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COMPARATIVE STUDY OF SAROGLITAZAR AND PIOGLITAZONE ON HIGH FAT DIET-LOW DOSE STREPTOZOTOCIN INDUCED TYPE-2 DIABETES IN WISTER RATS

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ABSTRACT

Hyperlipidemia is the major predisposing risk factor for occurrence of type-2 diabetes. The present study was planned to investigate the hypoglycaemic and lipid lowering comparative activity study of Saroglitazar (PPARα/γ agonist) and Pioglitazone (PPARγ agonist) in HFD- low dose Sreptozotocin induced type-2 diabetes in male Waster rats. Diabetes was induced by single *i.p* injection of low dose of Streptozotocin (40 mg/kg bd.wt) followed by 21 days of high fat diet (HFD) feeding in 6-8 week old male Wister rats. Body weight gain, blood glucose and lipid parameters were measured. Oral treatment of a PPARα/γ dual agonist Saroglitazar (4 mg/kg) and PPARγ agonist Pioglitazone (10 mg/kg) were significantly reduced the mean body weight, blood glucose, and plasma total cholesterol, triglycerides levels. Sarogliatazar and Pioglitazone showed no significant effect on LDL-C and HDL-C levels. Sarogliatazar showed better activity when compared with Pioglitazone, because of the dual agonistic action of Saroglitazar on PPARα/γ Receptors, it favours the concomitant reduction of blood glucose (PPARγ action) and lipid (PPARα/γ action) levels. Over all the results showed that Saroglitazar a PPARα/γ dual agonist, a drug approved in India for treatment of diabetic dyslipidemia shows significant reduction in body weight, blood glucose and lipid parameters when compared to PPARγ agonist (Pioglitazone) in high fat diet with chemical induced model of type-2 diabetes mellitus. Suggesting it's as first line drug for treatment of diabetic dyslipidemia.

KEYWORDS: Diabetes, Dyslipidemia, High fat diet (HFD), Pioglitazone, PPARα/γ, PPARγ, Saroglitazar.

1. INTRODUCTION

Diabetes mellitus is a group of heterogeneous disorders in which carbohydrate metabolism is reduced while that of proteins and lipids is increased. Hyperglycaemia is a common endpoint for all types of diabetes and is an important parameter to evaluate the efficacy of antidiabetic drugs virtually all forms of diabetes are due to either a decrease in the circulating levels of insulin (insulin deficiency) or a decrease in the response of target tissues to insulin (insulin resistance).Type-I diabetes mellitus is only managed with insulin and type-II can be treated with oral hypoglycaemic agents.[1]

The diabetic patients have an increased cardiac risk. This risk gets increased by dyslipidemia. Diabetic dyslipidemia characterized by elevated plasma glucose along with increased triglycerides (TG), LDL-Cholesterol, and decrease in HDL-Cholesterol. This increase in plasma lipid levels indicator for the onset of type-2 DM.[1]

Generally diabetes and its accompanying dyslipidemia were managed by variety of combinations of hypoglycaemic drugs which decrease the blood glucose levels by increasing the insulin secretion and sensitizing the tissue towards insulin. Commonly used oral hypoglycaemics are Sulfonyl ureas, biguanides and newer drugs like PPARα, PPARγ and PPARα/γ dual agonists.[3] Peroxisome proliferative receptor agonists are the drugs which act upon the peroxisome proliferator-activated receptor. They are used for the treatment of symptoms of the metabolic syndrome mainly for lowering triglycerides and blood sugar.[4] The combination of niacin and finofibrate with other hypoglycaemic agents lowers the risk of dyslipidemia along with diabetes mellitus, but because of higher toxicity and low efficacy profile of these agents' leads to discovery of newer drugs like PPARα agonists (Fenofibrate), PPARγ agonists (Pioglitazone) for targeted drug therapy in type-2 diabetes with hypolipidemia. However these agents also produced serious complications like congestive heart failure, fluid retention, and weight gain.[5]

Hence the research pointed towards the development of dual PPARα/γ agonists to control lipid and glycaemia

parameters with high safety profile. These agents activate both the PPAR**α** and PPARγ receptors simultaneously. They are used to control the hyperglycaemia (PPARγ action), hyperlipidaemia (PPARα action**)** and also reduce the body weight without affecting the food intake.[6]

Saroglitazar is the first approved dual PPARα/γ agonist for treatment of diabetic dyslipidemia which is having good safety profile and excellent efficacy for reducing glycaemia and lipid parameters.[7] DCGI approved Saroglitazar in 2013 usage in India. So many trails are conducting on finding out the efficacy of the Saroglitazar in diabetic dyslipidemia. The present study was evaluated for the comparative effect of Saroglitazar versus Pioglitazone in high fat diet and low dose Streptozotocin induced type-2 diabetes in Wister rats.

OBJECTIVES

The main objectives of the present study are.
Comparative study of PPARγ (Pioglitazone) and PPARα/γ dual agonist (Saroglitazar) on HFD + low dose Streptozotocin induced type-2 diabetic rats for following parameters.

1. Blood glucose levels
2. Lipid parameters
3. Reduction in body weight

2. MATERIALS AND METHODS

2.1 Selection of drugs and chemicals

Pioglitazone (Cipla pharmaceuticals limited, India), Saroglitazar (Cadila health care limited, India), Streptozotocin (Sigma Aldrich, India). Other chemicals used in this study are analytical grade procured locally.

2.2 Selection of animals

Healthy male Wister rats (150-200g body weight) used in this study. Animals were procured from National Institute of Nutrition Hyderabad. All the animals are housed in poly propylene cages with proper diet and animals are maintained according to CPCSEA guidelines.

Table 1: Selection of animals.

Species	Rat
Strain	Wister
Sex	Male
Age at initiation of study	6-8 weeks
Body weight	150-200 g
Source	NIN , Hyderabad
Number of animals per group	6
Number of groups	4
Number of animals	Acclimatization: 30; main study: 24

2.3 Preparation of High Fat Diet

High fat diet consists of 60% fat, 25% protein and 20% carbohydrate as a percentage of total k.cal.[8]

Table 2: Composition of HFD.

S.no	Ingredients	Quantity (gram/kg)
1	Powdered Normal pellet diet	465
2	Lard	410
3	Cholesterol	20
4	Coconut oil	10
5	Sodium chloride	1
6	Casein	94

2.4 Procedure for establishment of HFD fed STZ induced type-2 diabetes

30 animals are selected per the study and 6 animals are selected for Group-I fed with normal diet (normal healthy control), remaining 24 animals are fed with HFD (high fat diet and). All the animals were treated with Streptozotocin (40 mg/kg) except normal control animals.[9]

Those rats fasting blood glucose levels more than 200 mg/dl are selected for study and divided into following groups, each group containing 6 animals.

Table 3: Experimental design.

Groups	Streptozotocin		Treatment		No. of animals
	Dose (mg/kg bd. wt, *i.p)*	Dose conc. (mg/mL)	Dose (mg/kg bd. wt, *p.o*)	Dose conc. (mg/mL)	Male
G-I Normal Control (Normal Pellet Diet))	-	-	-	-	6
G-II- Diabetic Control + HFD	40	10	-	-	6
G-III Saroglitazar 4 mg/kg +DC+ HFD	40	10	4	2	6
G-IV Pioglitazone 10 mg/kg + DC+HFD	40	10	10	2	6

Distilled water (5 ml/kg) administered orally to normal control group, and this group was fed with normal pellet diet. High Fat diet feed was provided to G-II, G-III, G-IV groups. The rats were maintained with this food for 3 weeks. Test drug PPARα/γ dual agonist (Saroglitazar) was administered to G-III at dose of 4 mg/kg and other test drug PPARγ agonist (Pioglitazone) was administered to G-IV at dose 10 mg/kg respectively.

Blood glucose levels are measured on 0^{th}, 7^{th}, 14^{th}, 21^{st} day of the study and other parameters like body weight, cholesterol, triglycerides, HDL and LDL were determined before starting of the study (Day 0) and after end of the study (Day 21).[10]

2.5 Statistical Analysis

Data was expressed as mean±SEM. G-II was compared with G-I and remaining all groups were compared with G-II using ANOVA followed by dunnets test. (P) Value <0.05 taken as the level of significance.

3. RESULTS

Effect of PPAR agonists on body weight of rats

Table 4 shows the effect of PPARγ and PPARα/γ agonists on mean body weight of rats. The mean body weights were altered in Streptozotocin treated rats and the weights were restored after treatment with respective drugs in G-III and G-IV groups.

Progressive increase in the body weight was observed in normal, diabetic control and test drug treatment groups during HFD induction period (before treatment) but end of the study (after treatment) on 21^{st} day diabetic control group (G-II) showed significant (*P < 0.05) weight gain when compared to normal control (G-I) group and Saroglitazar treated animals (G-III) showed highly significant (**P < 0.01) reduction in weight gain when compared to diabetic control. The PPARγ agonist (Pioglitazone) treated animals (G-IV) were showed less significantly reduction in weight gain when compared with diabetic control (G-II).

Effect of PPAR agonists on blood glucose levels of rats

The plasma glucose levels were measured on day 0, day 7, day 14 and day 21. Table 5 shows the effect of PPARγ and PPARα/γ dual agonists on fasting plasma glucose levels. The mean plasma glucose levels were significantly increased (***P < 0.01) on all days in diabetic control animals (G-II). On day 0 there is no significant difference was observed between test drug treated (i.e.-III, G-IV) groups compared with diabetic treated animals (G-II).

PPARα/γ dual agonist (G-III) treated animals showed significantly (***P < 0.01) reduced glucose levels on Day 7, 14 and day 21 when compared to G-II group, similarly PPARγ treated animals (G-IV) also showed significantly (***P < 0.01) decreased blood glucose levels compared to diabetic control (G-II).

Effect of PPAR agonists on plasma lipid levels of rats

Plasma lipid levels are the major markers in diabetic dyslipidemic patients. The plasma lipids like HDL, LDL, TG and total Cholesterol are measured on day 0 (before treatment) and Day 21 (after treatment) are shown in table 6.

On day 0 the plasma total cholesterol (TC) was significantly (*P < 0.05) higher in diabetic control group (G-II) when compared with normal control group (G-I) and plasma LDL are higher, HDL cholesterol levels are lower when compared to G-I group, but there is no significant difference was exists. The plasma triglycerides levels are significantly higher in G-II group (***P < 0.001) when compared to G-I group. Before treatment (Day 0) TC, HDL-C, LDL-C, and TG levels in G-III and G-IV groups were showed no significant difference when compared to diabetic control.

On day 21 (after treatment) the diabetic control group showed significantly increased plasma TC (*P < 0.05), TG (**P < 0.01) when compared to normal control (G-I) however HDL-C, LDL-C cholesterol showed no significant difference from G-I. The G-III group (Saroglitazar + HFD + DC) showed significant decrease in TC (**P < 0.01) and TG (**P < 0.01) when compared to G-II (diabetic control) group, but there is no significant was observed on LDL-C, HDL-C levels. The G-IV group (Pioglitazone + HFD + DC) showed slightly differing effect on TC (*P < 0.05) and TG (*P < 0.05) when compared with G-II group.

Table 4: Effect PPAR agonists on body weight.

Groups	Before treatment (Day 0)	After treatment (Day 21)
G-I	164±9.7	202±11.8
G-II	172±8.2	245±13.6*
G-III	181±5.4	161±9.2***
G-IV	176±12.1	181±14.1**

Values are expressed as the mean ± SEM (n=6), G-II was compared with G-I and remaining groups are compared with G-II. *P < 0.05; **P < 0.01, ***P < 0.001; Data was analyzed by Two-way ANOVA followed by dunnets test.

Table 5: Effect PPAR agonists on fasting blood (plasma) glucose levels.

Groups	Day 0	Day 7	Day 14	Day 21
G-I	110±10.0	111±12.0	109±11.9	113±12.3
G-II	312±12.6***	345±16.1***	347±13.9***	339±11.0***
G-III	333±17.0	208±11.5***	125±16.2***	94±12.0***
G-IV	338±8.0	258±14.1***	141±12.8***	102±9.0***

Values are expressed as the mean ± SEM (n=6) G-II was compared with G-I and remaining groups are compared with G-II. *P < 0.05; **P < 0.01, ***P < 0.01; Data was analyzed by Two-way ANOVA followed by dunnets test.

Table 6: Effect PPAR agonists on other blood (plasma) parameters.

Groups	Day 0 (Before treatment)				Day 21 (After treatment)			
	TC	HDL	LDL	TG	TC	HDL	LDL	TG
G-I	65.6±2.8	22.5±3.7	30.8±5.6	91.2±9.5	69.3±7.9	22.0±3.1	33.8±8.8	98.5±9.6
G-II	90.7±3.8*	15.1±4.9	44.2±5.9	138±8.6***	110.1±10.8*	12.1±5.6^{ns}	51.6±14.8^{ns}	146±12.3**
G-III	89.5±3.4	15.3±3.8	42.5±2.9	131±3.1	58.4.±12.6**	28.7±11.9^{ns}	29.5±6.6^{ns}	96.3±8.2**
G-IV	93.9±2.7	15.8±2.4	45.1±5.3	129±4.7	71.9±12.6*	19.8±6.8^{ns}	35.1±11.8^{ns}	108±12.1*

Values are expressed as the mean ± SEM (n=6). G-II was compared with G-I and remaining groups are compared with G-II. *P < 0.05; **P < 0.01; Data was analyzed by Two-way ANOVA followed by dunnets test.

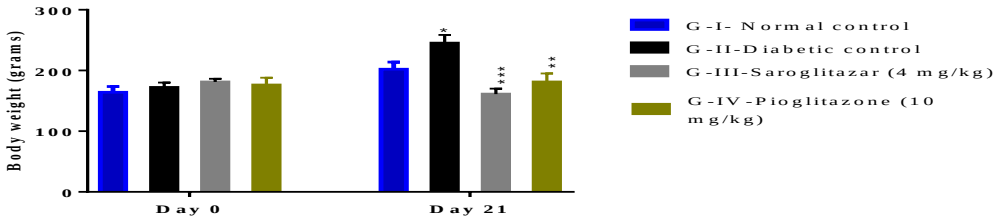

Figure 1: Effect PPAR agonists on body weight (g) of rats.

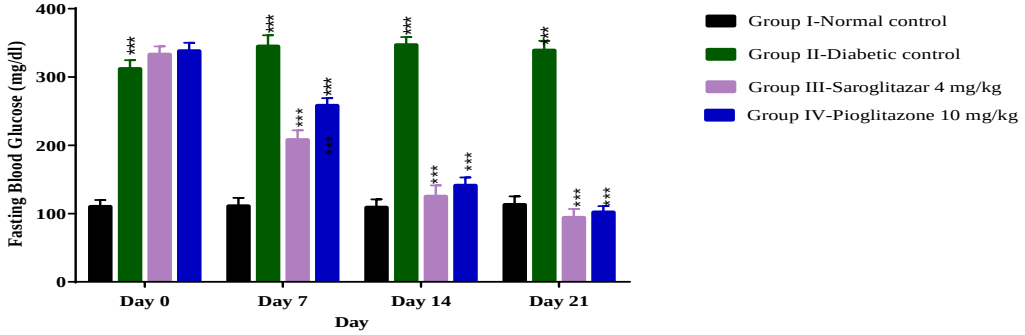

Figure 2: Effect PPAR agonists on fasting blood (plasma) glucose levels (mg/dl).

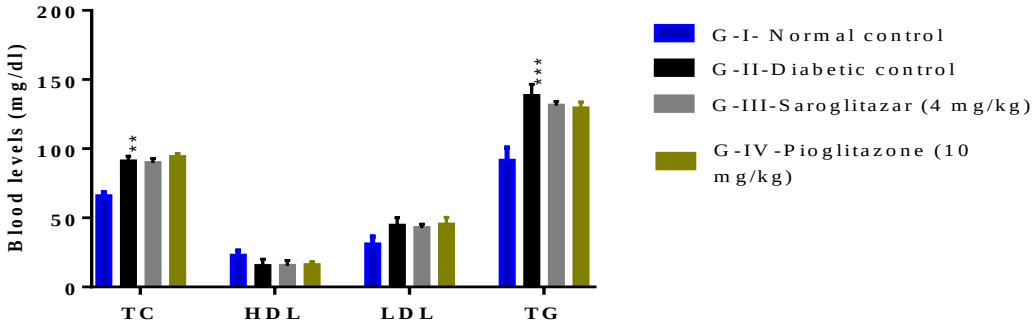

Figure 3: Effect PPAR agonists on other blood (plasma) parameters- Before Treatment.

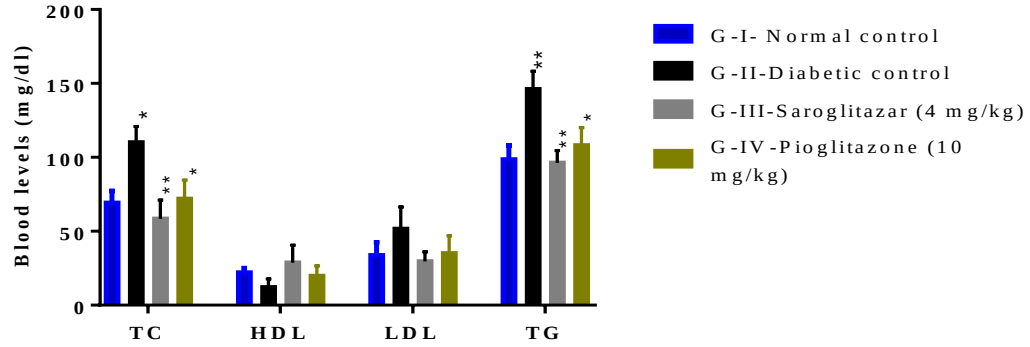

Figure 4: Effect PPAR agonists on other blood (plasma) parameters- After Treatment.

4. DISCUSSION

Type 2 diabetes mellitus (DM) has recently been described as "coronary risk equivalent". Lipoprotein metabolism disorder in type 2 DM is known as diabetic dyslipidemia. Dyslipidemia contributes to a substantial percentage in cardiovascular mortality and morbidity in diabetic patients. Thus lowering lipids is the first priority in treating diabetic dyslipidemia. Statins are the first drug of choice, followed by resins, ezetimibe, fenofibrate, niacin and others. If a single agent is inadequate to achieve lipid goals, combinations of the preceding drugs may be used [11].the traditional drugs associated with lot of toxicity and low efficacy profile alternative new drugs such as PPAR receptor agonists were developed for safe and effective management of diabetes and dyslipidemia.

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors of nuclear hormone receptor super family comprising of the following three subtypes: PPARα, PPARγ, and PPARα/γ. Activation of PPAR-α reduces triglyceride levels and activation of PPAR-γ causes reduction in blood glucose levels.[12] PPARγ receptor selective agonists like Pioglitazone was used for management of type-2 diabetes, but this class of drugs potential to cause cardiovascular toxicity. Research was pointed towards the development of newer and safer drugs than Piogllitazone. In 2013 new class of drugs PPARα/γ agonists like Saroglitazar was developed, which is majorly indicated for treatment of diabetic dyslipidemia. It was preferred over Pioglitazone because of the dual agonistic action on the both receptors (PPARα and γ) simultaneously reduced the glucose as well as lipid levels. Still extensive studies are required to establish the efficacy of PPARα/γ dual agonists (Saroglitazar) in diabetes along with dyslipidemia.

The present study was evaluated the comparative effect of PPARγ, and PPARα/γ agonists on HFD and low dose Streptozotocin induced model of type-2 diabetes mellitus. Previous literature explained the antidiabetic, antihyperlipidemic and comparative activity study of Saroglitazar versus Pioglitazone. They evaluated the comparative study in either Alloxan or Streptozotocin or HFD induced models, but none of the reported literature explained the comparative study of Saroglitazar and Pioglitazone in Streptozotocin along with HFD induction of type-2 diabetes. Novelty in the present study evaluation of comparative study of PPARγ (Pioglitazone) and PPARα/γ dual agonist (Saroglitazar) on HFD plus streptozotocin induced type-2 diabetic rats and also the doses used in this study for comparative evaluation were not reported previously.

5. CONCLUSION

Saroglitazar is a novel PPARα/γ dual agonist, showed significant lipid lowering and hypoglecemic affects with good safety profile in various preclinical models.

In the present study we evaluated the hyperglycaemic and lipid lowering comparative activity study of

Saroglitazar (PPARα/γ agonist) and Pioglitazone (PPARγ agonist).

- Saroglitazar showed better blood glucose lowering capacity when compared to Pioglitazone and this activity might be due to more specific agonistic action on PPARγ Receptors when compared with Pioglitazone.
- In lipid lowering study Saroglitazar showed more significant reduction in plasma total cholesterol (TC) and triglycerides (TG) when compared to Pioglitazone and this action might be due to more selectivity for PPARγ receptors when compared with Pioglitazone.
- Saroglitazar treated animals showed significant reduction in body weight when compared to Pioglitazaone, the possible mechanism for this activity due to dual agonistic capacity (PPARα/γ agonistic action) of Saroglitazar when compared to Pioglitazone (only PPAR γ agonistic action).
- Saroglitazar had the better activity when compared with Pioglitazone for reduction in body weight, blood glucose (hypoglycaemic) and lipid levels (hypolipdemic). The dual agonistic action of Saroglitazar favours the concomitant reduction in blood glucose (PPARγ action) and lipids (PPARα action). Pioglitazone had selective agonistic action only for PPARγ receptors; it produced more effect only on blood glucose rather than lipid parameters.
- Saroglitazar can reduces the usage of other combination regimens like Pioglitazone (PPARγ) and Fenofibrate (PPARα), because Saroglitazar single drug itself produced the both the actions.
- Finally from the results it was concluded that for the treatment of diabetic dyslipidemia Sarogliatzar might be the better drug of choice when compared with Pioglitazone.

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