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Pharmacological Evaluation of Saroglitazar And Gemfibrozil Combination Therapy In The Treatment Of Diabetic Dyslipidemia

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ABSTRACT:

Introduction

Diabetics have an increased cardiovascular risk. This risk gets exaggerated by lipid abnormalities additionally. Diabetics have an increased propensity to develop dyslipidemia. Diabetic dyslipidemia is a cluster of lipoprotein abnormalities characterized by increased triglyceride & low-density lipoprotein (LDL) levels, decreased high-density lipoprotein levels.

Methodology

From the pilot study potent dose of Saroglitazar and Gemfibrozil were selected for this study. In this study, the experimental rats were divided into five groups of six animals in each group.

Results

Combination therapy shows decrease in lipid profile, atherogenic index, histopathological studies of different organs and Insulin levels compared to individual drugs and shows better therapeutic efficacy.

Conclusion

Hence the combination of Saroglitazar and Gemfibrozil has shown good safety profile and may represent a novel therapeutic agent that will fulfill the unmet needs in T2DM and diabetic dyslipidemia.

KEY WORDS: Diabetics, dyslipidemia, PPAR-α/γ agonist, Gemfibrozil, Saroglitazar and high-density lipoprotein.

INTRODUCTION

Diabetes mellitus is a widespread and persistent health problem. However, the severity and accompanying problems are of little concern to anybody. Both industrialized and developing nations are feeling the effects of diabetes' alarming global rise in incidence. The number of people with diabetes is expected to rise from the current global estimate of 368 million in 2020 to 439 million in 2030, or 7.7 percent of the world's adult population aged 20-79. According to projections from the International Diabetes Federation's Diabetes Atlas 2009, the number of people with diabetes in India is now about 50.8 million and is predicted to climb to 87 million by the year 2030, making India the diabetes capital of the world. According to the Diabetes Atlas, between 85 and 95 percent of all diagnosed cases of diabetes are due to type 2 diabetes (T2DM). Impaired islet function and insulin resistance contribute to poor glucose tolerance and

an abnormal rise in fasting hepatic glucose production, two hallmarks of type 2 diabetes (T2DM). Obesity, lack of exercise, and advanced age all raise the risk of type 2 diabetes.[1]

Diabetic dyslipidemia is likely to be one of many reasons for the hastened macrovascular disease in diabetic subjects along with the insulin resistance. The potential of PPAR agonists to positively influence the cardiovascular disease risk in type 2 diabetics has remained an area of continuous medical interest. PPAR-α agonists and PPAR-γ agonist are approved respectively for lipid control and glycemic control in type 2 diabetes.[2]

However, increasing safety concerns with thiazolidinediones with regard to fluid retention, weight gain and congestive cardiac failure have resulted in new label warning for these agents. Hence, there was a strong need for a dual PPAR-α/γ agonist with beneficial effects in controlling both lipids and glycemic levels with all the necessary safety parameters. Gemfibrozil down-regulates systemic glucose level and glycogen storage in the liver dependent on PPARα, suggesting its potential value for treatment of dyslipidemia with concurrent diabetes or high glucose levels. Therefore the need of the hour is to evaluate the efficacy of Gemfibrozil with PPAR-α/γ agonist combination therapy for the patients suffering from diabetic dyslipidemia, which is expected to show efficacy in improving both, the lipid as well as the glycemic parameters. Treatment with the fibric acid derivative gemfibrozil is likely to benefit patients with CHD and diabetes who have low levels of HDL and LDL. These benefits may occur even as traditional lipid measures change only modestly. The role of combination therapy for diabetic dyslipidemia requires further study. Hence the study was aimed to evaluate the efficacy of Saroglitazar

(PPAR-α/γ agonist) and Gemfibrozil combination therapy, for effective management of diabetic dyslipidemia.

MATERIALS AND METHODS Methodology

From the pilot study potent dose of Saroglitazar and Gemfibrozil were selected for this study. In this study, the experimental rats were divided into five groups of six animals in each group as follows:

Treatment schedule for HFD+STZ diabetic rats

NC- Normal control; DC- Diabetic control; NPD- Normal pellet diet; HFD- High fat diet; SARO-Saroglitazar; GEM-Gemfibrozil.

The treatment of drugs was started on the 21st day of the study. All the compounds were administered orally as suspension by mixing with vehicle 1% Na-CMC at a dose volume of 1 mL/kg body weight of rats till 48th day of study (i.e. 4 weeks of drug treatments). At the end of the study, the rats were fasted overnight, anaesthetized (sodiumpentobarbital 40 mg/kg bw) and blood was collected by retro-orbital puncture, with or without EDTA for plasma or serum separation, respectively. Further animals were sacrificed by cervical decapitation. The pancreas was excised immediately, rinsed with phosphate buffer saline, and weighed. All the samples were stored at -70°C until analysis.

Pharmacological evaluation Effects of single dose of drugs on oral sucrose tolerance test(OSTT)

As a pilot study, effects of single dose of test drugs were evaluated in the oral sucrose tolerance test. The peak blood glucose level was achieved at 30 min in all the treatment groups and it was significantly lowered by pretreatment with all the compounds (P<0.01). At 120 min, Saroglitazar normalized the blood glucose levels as depicted in Figure 1. Further, Figure 2 showed the area under the curve (AUC) of blood glucose levels over 120 min for

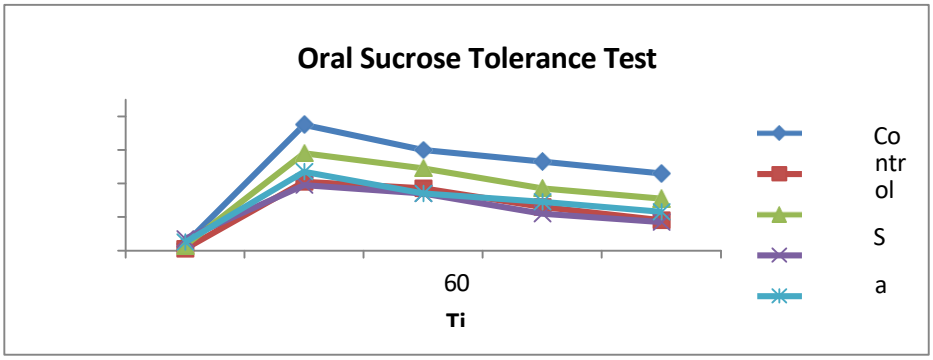


Figure 1. Oral sucrose tolerance test of various test drugs and acarbose in Wistar albino rats

Saroglitazar and Gemfibrozil were 12.37%, 23.72% and 10.77%, lower than that of the control group, respectively which was comparable to acarbose 15.24%. Overall the combination of drugs proved better candidate to suppress hyperglycemia.[3] So the further study was carried out for their antidiabetic and dyslipidemic activity in HFD+STZ rat model for 28 days treatments.

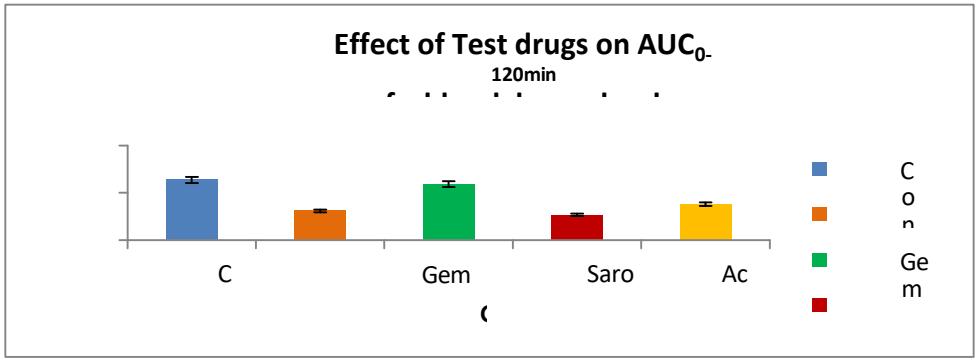


Figure2.Effect of test drugs and acarbose on AUC0-120 min for blood glucose level after sucrose (2g/kg) administration. Results are mean ± S.E.M. ofn =6, *& are significantly different vs. control at p<0.05 and p<0.01 and # significantly different vs. acarbose (p<0.05).**

HFD plus STZ (low dose) induced type2 diabetic rat model

Table1.Effect of HFD and HFD+STZ on body weight and biochemical parameters in Wistarrats

Parameters	NPD group	HFD group (on 15th day, before STZ injection)	HFD+STZ group (on 21st day, after STZ injection)
Bodyweight(g)	224.83±1.54	249.67±2.80**	242.15±3.15**
Blood glucose(mg/dl)	93.83±2.21	124.86±2.06**	318.39±4.71**##
Total cholesterol (mg/dl)	86.46±3.51	110.89±3.18**	154.82±5.24**##
Triglycerides (mg/dl)	88.28±2.62	112.62±4.02**	148.81±4.79**##
Plasmainsulin(pmol/L)	53.72±3.26	73.45±4.12**	41.13±3.68*##

Values are Mean ± SEM (n=8); **NPD**-normal pellet diet, **HFD**-high fat diet

Values are Mean ± SEM (n=8); **NPD-** normal pellet diet, **HFD-** high fat diet,
**P*< 0.05 and ***P*< 0.01 vs. NPD group, and ##*P*< 0.01 vs. HFD group

In the present study, after two weeks of feeding with high fat diet (HFD), there was a significant increase (*P*<0.01) in body weight as well as fasting blood glucose, triglycerides, total cholesterol and plasma insulin levels in rats as compared to NPD-fed rats (Table 1)[4]. The streptozotocin (STZ) injection was given (35 mg/kg bw, i.p) on 15th day (after 2 weeks of dietary manipulation).[5] and blood glucose was measured at 21st day of the study (after 1 week of STZ injection), which resulted further increase blood glucose levels significantly (*P*<0.01) in HFD-fed rats (HFD+STZ group) compared to control group.[6] In addition, STZ injection also increased significantly (*P*<0.01) total cholesterol and triglycerides levels while decreasing serum insulin levels significantly in HFD-fed rats (HFD+STZ group) compared to HFD group (*P*<0.01) and NPD groups (*P*<0.05) as shown in Table 1. Additionally, At the end of the study (49th day, after 28days of respective treatments), diabetic control rats (HFD+STZ group) had significantly (*P*<0.01) increased in food and water intake, HbA1c, oral sucrose tolerance (OSTT), HOMA-IR values, atherogenic index and DPP IV level while significantly (*P*<0.01) decreased liver glycogen, HDL cholesterol and GLP-1 level. Furthermore, histopathological changes in pancreas of diabetic rats showed damaged, shrunken islets of Langerhans.[7]

Effect of test drugs on insulin levels in HFD+STZ diabetic rats

Additionally, the insulin levels observed in the present study has shown significanteffects of 2 mg of Saroglitazar/kg body weight, 150 mg of Gemfibrozil /kg body weight and combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body weight on insulin secretion in HFD+STZ induced diabetic rats during 28 days treatments.[8] Treatment with 2 mg of Saroglitazar/kg body weight, 150 mg of Gemfibrozil /kg body weight and combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body weight for 28 days increased insulin levels to 58.78 pmol/L, 69.56 pmol/L and 60.36 pmol/L, respectively compared to diabetic control rats. STZ significantly decreased plasma insulin levels in diabetic rats by damaging β-cells[9] the present study results suggest that 2 mg of Saroglitazar/kg body weight, 150 mg of Gemfibrozil /kg body weight and combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body weight are able to support the pancreas to recover β-cell function and/or regenerate β-cells in diabetic rats. Surprisingly, combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil/kg body weight treated rats had significantly increased (*P*<0.01) serum insulin level compared to the normal control rats (NC).[10] These effects may be due to strong DPP IV enzyme inhibition which leads to increase the concentration of GLP-1, which stimulate the insulin secretion and inhibit glucagon secretion.[11]

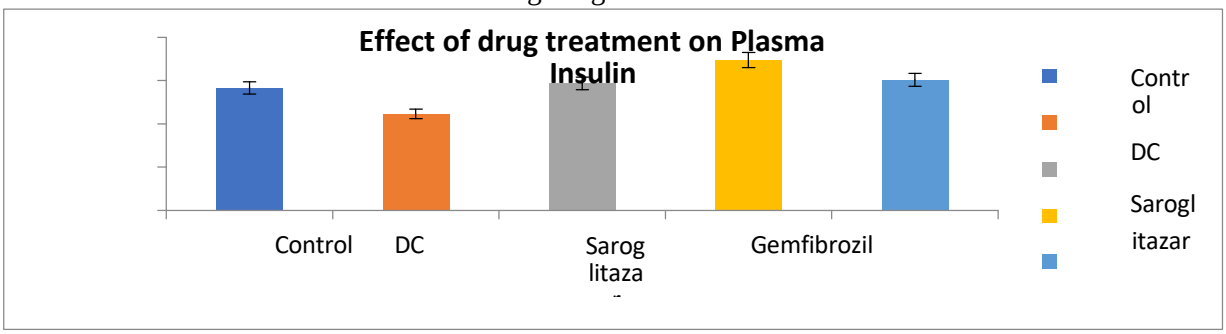
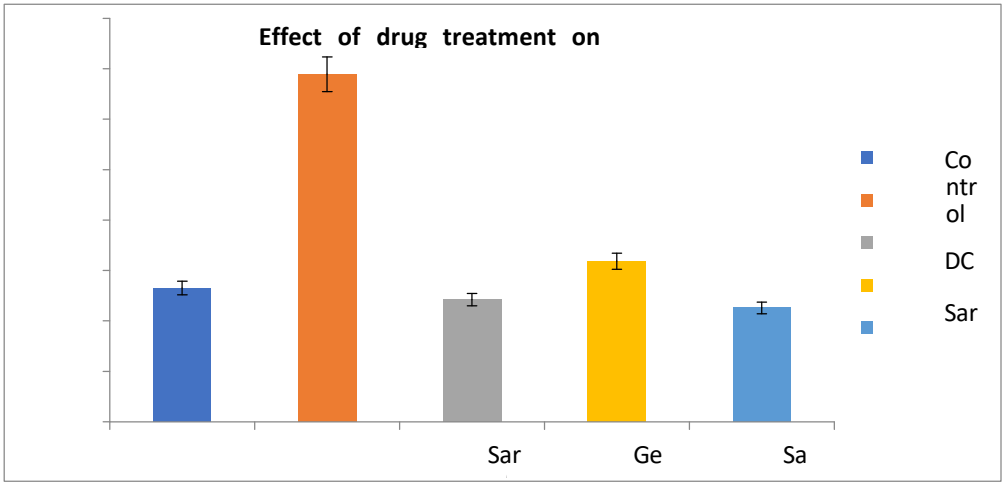


Figure 3.Effect of test drugs on serum insulin in HFD+STZ diabetic rats

Effect of test drugs on HbA1clevels in HFD+STZ diabetic rats

WHO recommends the HbA1c levels to diagnosis of DM, which replicates average blood glucose over the previous 8-12 weeks. It can be done in any condition either fasting or feeding, so it is preferred test for

evaluating glycemic control in diabetes. Measurement of HbA1c levels is useful for monitoring the efficiencyin the treatment of diabetes.[12] In the present study, HbA1c levels were also increased by three folds (P<0.01) in diabetic control rats in comparison to normal control group. The observed increment of HbA1c levels in diabetic rats is due to excessive amounts of blood glucose present in the blood and this excess of glucose reacts with hemoglobin (Hb) and converted to glycosylated hemoglobin.[13] In the present study, showed the treatment with 2 mg of Saroglitazar/kg body weight, 150 mg of Gemfibrozil /kg body weight and combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body weight for 28 days decreased significantly (P<0.01) HbA1c levels to 4.85%, 6.37% and 4.52%, respectively compared to diabetic control rats (Table 3; Figure 3).[14]



Effect of test drugs on Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) in HFD+STZ diabetic rats

The effect of 28 days oral administration of 2 mg of Saroglitazar/kg body weight, 150 mg of Gemfibrozil /kg body weight and combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body in diabetic rats on HOMA-IR values. Diabetic rats had significant (P<0.01) increase in HOMA-IR value as compared to normal control group *(i.e.* from 2.299±0.23to 7.165±0.61) which indicated the insulin resistance. Treatment with combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil/kg body weight in diabetic rats caused significant reduction (P<0.01) in HOMA-IR values from 7.165±0.61 to 1.966±0.95 as displayed in Figure 6.2.10. Whereas, 2 mg of Saroglitazar/kg body weight and 150 mg of Gemfibrozil /kg body weight caused significant reduction (P<0.01) in HOMA-IR values from 7.165±0.61 to 2.045±0.72 and 3.760±0.89, correspondingly as compared to diabetic control group.[15] These results clearly showed theprevention of pathogenesis of diabetes and complications caused by impaired glucose metabolism more effectively by combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body weight.

Table 2. Effect of test drugs on fasting blood glucose, plasma insulin, HbA1C and HOMA-IR in HFD+STZ diabetic rats

Group	al cholesterol (mg/dl	) HDL-C (mg/dl)	ig/dl)	LDL-C (mg/dl)	VLDL-C (mg/dl)
Gemfibrozil	131.34±4.42	36.12±2.42	69.56±3.42	6.37±0.38	3.760±0.89#
NC	76.53±2.76	34.31±2.1	60.03±3.15	33.56±3.25	12.01±2.58
DC	214.69±10.32**	20.12±2.46*	198.56±9.98**	157.12±7.83**	39.71±3.68**
Saroglitazar	75.67±4.37#	33.56±2.78	60.43±5.36	31.58±3.45#	11.29±1.53##
Gemfibrozil	80.25±2.65	31.56±3.56	57.52±3.56##	32.85±2.45	12.50±1.16
Saro+Gem	72.45±3.1##	38.45±3.13##	54.67±2.14##	29.53±2.97##	10.93±3.54##
Saro+Gem	72.34±4.69##**	60.36±3.09	4.52±0.36##**	1.966±0.95##**	Saro+Gem 72.34±4.69##**

NC-normal control, **DC-** Diabetic control, **Saro+Gem -** Combination of Saroglitazar & Gemfibrozil, **HOMA- IR** – Homeostatic model assessment of Insulin resistance.

Values represent the mean ± SEM (*n*=8), ANOVA followed by Dunnett‟s multiple comparisons test. **P*< 0.05, ***P*< 0.01 -as compared to NC group; #*P*< 0.05, ##*P*< 0.01-as compared to DC group.

Effect of test drugs on oral sucrose tolerance test (OSTT) in HFD+STZ diabetic rats

To determine the insulin-sensitizing capability of 2 mg of Saroglitazar/kg body weight, 150 mg of Gemfibrozil /kg body weight and combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body weight, OSTT was performed on 28th day of the treatments. Diabetic control rats showed severe impaired glucose tolerance. All the treated animal demonstrated significant improvement in oral sucrose tolerance test compared to the diabetic control, which indicates alleviation of insulin resistance potentially. 2 mg of Saroglitazar/kg body weight, 150 mg of Gemfibrozil /kg body weight and combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body weight significantly (*P*<0.01) decreased blood glucose excursion by 58.62%, 49.49% and 66.08% respectively as shown by AUC0-120mins.[16] In the OSTT for the combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body weight significantly (*P*<0.05 & *P*<0.01) lowered the blood glucose levels compared to normal control rats at the all-time points. AUC of blood glucose levels over 120 min for 2 mg of Saroglitazar/kg body weight and combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body weight groups were 16% and 14% respectively lower than that of the control group. AUC of blood glucose levels over 120 min for 150 mg of Gemfibrozil /kg body weight was 27%.

Table 3. Effect of test drugs on serum lipid levels and atherogenic index (AI) in HFD+STZ diabetic rats

Group	Blood glucose (mg/dl)	Plasma (pmol/L)	Insulin HbA1C (%)	HOMA-IR
NC	98.47±3.69	56.73±2.22	5.31±0.23	2.299±0.92
DC	389.78±9.39**	44.67±1.78**	13.79±0.85**	7.165±1.27**
Saroglitazar	77.53±3.14##*	58.78±2.14	4.85±0.31##	2.045±0.72##*

NC-normal control, **DC-** Diabetic control, **HDL-** High density lipoproteins, **LDL-** Low density lipoproteins, **VLDL-** Very low density lipoproteins. Values represent the mean ± SEM (*n*=8), ANOVA followed by Dunnett‟s multiple comparisons test. **P*< 0.05, ***P*< 0.01 -as compared to NC group; #*P*< 0.05, ##*P*< 0.01- as compared to DC group.

Serum lipid levels and atherogenic index (AI) of different groups were shown in Diabetic control rats exhibited about three folds increase in total cholesterol levels, triglycerides levels, LDL-C levels and VLDL-C levels as compared to normal control rats. There were significant decrease (P<0.01) in HDL levels as compared to normal control group and atherogenic index (AI) was four fold increased in diabetic control ratsas compared to the normal control rats.[17]

Histopathological analysis

The 28 days treatment of diabetic rats with 2 mg of Saroglitazar/kg body weight, 150 mg of Gemfibrozil /kg body weight and combination of 2 mg of Saroglitazar/kg and 150 mg of Gemfibrozil /kg body weight had shown restoration of islets of Langerhans and absenteeism of islet damaged and hyperplasia and increases in β-cell mass in tissues of pancreas.[18]

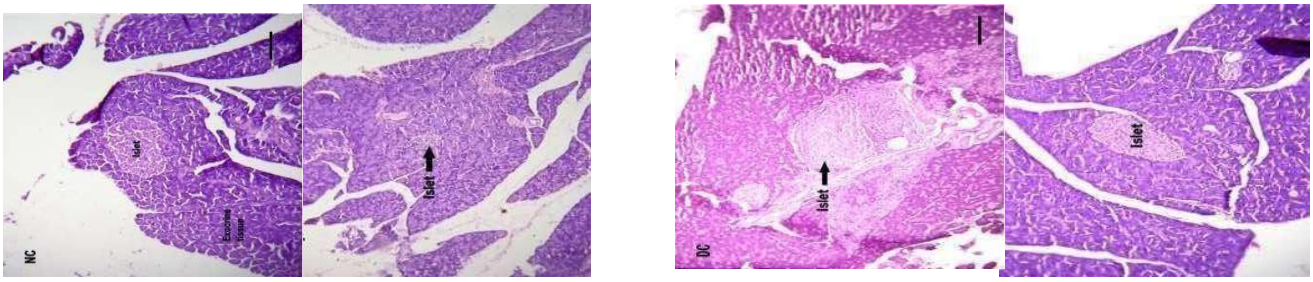


Figure 4. Histopathology pancreatic tissue of experimental rats

Low power photomicrograph of pancreatic tissues,

i. **Normal control** (**NC**) showing normal appearance of tissue architecture with islet of Langerhans,

ii. **Diabetic control** (**DC**), pancreas shows damaged and shrunken islets,

iii. **Saroglitazar** treated groups showed restoration of normal cellular population size of islets of Langerhans and absence of islet damage. The Islet size is also within the normal range (H&EX100). Scale bar: 10 µm.[19] iv. **Gemfibrozil** treated groups showed restoration of normal cellular population size of islets of Langerhans and absence of islet damage. The Islet size is also within the normal range (H&EX100). Scale bar: 10 µm.[20]

v. Groups treated with **combination of Saroglitazar and Gemfibrozil** showed restoration of normal cellular population size of islets of Langerhans and absence of islet damage. The Islet size is also within the normal range (H&EX100). Scale bar: 10 µm.

CONCLUSIONS

In conclusion, Saroglitazar is a nonfibrate, non-TZD next generation PPAR agonist that has shown beneficial effects on lipids and glucose in various preclinical and clinical studies.[21] This study indicated that gemfibrozil treatment of experimental rats restored the diabetes-induced impaired endothelium dependent relaxation. Furthermore, it reduced the increased plasma lipids, lipoproteins and lipid peroxidation although it did not have significant effect on high blood glucose levels in experimental animals. Hence the combination of Saroglitazar and Gemfibrozil has shown good safety profile and may represent a novel therapeutic agent that will fulfill the unmet needs in T2DM and diabetic dyslipidemia**.**

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