declared.

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