Bull. Egypt. Soc. Physiol. Sci. Vol. (42). Issue (3), 294-302

Bull. of Egyp. Soc. Physiol. Sci.

(Official Journal of Egyptian Society for Physiological Sciences)

(pISSN: 1110-0842; eISSN: 2356-9514)

Effect of Fenofibrate on biochemical and vascular reactivity changes in aged rats

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Submit Date: 06 Feb. 2022
Revise Date: 16 March 2022
Accept Date: 20 March 2022

Keywords

- Aging
- Lipid profile
- Oxidative stress
- Vascular.

Abstract

Background: Risk of vascular hemodynamic impairment increases with age. So, finding a new therapeutic approach to counter the age-related vascular complications has been a challenge. Hence, we evaluated the therapeutic effects of fenofibrate (FEN) in ageing. We also studied the FEN anti-ageing effects, and the possible molecular mechanisms that may clarify these effects. **Methods:** Thirty male rats were equally divided into three groups: 1- Control group: Received (1% CMC) via gastric lavage, 2- aged non treated group: Received (1% CMC) via gastric lavage, and 3- Aged (FEN) treated group: received FEN (30 mg/kg) dissolved in (1% CMC) via gastric lavage for 7 weeks. At the end of study, serum lipid profile**,** inflammatory and oxidative stress markers were performed. Lastly, rats were subjected for measurement of invasive mean arterial blood pressure (MABP) and vascular reactivity to NE and Ach. **Results:** Aging resulted in dyslipidemia and elevation of inflammatory biomarkers, with altered oxidative stress markers. Increased MABP and decreased vascular reactivity to NE and Ach were also notice. FEN restored significantly aged related biochemical and vascular pathophysiological changes. **Conclusion**: FEN could be a good candidate for cardiovascular deficits due to ageing via amelioration of dyslipidemia, inflammation, attenuation of oxidative stress, reduction of MABP and improvement of vascular reactivity.

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INTRODUCTION

Aging is a complicated multifactorial process associated with progressive physiological changes with subsequent multiple dysfunctions in the body systems. Aging is accompanied by lipid metabolism disorder and a complex of inflammatory processes involves the release of reactive oxygen species (ROS) and inflammatory cytokines which contribute to atherosclerotic cardiovascular disease (1).

Oxidative stress has an essential role in age related vascular impairment as a result of marked production of (ROS) without a compensatory increase in the activity of antioxidant enzymes. Moreover, oxidative stress is considered a crucial risk factor that contributes to vascular endothelium dysfunction by enhancing free radicals production with subsequent vascular smooth muscle damage. These vasculature changes caused by increasing oxidative stress with aging are the key mechanism that clarify impairment of vascular endothelium dependent dilation to chemical stimuli due to lack of nitric oxide (NO) production (2).

Fenofibrate (FEN) is an oral drug belongs to a fibrate class used to reduce high cholesterol and triglyceride levels. So it is often used in the patient with sever hypercholesterolemia and mixed dyslipidemia to reduce accumulation of cholesterol in the blood vessels with subsequent serious health problems as atherosclerosis (3)**.**

FEN is a strong activator of peroxisome proliferator-activated receptor-α (PPAR α), which is the most important mechanism that mediate its lipid-modifying effects. In addition, FEN has a non-lipid, pleiotropic effect that considers the main molecular mechanism behind improvement of microvascular complications. Pleiotropic effect of FEN is mediated by reducing levels of numerous pro-inflammatory markers, and improving flow-mediated dilatation by enhancing release of nitric oxide (NO) (4).

In our study, we investigate the effect of FEN administration on age-related biochemical and vascular hemodynamic changes in aged rats

Material and Methods

After obtaining approval from "Research Ethical Committee", Faculty of Medicine, Menoufia University, Egypt, the study was carried out according the Guide for Care and Use of Laboratory Animal, 8 th edition(National Research Council 2011)

Animals

Thirty male albino rats weighting 250-300 gram of local strain were used in this study. Rats were housed in wire mesh, fully ventilated cages (80x40x30 cm), 5 animals / cage. They were given free access to water and chow throughout the study period. All rats were acclimatized for 2 weeks before the start of the experiment.

Experimental design

The animals divided into three groups

(10 /group)

Group I: control group: Adult rats received 1% carboxymethylcellulose (1% CMC) via gastric lavage

Group II: Aged non-treated group: Aged rats (age 19 – 21 month) received (1% CMC) via gastric lavage

Group III: Aged FEN-treated group (FEN): Aged rats received FEN (30 mg/kg) in 1% CMC daily for 7 weeks (5).

Biochemical Analysis

After 7 weeks; the end of study, fasting blood samples were collected from rats retro-orbital venous plexus using heparinized capillary tubes.

Samples were centrifuged for 15 minutes at a rate of 3000 rpm. The serum was collected and used for estimation of the lipid profile (total cholesterol (TC), low density lipoprotein (LDL-C), high density lipoproteins (HDL-C) and triglycerides (TGs) using a colorimetric enzymatic method (Bioclin Diagnostic company, Egypt). By the formula of (TG/5) very low density lipoprotein (VLDL-C) could be estimated (6).

Malondialdehyd (MDA) and activity of superoxide dismutase (SOD) were measured using the conventional colorimetric (QuantiChrom™, BioAssay Systems, USA. According to the manufacturer's instruction. Tumour necrosis Factor (TNF-α) and interleukin 6 (IL6) were estimated by using ELISA kit (Quantikine, Abcam company Cambridge, UK for TNF-α and Sigma Chemical Company, USA for IL-6

Measurement of invasive mean blood pressure (MABP) and vascular reactivity

Under a septic condition, rats were anesthetized with (2% pentobarbital sodium, 50 mg/kg, i.p.) and placed on a rodent surgical table. The aortic artery (red in color) was exposed and cannulated by using a cannula filled with heparinized saline and the other end of cannula was connected to a pressure transducer (Narco -biosystem model PR 1500, P/N 700–1010) and the recording 4 channel physiography (MK-III-S Narco- biosystem, USA). By measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP), (MABP) was calculated using this equation:

$$\textbf{MABP} = \frac{SBP + DBP}{2}$$

Vascular reactivity (VR) to norepinephrine (NE) and acetylcholine (Ach).

Rats were atropinized by atropine sulphate (1mg/Kg i.v.) and ganglion blockaded by hexamethonium (10mg/Kg i.v.) to avoid the reflex changes that may occur in the heart rate and vasomotor tone. The femoral vein was cannulated for NE (200 ng/rat) and Ach ($1x10^{-8}$) injection. Before drug injection MABP was recorded as a baseline level and then recorded after drugs injection. In vivo aortic vascular reactivity to NE and Ach (El-Gomhoryia company, Egypt) was measured by the increase in the magnitude of MABP and the percentage of increase (7).

Statistical analysis

Results are expressed as mean ± standard deviation (SD). Analysis of Variances (ANOVA) was used for statistical analysis of the different groups, using Origin® software and the probability of chance (p values). P values < 0.05 were considered significance

Results

Fasting serum lipid profile

Table 1: The cholesterol level in aged-non treated group was significantly higher than control group ($P < 0.001$) while its level in FEN group was significantly lower than aged group ($P < 0.001$) but still significantly higher than control group ($P < 0.05$).

The triglycerides (TGs) and VLDL-C mean values in aged-non treated rats were non significantly changed in comparison to control rats ($P > 0.05$), and in FEN-treated rats were also non significantly decreased when compared to aged rats ($P > 0.05$) and insignificantly increased in comparison to control rats ($P > 0.05$).

The HDL-c mean value in aged-non treated group was significantly lower than control group ($P < 0.001$). However, FEN group reported a higher level of HDL-c than aged- group ($P < 0.001$) but insignificantly changed than control group ($P > 0.05$). Regarding LDL-c mean value, the untreated aged group was significantly higher than control group ($P < 0.001$). On the other hand, FEN significantly decreased the LDL-c level compared

with untreated aged group ($P < 0.001$), but insignificantly changed than control group ($P > 0.05$).

Oxidative stress and pro-inflammatory cytokines markers

Table 2: IL6 (pg/ml) and TNF-α (ng/ml) mean values were significantly higher in aged-untreated group ($p < 0.001$) than control group. On the contrast, FEN administration significantly decreased IL6 and TNF-α ($p < 0.001$) compared with aged-untreated group and significantly increased their mean values than control group ($P < 0.05$).

MDA (nmol/ml) mean value in aged untreated group was significantly elevated than control group ($p < 0.001$). FEN treatment significantly decreased MDA level than the untreated group ($p < 0.05$), but still significantly higher than the control group ($P < 0.001$). SOD (U/ml) level was significantly decreased in aged-untreated group ($p < 0.001$) than control group. FEN-treated group showed significant elevation in the SOD activity compared to the untreated group ($p < 0.05$) but still significantly lower than the control group ($P < 0.001$).

(MABP) and vascular reactivity (VR) to NE and Ach.

Table 3: The MABP was significantly increased, ($p < 0.001$) in aged untreated group compared with control group. However, MABP in FEN group was significantly lower than aged nontreated group ($p < 0.001$) but still significantly higher than control group ($p < 0.001$).

Regarding vascular reactivity to NE, the MABP was significantly increased ($p < 0.001$) in aged untreated group than control group. MABP with NE in FEN group was significantly lower than aged non treated group ($p < 0.05$) but still significantly higher than control group ($p < 0.001$). The % of change of MABP was significantly decreased ($p < 0.001$) in aged untreated group compared with control group. % of change of MABP in FEN group was significantly higher than aged nontreated group ($p < 0.001$) but still significantly lower than control group ($p < 0.001$). **(Table 3 and Fig 1**)

Regarding vascular reactivity to Ach, the MABP was significantly elevated ($p < 0.001$) in aged untreated group relative to control group. MABP with Ach in FEN group was significantly lower than aged nontreated group ($p < 0.001$) but still significantly higher than control group ($p < 0.001$). The % of change of MABP to Ach was significantly decreased ($p < 0.001$) in untreated group compared to control group. % of change of MABP to Ach in FEN group was significantly higher than aged nontreated group ($p < 0.001$) but still significantly lower than control group ($p < 0.001$). **(Table 3 and Fig 2**).

Table1. Serum lipid profile in the studied groups

	Control group	Aged non-treated group	Aged Fenofibrate-treated group (FEN))
TC (mg/dl)	62.22±1.84	90.78±0.81*	65.3±2.7*@
TGs (mg/dl)	59.7±1.2	63.4±0.91	61.6±1.1
HDL-C (mg/dl)	27.22±0.95	16.9±1.4*	28.47±5.4@
LDL-C (mg/dl)	20.6±0.73	29.9±1.3*	19.15±1.3@
VLDL-C(mg/dl)	12.4±1.5	13.9±1.1	13.2±1.8

Data are expressed as mean ±SD (n=10) .Significance was considered when P values <0.05. TC: total cholesterol; TGs: triglycerides; HDL-C: high density lipoproteins; LDL-C: low density lipoprotein; VLDL-C: very low density lipoprotein. The marks * and @ indicate that values are significantly different when compared to the corresponding values of the control and the aged non treated groups respectively

Table 2: Inflammatory cytokines and oxidative stress markers in the studied groups.

	Control	Aged non treated group	Aged fenofibrate treated group (FEN)
IL6 (pg/ml)	9.2±0.8	16.3±1.4*	11.1±0.42*@
TNF (ng/ml)	9.7±1.1	14.9±0.82*	11.5±0.46*@
MDA (nmol/ml)	25.2±1	32.9±2.1*	28±1.6*@
SOD (U/ml)	5.6±0.22	3.02±0.7*	3.9±0.5*@

Data are expressed as mean ±SD (n=10) .Significance was considered when P values <0.05. IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha; MDA: malondialdehyde; SOD: superoxide dismutase. The marks * and @ indicate that values are significantly different when compared to the corresponding values of the control and the aged non treated groups respectively.

Table : (MABP) and vascular reactivity to NE and Ach in the studied groups.

	Control	Aged non treated group	Aged Fenofibrate - treated group (FEN)
MABP	78.8±1.4	114.5±1*	92.1±2.6*@
MABP after NE	110.6±2	129.8±1.4*	120.3±1.9*@
% of change of MABP	+40.35±0.8	+13.4±0.82*	+30.6±0.61*@
MABP after Ach	39.2±4.9	96.8±1*	53.7±1.4*@
%of change of MABP	-50.2±0.9	-15.4±0.7*	-41.7±0.6*@

Data are expressed as mean ±SD (n=10) .Significance was considered when P values <0.05. **MABP**: mean arterial blood pressure; NE: norepinephrine; Ach: acetylcholine. The marks * and @ indicate that values are significantly different when compared to the corresponding values of the control and the aged non treated groups respectively.

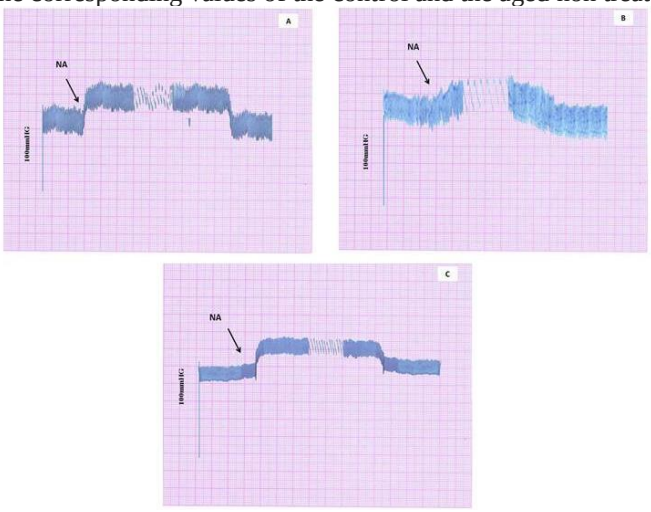

Fig 1: Vascular reactivity to NE on (A) control group, (B) aged non treated group and (C) and aged FEN treated group.

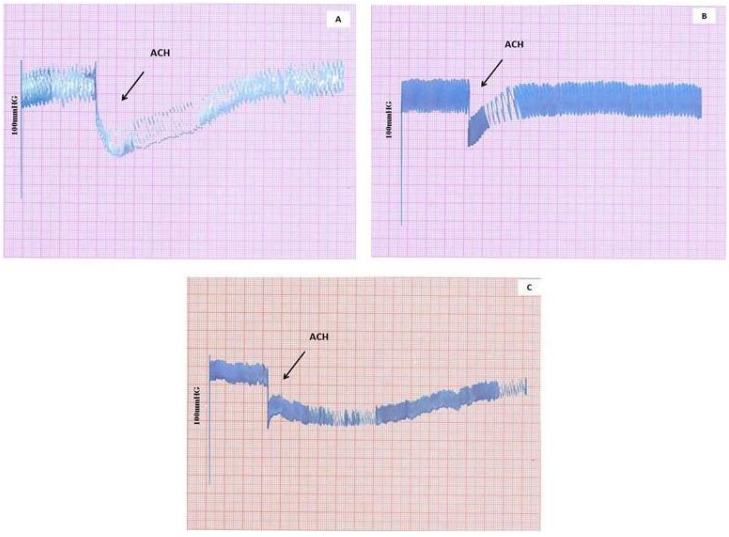

Fig 2: Vascular reactivity to Ach on (A) control group, (B) aged non treated group and (C) aged FEN treated group

Discussion

Ageing is commonly associated with metabolic disorders characterized by serious complications such as the co-existence of dyslipidemia and hypertension (8). In this study, serum cholesterol, and LDL-C were elevated in the aged rats than young control ones. These results were in agreement with previous studies by (9), who suggested that the increased level of cholesterol caused by the gradual reduction in the capacity of cholesterol clearance from plasma with ageing by reverse cholesterol transport, which is a biological process that transfers cholesterol to bile acid in the liver. Concerning the increased level of LDL-C in the aged rats**,** (10), reported that aging is associated with marked release of free fatty acids (FFAs) from adipose tissue, which results in hyperinsulinemia with massive insulin resistance and fatty acids inflow from the adipocytes to the liver to stimulate gluconeogenesis and enhance the production of low density lipoproteins**.** Studies have shown that FEN could inhibit the synthesis of cholesterol, and increase the LDL-C clearing. In addition FEN could reduce the body weight, which was indicated by inhibiting accumulation of fat in subcutaneous tissue through down regulation of STAT3 signaling which plays the main role in glucose homeostasis and body weight regulation (11).

On the other hand, plasma triglyceride was insignificantly changed in aged rats. Supporting our results, previous study of (12). In contrast, (13) have been confirmed that aging could decrease triglyceride by inhibiting activity of lipoprotein lipase in skeletal muscle and other tissues secondary to a reduction in activity of old animals. In addition, (14) confirmed that aging could increase plasma TGs by inhibiting triglyceride clearance. This variety of these results may be related to the difference in the age and or the sex of rats used in our study.

The present study revealed that treatment of aged group with FEN significantly decreased dyslipidemia, this was in agreement with (15), who mentioned that FEN administration could reduce serum cholesterol and LDL-c a with increased HDL level by its action on (PPARα) and that increases free fatty acids oxidation and decreases circulating cholesterol level and dyslipidemia. FEN action on HDL cholesterol is mediated by the PPAR-α due to its ability to induce transcriptional synthesis of the main apolipoproteins such as apo A-I and apo A-II. Moreover, FEN could stimulate cellular uptake of fatty acid and induce its conversion to acyl-CoA derivatives, and catabolism by the β-oxidation pathways, which, associated with a reduction in fatty acid and triglyceride synthesis, results in a decrease in LDL production (16)

Regarding inflammatory status, aged group showed significant elevation in serum IL-6 and TNF-α than control young group. Elevated inflammatory markers in aged rats may be due to increase in the total and visceral adiposity and, it is known that adipose tissue considers an endocrine organ, able to secrete several cytokines and adipokines such as IL-6 and TNF-α (17). Treatment of aged group with FEN caused significant improvement in the inflammatory status indicated by decreasing IL6, TNF-α levels. The anti-inflammatory effects of FEN could be attributed to PPARα activation which suppresses inflammation, mainly by inhibiting of nuclear factor kappa B (NF-κB) pathway (18). Concerning oxidative stress, aged untreated group showed a significant increase in MDA with a

significant decrease in SOD in comparison to control group. Many theories of aging have been postulated, but the most famous one is the free radical theory and generation of ROS via oxidative damage to DNA, lipids and proteins (19). Treatment of aged group with FEN caused significant improvement in the redox status by decreasing MDA level with significant increase of SOD when compared to aged group, this was in agreement with (20), who reported that, FEN not only improved serum lipid profile, but also suppressed oxidative stress markers through reduction of ROS production and lipid peroxidation.

In our work, MABP was significantly increased in aged untreated rats than control group, which was consistent with (21), who had found that elevation of ABP were consequences of overproduction of ROS and a decrease in the bioavailability of nitric oxide leading to vascular endothelial dysfunction, In addition, (22)**,** stated that blood pressure elevation may be due to diminution in the baroreceptor reflex. Treatment of aged rats with FEN could significantly decrease MABP. These results agreed with those (23), who suggested that the decreased ABP is due to its potent lipid lowering effects, antioxidant effects and its ability to increase in endothelial nitric oxide synthase that improve endothelial dependent relaxation in the microcirculation.

Aged untreated rats showed a decrease in the vascular reactivity to both vasoconstrictor (NE) and vasodilator (Ach) when compared to control group. In support with these finding (19), had reported that Atherosclerosis, oxidative stress mainly with hyperinsulinemia and glucose intolerance during the aging process contributing to vascular endothelial damage with the inability to produce vasodilators such as NO and reduce Ach-mediated vasodilation. Decreased vascular reactivity to NE in aged untreated rats is due to impaired activity of β adrenergic receptors with its vasodilator (24). Diminished endothelium-dependent relaxation, is one of the most vascular disorders had been demonstrated in ageing humans and animals, these may due to decreased number of vasodilator endothelium receptors with its diminished ability to generate NO, and reduction in the activity of guanylate cyclase enzyme; the key enzyme of NO signaling pathway in the vascular smooth muscle (25). In our study, treatment of aged rats with FEN could improve the vascular reactivity to NE and Ach. Endothelial function improvement to by FEN is mediated by increasing production of NO through activation of eNOS enzyme and by stimulating NO/cGMP signaling pathway. So, FEN restored the balance of endothelium dependent relaxation and constriction by suppression the activity of cyclooxygenase (COX-1 and COX-2) and enhancing production of NO and antioxidant capacity of the vessel wall (26). So, the use of fenofibrate appears to be an important issue helping to reduces hyperlipidemia, inflammation, oxidative stress and ageing associated hypertension and endothelial damage.

Conclusion

Fenofibrate administration provides protection against aged related vascular impairment primarily by improving dyslipidemia and indirectly by attenuation of inflammation and oxidative stress. Therefore, our findings suggest that fenofibrate is a useful anti-aging agent.

Acknowledgement

We acknowledge to Eman Ghobashy, the technician of central lab at Faculty of Medicine, Menoufia University, Egypt for her helping to perform the biochemical assay

CONFLICT OF INTERESTS

No conflict of interests

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