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Comparative Study on Effect of Fenofibrate and Simvastatin in Streptozotocin Induced Diabetic Albino Rats

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ABSTRACT

Background: Diabetes mellitus is one of the most common diseases in the world and number of patients with this disease increases every day. This disease with long time leads to harmful effects and has many complications as increase in blood pressure, disturbance in kidney functions and increase in blood lipids. It is, therefore, important to search for drugs which prevent harmful effects that result from diabetes mellitus. **Objective:** To study the effect of pioglitazone, fenofibrate and simvastatin treatment on diabetic albino rats. **Materials and methods:** A total number of 80 male albino rats weighing 150–200 g were obtained from Animal House, Assiut University (Assiut, Egypt) was used. They were housed at ordinary room temperature, exposed to natural daily light-dark cycles, fed with standard laboratory diet pellets and were given tap water. The standard diet was obtained from Animal Experimental Central.

Results: Serum superoxide dismutase (SOD) increased significantly in diabetic rats treated with pioglitazone and diabetic rats treated with fenofibrate or simvastatin. Combination therapy of pioglitazone and simvastatin or fenofibrate have no synergistic effect on serum SOD. Serum glutathione (GSH) increased significantly in the diabetic rats treated with pioglitazone and the diabetic rats treated with fenofibrate or simvastatin. Combination therapy of pioglitazone and simvastatin or fenofibrate have no synergistic effect on serum GSH.

Conclusion: The present study showed that treatment with fenofibrate or simvastatin did not increase body weight or lower blood glucose level of the diabetic albino rats significantly, but they improved significantly blood pressure, lipid profile, and serum level of antioxidants (GSH and SOD).

Keywords: Diabetic albino rats, Fenofibrate, Simvastatin, Streptozotocin.

INTRODUCTION

Nowadays diabetes has become an alarming to the public health globally and day by day its prevalence is getting severe. Recent statistics showed that 4% of the world population are affected by diabetes and this matter is very alarming because this percentage will raise to 5.4 % in 2025. By 2030, this disease may become the 7th leading cause of death [(1)]. Diabetes is a chronic disease that is responsible for long-term tissue damage and complications such as liver and kidney dysfunctions. It is often, associated with serious diseases life organ damage [(2)]. Diabetes mellitus is associated with a marked increase in the risk of coronary heart disease (CHD) or stroke (by a factor of two to three compared with non-diabetic patients) and cardiovascular disease (CVD), which account for the majority of deaths among patients with diabetes [(3)].

Persistent hyperglycemia in diabetes provokes excessive production of reactive oxygen species (ROS) and inflammation, which play a key role in diabetic cardiomyopathy [(4)]. Hyperglycemia induces glucose auto-oxidation and surplus generation of reactive oxygen species (ROS). Hyperlipidemia can also increase reactive oxygen species (ROS) production through stimulating nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and inducing leakage of the mitochondrial electron transport chain [(5)].

Fenofibrate is fibric acid linked to an isopropyl ester. It lowers lipid levels by activating peroxisome proliferator activated receptor alpha (PPARα). PPARα activates lipoprotein lipase and reduces apoprotein CIII, which increases lipolysis and elimination of triglyceride-rich particles from plasma [(6)]. Simvastatin is 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Simvastatin reduces cholesterol level and prevent coronary heart disease [(7)]

Treatment with combination therapy has an effect on reviving ß-cells and restoring the fluctuation in glucose level and cholesterol biosynthetic pathway. At present, various types of drugs such as biguanides, thiozolidinediones, and sulfonylureas are used to treat diabetes. To control diabetes with cardiovascular disease (CVD) and other complications, monotherapy of these drugs are not enough [(8)]. As a result, combination therapy has become very popular for controlling glucose level [(9)] and inhibiting cholesterol level [(3)].

The aim of the present study was to evaluate the effect of fenofibrate and simvastatin in diabetic albino rats regarding these parameters: body weight, random blood glucose, lipid profile, blood pressure, detection of the antioxidant activity of both drugs plus pioglitazone.

MATERIALS AND METHODS

Experimental animals: A total number of 80 male albino rats weighing 150–200 g were obtained from Animal House, Assiut University (Assiut, Egypt). They were housed at ordinary room temperature, exposed to natural daily light-dark cycles, fed with standard laboratory diet pellets and were given tap water. The standard diet was obtained from Animal Experimental Central.

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Drugs and chemicals: Streptozotocin (STZ) was purchased from Sigma Biosciences, Egypt as 1-gram pure white yellowish powder kept in cold store and refrigerator temperature (2-8°C) away from light. Fenofibrate powder was purchased from (Abbot, Egypt), simvastatin powder was purchased from (MSD, Egypt) and pioglitazone powder was purchased from (Amoun Pharmaceutical Company, Egypt).

Experimental designs:

Group I: Normal untreated rats**.**

Group II: Diabetic control group (untreated rats**)**. Diabetes induced in normal rats by intraperitoneal (i.p.) single injection of freshly prepared streptozotocin (STZ) at a dose of 50 mg/kg body weight (wt)**[10].**

Group III: Diabetic rats treated with pioglitazone (10 mg /kg body wt. once daily) for 8 weeks **[11]**.

Group IV: Diabetic rats treated with fenofibrate (100 mg/kg body wt. once daily) oral for 8 weeks **[12]**.

Group V: Diabetic rats treated with simvastatin (10 mg/kg body wt. once daily) oral for 8 weeks **[13]**.

Group VI: Diabetic rats treated with fenofibrate (100 mg/kg body wt. once daily) oral for 8 weeks with standard oral antidiabetic (pioglitazone 10 mg /kg body wt. once daily) for 8 weeks.

Group VII: Diabetic rats treated with simvastatin (10 mg/ kg body wt. once daily) oral for 8 weeks with standard oral antidiabetic (pioglitazone 10 mg /kg body wt. once daily) for 8 weeks.

Group VIII: Diabetic rats treated with fenofibrate (100 mg/kg body wt. once daily) oral for 8 week and simvastatin (10 mg/ kg body wt. once daily) oral for 8 weeks with standard oral antidiabetic (pioglitazone 10 mg /kg body wt. daily) for 8 weeks.

N.B. Mortality rates: Two rat died in the diabetic untreated group with mortality rate 20%, one rat died in the diabetic group treated with fenofibrate with mortality rate 10% and one rat died in the diabetic group treated with simvastatin with mortality rate 10%. No rats died in other groups.

Procedures:

Experimental induction of diabetes

Diabetes was induced in rats by single intraperitoneal injection of aqueous solution of streptozotocin (STZ) at a dose of 50 mg/kg body weight dissolved in 0.1 M (ph 4.5) citrate buffer. STZ induces diabetes within 2 days by destroying B cells **[10]**.

Diabetes was confirmed through detecting blood glucose concentration using glucometer (accu check) with glucose test strip (One Touch Basic) then followed up by enzymatic colorimetric method. Two days after STZ injection, rats with blood glucose levels more than 250 mg/dl were considered diabetic and included in the study **[10].**

1- Collection of blood samples

The animal was anaesthetized with ether by placing the rat in an anesthetic box filled with ether vapor, which was maintained by periodically applying liquid ether to a cotton wool on the base of the box. When surgical stage of anesthesia was reached (judged by loss of withdrawal reflexes) the animal was removed and placed on a table. Blood was collected from the retro-orbital plexus using capillary tube (0.75-1.0 mm internal diameter) inserted in the medial canthus medial to the eye globe.

Blood was collected from carotid artery after sacrificing of animals to obtain serum. The blood was collected into a dry clean graduated glass centrifuge tube. It was rapidly set to centrifuge at 5000 r.p.m for 10 minutes about half of the supernatant serum was sucked out into a clean dry glass serology tube using Pasteur pipette and stored in refrigerator in 20°C.

2- Blood Pressure Measurement Procedure

Rats were trained daily for the measurement of BP by the tail-cuff method. Each day, rats were placed (9 AM) in their maintenance cages for 2 hours. Afterward, systolic BP was measured in unrestrained animals. Once the rats were considered to be trained and not susceptible to stress from the tail-cuff procedure, systolic BP measurements were performed. And at week 8, systolic BP was measured on 2 consecutive days at the same time of the day (11 AM).

Biochemical measurements:

1- Blood glucose measurements.

2-Lipid Profile: Serum cholesterol measurements, serum triglycerides measurements, determination of serum high density lipoproteins, and determination of serum low density lipoproteins**.**

3- Determination of anti-oxidant activity of fenofibrate and simvastatin and pioglitazone.

Ethical approval:

All the experimental procedures were carried out according to the principles and guidelines of the Ethics Committee of the of Faculty of science, Al-Azhar University, Egypt conformed to "Guide for the care and use of Laboratory Animals" for the use and welfare of experimental animals, published by the US National Institutes of Health (NIH publication No. 85–23, 1996).

Statistical analysis

All statistical calculations were done using SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) version 22. Quantitative data were statistically described in terms of mean ± standard error (±SE). Comparison of quantitative variables was done using Mann Whitney U test because the data were non-normally distributed. P-value was always 2 tailed set significant at 0.05 level.

RESULTS

Body weight in the diabetic groups treated with pioglitazone alone or in combination of other drugs was significantly higher than in the diabetic untreated rats, but still with significant decrease in comparison with the normal rats (Table 1).

Table (1): Comparison between the effect of pioglitazone, fenofibrate and simvastatin alone or combined on body weight of diabetic rats

Studied groups	Body weight (gm)
Normal	197.40±0.73
Diabetic	146.22±0.79 [a]
Diabetic + Pioglitazone	169.90±1.30 [a, b]
Diabetic + Fenofibrate	147.20±0.89 [a, c]
Diabetic + Simvastatin	145.40±0.83[a, c]
Diabetic +Pioglitazone+ Fenofibrate	172.50±0.78[a, b]
Diabetic+Pioglitazone+Simvastatin	171.50±0.93[a, b]
Diabetic +Pioglitazone+ Fenofibrate+Simvastatin	172.60±0.92[a, b]

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic + Pioglitazone group.
*Each value represents the mean ± SE (standard error).

Random blood glucose in the diabetic groups treated with pioglitazone alone or in combination of other drugs was significantly lower than in the diabetic untreated rats, but still with significant increase in comparison with the normal rats (Table 2).

Table (2): Comparison between the effect of pioglitazone, fenofibrate and simvastatin alone or combined on random blood glucose level of diabetic rats

Studied groups	Random blood glucose level (mg/dL)
Normal	86.20±0.94
Diabetic	255.22±0.97 [a]
Diabetic + Pioglitazone	110.60±2.21 [a,
Diabetic + Fenofibrate	256.80±1.15 [a,
Diabetic + Simvastatin	257.50±1.28 [a,
Diabetic +Pioglitazone+ Fenofibrate	111.10±0.86 [a,
Diabetic+Pioglitazone+Simvastatin	110.16±1.39 [a,
Diabetic +Pioglitazone+ Fenofibrate+Simvastatin	112.80±1.39 [a,

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic + Pioglitazone group.
*Each value represents the mean ± SE (standard error).

All the treated diabetic groups had significantly lower systolic blood pressure than the untreated group. The treated groups by combination of drugs had significantly lower systolic blood pressure than the groups treated with pioglitazone alone (Table 3).

Table (3): Comparison between the effect of pioglitazone, fenofibrate and simvastatin alone or combined on systolic blood pressure of diabetic rats

Studied groups	Systolic blood pressure (mmHg)
Normal	115.30±1.19
Diabetic	149.44±0.89 [a]
Diabetic + Pioglitazone	137.80±1.58 [a, b]
Diabetic + Fenofibrate	135.70±1.15 [a, b]
Diabetic + Simvastatin	136.60±5.52 [a, b]
Diabetic +Pioglitazone+ Fenofibrate	130.80±0.98 [a, b, c]
Diabetic+Pioglitazone +Simvastatin	132.00±1.25 [a, b, c]
Diabetic +Pioglitazone+ Fenofibrate+Simvastatin	132.30±0.34 [a, b, c]

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic + Pioglitazone group.
*Each value represents the mean ± SE (standard error).

All the diabetic treated groups had significantly lower cholesterol than the untreated group. The treated groups by combination of drugs had significantly lower cholesterol than the group treated with pioglitazone alone (Table 4).

Table (4): Comparison between the effect of pioglitazone, fenofibrate and simvastatin alone or combined on total cholesterol of diabetic rats

Studied groups	Total cholesterol (mg/dL)
Normal	133.40±0.86
Diabetic	233.22±0.68 [a]
Diabetic + Pioglitazone	153.10±1.62 [a, b]
Diabetic + Fenofibrate	152.30±2.59 [a, b]
Diabetic + Simvastatin	151.80±0.39 [a, b]
Diabetic +Pioglitazone+ Fenofibrate	148.20±1.01 [a, b, c]
Diabetic+Pioglitazone +Simvastatin	149.60±0.83 [a, b, c]
Diabetic +Pioglitazone+ Fenofibrate+Simvastatin	140.30±1.04 [b, c]

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic + Pioglitazone group.
*Each value represents the mean ± SE (standard error).

All the diabetic treated groups had significantly lower serum triglycerides than the untreated group. The treated groups by combination of drugs had significantly lower serum triglycerides than the group treated with pioglitazone alone. Diabetic group treated with the combination of 3 drugs had similar value to that

of the normal group as regard serum triglycerides (Table 5).

Table (5): Comparison between the effect of pioglitazone, fenofibrate and simvastatin alone or combined on serum triglycerides of diabetic rats

Studied groups	Triglycerides (mg/L)
Normal	146.60±0.79
Diabetic	224.11±1.37 [a]
Diabetic + Pioglitazone	153.50±0.87 [a, b]
Diabetic + Fenofibrate	154.00±2.67 [a, b]
Diabetic + Simvastatin	152.90±0.53 [a, b]
Diabetic +Pioglitazone+ Fenofibrate	150.40±1.69 [a, b, c]
Diabetic+Pioglitazone+Simvastatin	150.80±0.51 [a, b, c]
Diabetic +Pioglitazone+ Fenofibrate+Simvastatin	147.20±1.10 [b, c]

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic + Pioglitazone group.
*Each value represents the mean ± SE (standard error).

All the diabetic treated groups, had significantly lower low density lipoprotein and significantly higher high density lipoprotein than the untreated diabetic group. The treated groups by combination of drugs had significantly lower low density lipoprotein and significantly higher high density lipoprotein than the group treated with pioglitazone alone. Diabetic group treated with the combination of 3 drugs had similar values to those of the normal group as regard both LDL-C and HDL-C (Table 6).

Table (6): Comparison between the effect of pioglitazone, fenofibrate and simvastatin alone or combined on Low density lipoprotein (LDL-C and HDL-C) of diabetic rats

Studied groups	LDL (mg/L)	HDL-C (mg/dL)
Normal	73.70±0.79	54.80±1.45
Diabetic	162.33±1.03 [a]	34.67±0.96 [a]
Diabetic + Pioglitazone	88.10±1.23 [a, b]	45.80±0.77 [a, b]
Diabetic + Fenofibrate	86.50±1.53 [a, b]	45.60±0.8 [a, b]
Diabetic + Simvastatin	87.10±1.43 [a, b]	46.30±0.79 [a, b]
Diabetic +Pioglitazone+ Fenofibrate	83.30±0.91 [a, b, c]	48.70±1.06 [a, b, c]
Diabetic+Pioglitazone+Simvastatin	83.20±0.98 [a, b, c]	48.60±1.00 [a, b, c]
Diabetic +Pioglitazone+ Fenofibrate+Simvastatin	79.90±2.24 [b, c]	51.80±0.63 [b, c]

(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic + Pioglitazone group.
*Each value represents the mean ± SE (standard error).

All the diabetic treated groups, had significantly higher GSH and SOD than the untreated diabetic group. There was no significant difference between normal rats and the diabetic group treated with the combination of 3 drugs as regard GSH and SOD (Table 7).

Table (7): Comparison between the effect of pioglitazone, fenofibrate and simvastatin alone or combined on serum glutathione (GSH and SOD) of diabetic rats

Studied groups	GSH (mu mol/l)	SOD (unit/ml)
Normal	3.77±0.14	13.91±0.85
Diabetic	1.76±0.17 [a]	4.30±0.46 [a]
Diabetic + Pioglitazone	3.62±0.22 [b]	12.17±0.52 [b]
Diabetic + Fenofibrate	3.25±0.28 [b]	13.04±0.93 [b]
Diabetic + Simvastatin	3.10±0.23 [b]	12.82±0.69 [b]
Diabetic +Pioglitazone+ Fenofibrate	3.45±0.19 [b]	12.61±0.63 [b]
Diabetic+Pioglitazone +Simvastatin	3.02±0.08 [b]	12.39±0.68 [b]
Diabetic +Pioglitazone+ Fenofibrate+Simvastatin	3.55±0.21 [b]	13.55±0.72 [b]

GSH: Glutathione, SOD: Superoxide dismutase
(a) P < 0.05 significantly different from Normal group.
(b) P < 0.05 significantly different from Diabetic group.
(c) P < 0.05 significantly different from Diabetic + Pioglitazone group.
*Each value represents the mean ± SE (standard error).

DISCUSSION

In the present study, we clearly demonstrated that the average body weight (g) of all studied groups (DM, DM+P, DM+F, DM+S, DM+P+F, DM+P+S and DM+P+F+S groups) were significantly lower than that of the normal control group, also there was significant increase in body weight of (DM+P, DM+P+F, DM+P+S and DM+P+F+S groups) in comparison with the DM untreated group, while (DM+F and DM+S) showed no significant difference with DM untreated group. When pioglitazone was combined with fenofibrate and/or simvastatin to the diabetic rats it showed no significant difference in body weight when compared to DM+P.

The present study agrees with **Zhong-Xia and coworkers[(14)]** study, which found that the diabetic rats demonstrated a significant loss in the body weight and treatment with pioglitazone slightly increased the body weight of pioglitazone-treated rats. Body weight of

diabetic rats treated with pioglitazone significantly increased when compared with the body weight of the diabetic rats. Our finding could be explained by the fact that pioglitazone is one member of thiazolidinediones (TZD) drugs, which are known to promote body weight gain both in animals and humans [15,16]. Pioglitazone increased body weight through up-regulation of genes including phosphoenolpyruvate carboxykinase, glycerol-3-phosphate dehydrogenase, and acetyl-CoA synthetase facilitating adipocyte lipid storage pathways [17].

The present study is supported by the study of **ElBatsh** [18], which reported that simvastatin failed to prevent weight loss among the studied samples. On the other hand, **Mohamadin and coworkers**[19] study, which aimed to evaluate the possible protective effects of simvastatin against oxidative stress in STZ-induced diabetic rats. The authors found significant difference in body weight gain between control and diabetic rats. Decreased body weight was observed in diabetic rats compared with control rats. Administration of simvastatin tended to increase body weight to that seen in untreated control rats.

In the present study we found that random blood glucose of all studied groups (DM, DM+P, DM+F, DM+S, DM+P+F, DM+P+S and DM+P+F+S groups) were significantly higher than that of the normal control group. Also we found that the combination of pioglitazone with either fenofibrate or simvastatin or both namely (DM+P, DM+F+P, DM+S+P and DM+F+S+P) showed significant reduction in blood glucose level as compared to DM uncontrolled group. Meanwhile (DM+F and DM+S) groups showed no significant difference with the diabetic untreated group.

Finding of present study agrees with **Gad and coworkers** [20] who stated that; pioglitazone is considered "insulin sensitizers" and used as anti-hyperglycemic agents for type 2 diabetes treatment. Although it is commonly stated that thiazolidinediones "e.g. pioglitazone" lower glucose concentration primarily by increasing glucose uptake [21].

The present study agrees with **Olukman and coworkers** [22] reported that finofibrate treatment did not alter high glucose levels in diabetic animals and also the study of **Kadian and coworkers** [23], which aimed to the compare pre- and post-treatment effects of low-dose fenofibrate in diabetes-induced onset of nephropathy.The authors found that marked increase in serum glucose level was noted in diabetic rats as compared to normal rats. The low-dose fenofibrate at the level of either pre-treatment or post-treatment did not affect the elevated serum glucose level in diabetic rats.

The present study revealed that the systolic blood pressure (SPB) (mmHg) was elevated in STZ-diabetic uncontrolled rats over all other studied groups, also the same difference was observed when we compared other studied groups, which received either anti-hyperglycemic or anti-hyperlipidemic drugs both as mono or combined therapy (DM+P, DM+F, DM+S, DM+P+F, DM+P+S and DM+P+F+S) with the normal controlled group. Interestingly, we found that groups, which received combined therapy (DM+P+F, DM+P+S and DM+P+F+S), have lower SBP over the pioglitazone mono-therapy which indicates possible synergistic effect, larger randomized multi-center studies are needed to confirm our finding.

Increase SPB among diabetic rats could be explained by that the cardiovascular (CV) status is known to be deteriorated in diabetic rats after induction of diabetes [24].

The present study agrees with **Crespo and coworkers** [25] who aimed to investigate the effect of statins in improving cardiovascular (CV) status of diabetics rats. The author found that; in diabetic rats, SBP was higher than in control group, and was significantly reduced by all three statins used "Simvastatin, atorvastatin, and pravastatin". Decreased SBP by statins is explained by that improvement of systolic blood pressure may result from reductions in peripheral resistance secondary to increased endothelial function and the vascular remodeling regression observed with all three statins.

By comparing the lipid profile of the studied samples we found that, diabetic untreated rats have significant increase in TC, TG and LDL and significant decreased in HDL-C as compared to all other studied groups, also we observed that the level of TC, TG, LDL and HDL-C were (i) partly improved after exposure to either pioglitazone, fenofibrate, or simvastin, and (ii) completely improved with no difference with the normal control group in rats group treated with a combination of all three drugs. These data establish that the combined use of pioglitazone, fenofibrate and simvastin additively improved the lipid profile of the studied samples.

Results of the present study agrees with study of **Carmona and coworkers** [16] who reported that fenofibrate alone significantly reduced serum triglyceride, nonesterified fatty acid and total cholesterol levels. Also several previous studied reported the favorable effect of fenofibrate on HDL-C concentrations in various models of obesity and hypertension [26, 27]. On the other hand **Ibarra-Lara and coworkers**[12] did not find a significant change in HDL-C concentrations in metabolic syndrome rats treated with fenofibrate group.

The present study agrees with **Kadian and coworkers**[23] who reported that a significant increase in serum total cholesterol and consequent decrease in HDL level were noted in diabetic rats as compared to normal rats. Both pre-and post-treatments with low-dose fenofibrate significantly reduced diabetes mellitus-induced elevation of total cholesterol. Although the low-dose fenofibrate pretreatment significantly increased the reduced HDL level in diabetic rats.

The present study agrees with **Schaalan**[28] who reported that pioglitazone improved both glucose

and lipid metabolism; it caused a significant decline in serum glucose, TG, T-Chol, and LDL-C and an increase in HDL-C (all values relative to high-fat diet (HFD)-only hosts), also simvastatin caused reductions in serum TG, T-Chol, LDL-C (all values relative to HFD-only hosts). Co-administration of pioglitazone plus simvastatin was superior in improving overall metabolic parameters compared to each mono-therapy. Co-treatment was most efficacious in improving serum lipid profiles.

The present study agrees with **Islam and coworkers**[29] who reported that combination therapy of pioglitazone and fenofibrate reduced total cholesterol, triglyceride and LDL-cholesterol level significantly and increased HDL-cholesterol level in comparison with their respective diabetic control groups. These changes were significantly better than those of pioglitazone and fenofibrate mono-therapy.

In the present study the oxidative stress was significantly increased in STZ-induced uncontrolled diabetic rats as compared to all other treated groups, SOD and GSH were significantly decreased. Pioglitazone and/or fenofibrate and/or simvastatin treatment significantly increased levels of endogenous antioxidants (SOD and GSH) to near normal values with no significant difference with the normal group.

The present study agrees with **Majithiya and coworkers**[30] who stated that pioglitazone reduced oxidative stress in diabetic rats, also **Matsumoto and coworkers**[31] who reported that SOD activity was reduced significantly in untreated STZ induced diabetic, meanwhile pioglitazone treatment markedly corrected this abnormality. Collectively, these results suggest that pioglitazone treatment improves endothelium-dependent relaxation by reducing oxidative stress via increased SOD activity and decreased NAD(P)H oxidase activity [29].

The present study disagrees with **Gumieniczek**[32] who showed that in diabetics, SOD was decreased and pioglitazone therapy did not exert any effect on its level. Also **Kuru and coworkers**[33] showed no statistically significant difference among mean SOD and GSH values of diabetic control and pioglitazone groups.

The present study agrees with **Olukman and coworkers**[22] who reported that erythrocyte and liver-SOD level were markedly lower in the diabetic group than in the control group, and fenofibrate treatment caused a significant increase in these parameters with no difference with the control group. Also **Helmy and coworkers** [34] reported that cisplatin caused significant decreases in cellular SOD activity and increases in TNF-α, IL-6, caspase-3 levels. These effects of cisplatin were less manifest in cells co-treated with pioglitazone, fenofibrate, or thalidomide, but remained significantly different from respective control values. The incubation of human embryonic kidney (HEK) cells with a mixture of all 3 drugs (pioglitazone, fenofibrate, and thalidomide) fully abolished the detrimental cisplatin effects on biomarkers of the inflammatory, oxidative, and apoptotic profiles. This could explain the additive effect of pioglitazone and fenofibrate in increasing SOD level in our study.

The present study agrees with **Mohamadin and coworkers** [19] who reported that SOD, catalase (CAT), and phospholipid hydroperoxide glutathione (GSH-Px) showed lower activities in liver and kidney during diabetes. Treatment of the diabetic rats with SMV restored the altered antioxidant enzyme activities significantly.

CONCLUSION

The present study showed that treatment with fenofibrate or simvastatin did not increase body weight or lower blood glucose level of the diabetic albino rats significantly, but they improved significantly blood pressure, lipid profile, and serum level of antioxidants (GSH and SOD), so we recommend that uses of (fenofibrate and simvastatin) in combination with standard antidiabetic as they have a valuable antihyperlipidaemic and antioxidant activity as treatment of diabetes mellitus.

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