**Original Research Article**

# Effects of Rosiglitazone and Metformin as monotherapy and in combination on high fructose diet induced hyperglycemia and dyslipidaemia in rats

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## ABSTRACT

**Background:** Type II diabetes mellitus is a chronic disease causing considerable morbidity and mortality worldwide. It has now been well established that insulin resistance plays a major role in the pathogenesis of type II diabetes. Rosiglitazone and Metformin are two most common drugs belonging to different classes and acting through varied mechanisms. The aim of the study was to better evaluate their beneficial and adverse effects as monotherapy and also as combination in a high fructose diet induced diabetic model.

**Methods**: Male wistar albino rats (04 weeks old) weighing 160-180 gms were made diabetic by feeding a high fructose diet for 04 weeks. These rats while continuing to be on high fructose diet were divided into four groups and administered orally, vehicle (5% gum acacia), Rosiglitazone (3mg/kg), Metformin (300mg/kg) and Rosiglitazone (3mg/kg) + Metformin (300mg/kg). All the above treatments were given for 04 weeks and the effects were studied.

**Results:** The biochemical parameters viz. hyperglycemia, hypertriglyceridemia and increased FFA levels were brought down significantly by Metformin ($p<0.05$) and Rosiglitazone ($p<0.01$) monotherapy; Rosiglitazone being more effective than Metformin. The co-administration of Rosiglitazone and Metformin had a synergistic effect and resulted in much greater efficacy in ameliorating the parameters. Moreover the adverse effects of Rosiglitazone like weight gain and lowering of haemoglobin were significantly mitigated by co-administration of Metformin. Rosiglitazone showed a tendency towards elevation of serum bilirubin and liver enzymes

**Conclusions:** The results suggest that monotherapy with Rosiglitazone is superior to Metformin in treating a diabetic state. However the combination of Rosiglitazone and Metformin had a much greater efficacy with the added advantage of reducing the adverse effects. It is further recommended to keep the hepatotoxic potential in mind during the therapy with Rosiglitazone.

**Keywords:** Rosiglitazone, Metformin, High fructose diet

## INTRODUCTION:

Type II Diabetes mellitus or Non- Insulin Dependent Diabetes Mellitus (NIDDM) is a chronic and disabling disease causing considerable morbidity and mortality worldwide. It is a global health problem afflicting approximately 420 million people worldwide, with far reaching effects on patient's quality of life and considerable burden on health care. [(1)] Its chronic complications include retinopathy, nephropathy, neuropathy and accelerated atherosclerosis, which result in blindness, end-stage renal disease, amputations, and premature cardiovascular mortality.[(2)]

It has now been well established that insulin resistance plays a major role in the pathogenesis of type II diabetes and any treatment modality that tackles insulin resistance will have far-reaching beneficial effects in NIDDM. Subsequently it was

suggested that insulin resistance might be the primary patho-physiological feature of NIDDM. [3] The concept of insulin resistance as a pathogenetic mechanism for glucose intolerance and diabetes mellitus emerged from early observations that patients with NIDDM had hyperglycemia despite having plasma insulin concentrations that were well above normal.[4]

Rosiglitazone is an insulin-sensitizing agent belonging to the thiazolidinedione group .It acts primarily by decreasing the insulin resistance prevailing in patients of NIDDM. Rosiglitazone targets insulin resistance by binding to the transcription factor, Peroxisome Proliferator Activated Receptor–gamma (PPAR-γ), promoting synthesis of glucose transporters (GLUTs) and adipocyte differentiation. Rosiglitazone promotes glucose uptake into muscle and adipose tissue, reduce hepatic glucose production and increase hepatic glucose uptake. So far, Rosiglitazone appears to be devoid of fulminant hepatotoxicity that was associated with earlier glitazones but doubts still persist.[5]

Metformin is a drug of biguanide class used to lower blood glucose concentrations in patients with non-insulin-dependent diabetes mellitus (NIDDM). The glucose-lowering effect is attributed to multiple mechanisms like decreased hepatic glucose output, decreased intestinal absorption of glucose, though increased sensitivity to insulin also plays an important part. Metformin therapy helps in improving insulin sensitivity and thus decreases the insulin resistance that is prevalent in NIDDM. [6]

There is a paucity of studies in the literature where the comparative efficacy of these drugs as monotherapy as well as combination therapy for the treatment of insulin resistance has been studied. Under these circumstances it becomes important to evaluate the efficacy of rosiglitazone in comparison to metformin, and also to study its effects in combination with metformin. In view of the above it was felt necessary to undertake this study.

**METHODS:**

Healthy adult male wistar albino rats, weighing between 160-180 gms were used in this study. They were housed in clean cages and were maintained on standard laboratory diet and water ad-libitum. After a five-day acclimatization period the rats were used for the study as per guidelines of committee for the purpose of control and supervision on experiments on animals (CPCSEA) after the approval from institutional animal ethics committee.

All animals were given a high fructose diet for 04 weeks, which resulted in a rodent model of insulin resistant diabetes with hyperglycemia, hypertriglyceridemia and high levels of free fatty acids. High fructose diet was prepared in the lab using casein, high protein 207 g, DL- methionine 3 g, fructose 600 g, lard 50 g, cellulose 9.81 g, mineral mix 50 g, zinc carbonate 0.04 g, vitamin mix 10 g and food color, green 0.15 g.

The drugs were administered orally as suspension with gum acacia. Rosiglitazone and Metformin were administered in the doses of 20mg/kg/day and 300 mg/kg/day respectively to the rats. A 5 percent suspension of gum acacia was prepared for administration to control rats. A fixed volume of 1.5 ml with or without drugs was administered orally to all the rats.

The rats were randomly divided into four groups of 10 rats each. Each of the four groups received various treatment modalities daily for 04 weeks as given below.

Group 1: Control (5% gum acacia)

Group 2: Rosiglitazone (3 mg/kg)

Group 3: Metformin (300 mg/kg)

Group 4: Rosiglitazone (3 mg/kg) + Metformin (300 mg/kg)



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Blood samples were drawn on 28th day under anaesthesia. Various parameters were estimated like serum glucose, total triglycerides, free fatty acids, haemoglobin, AST (SGOT), ALT (SGPT), serum bilirubin and body weight.

**Statistical analysis:**

All data are expressed as mean + SEM. The effects of various treatment modalities were analyzed using one-way analysis of variance (ONE WAY ANOVA) followed by post hoc comparisons by tuckey test. The effects of Rosiglitazone on liver function test parameters were assessed using paired t teat. Significance was fixed at a value of P< 0.05 for all the statistical calculations.

**RESULTS:**

The effects of the test drugs on the various important parameters are given below in **Table 1**.

Table 1: Effects of individual drugs: Rosiglitazone and Metformin in fructose fed rats

| Group | Serum Glucose (mg/dl) | Serum Triglycerides (mg/dl) | Serum Free fatty Acids (mg/dl) | Blood Haemoglobin (gm/dl) | Body weight (grams) |
|---|---|---|---|---|---|
| Control (5%gum acacia) | 151.5±6.1 | 161.3±8.6 | 48.4±5.1 | 15.26±0.8 | 338.5±7.8 |
| Rosiglitazone (3mg/kg) | 105.5±4.9 [c] | 108±6.4 [c] | 27.7±3.9 [b] | 12.22±0.6 [a] | 365.5±7.2 |
| Metformin (300mg/kg) | 123.5±7.3 [a] | 118±9.3 [b] | 40.2±3.8 | 14.17±0.7 | 312.5±11.8 [e] |
| Rosiglitazone+ Metformin (3+300mg/kg) | 87.2±5.3 [c,i] | 85.6±7.4 [c,g] | 21.4±2.7 [c,h] | 15.1±0.6 [d] | 333±14.1 |
| One way Anova df(3,36) | F=21.06 P<0.0001 | F=15.74 P<0.0001 | F=9.39 P<0.0001 | F=4.22 P<0.05 | F=4.23 P<0.05 |

All values represent mean ± SEM

**a**, **b** and **c**: p< 0.05, 0.01 and 0.001 respectively compared to control

**d**, **e** and **f**: P< 0.05, 0.01 and 0.001 respectively for Rosiglitazone and Rosiglitazone + Metformin compared to Rosiglitazone

**g**, **h** and **i**: P< 0.05, 0.01 and 0.001 respectively for Rosiglitazone + Metformin compared to Metformin

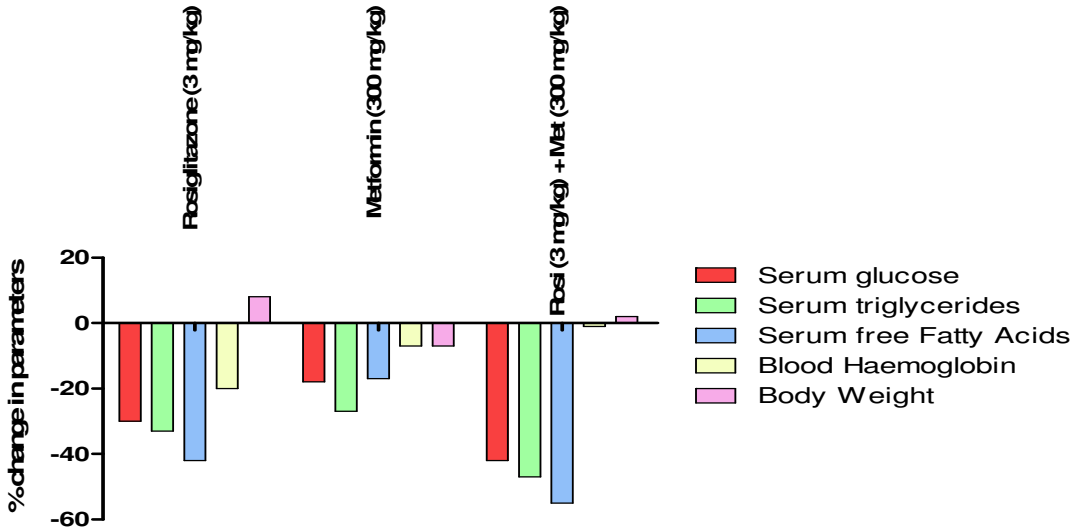
All the three groups (Rosiglitazone 3 mg/kg, Metformin 300 mg/kg, Rosiglitazone + Metformin) significantly decreased serum glucose level as compared to control. P< 0.001, 0.05 and 0.001 for Rosiglitazone, Metformin and Rosiglitazone + Metformin groups respectively as compared to control. The change in serum glucose was significant with Rosiglitazone + Metformin group compared to Metformin group (P<0.001).

Rosiglitazone, Metformin and Rosiglitazone + Metformin groups significantly reduced serum triglyceride levels compared to control group (P<

0.001, 0.01 and 0.001 respectively). Rosiglitazone + Metformin group significantly decreased serum triglycerides compared to metformin group (P< 0.05). Decrease in serum free fatty acids level was significant with Rosiglitazone and Rosiglitazone + Metformin group compared to control (P< 0.01 and 0.001 respectively). The decrease was significant with Rosiglitazone + Metformin group (P< 0.01) compared to Metformin group.

Only Rosiglitazone group caused significant decrease in blood haemoglobin compared to control (P < 0.05). Rosiglitazone + Metformin significantly decreased blood haemoglobin compared to Rosiglitazone group (P < 0.05). The change in body weight was significant with metformin group only compared to Rosiglitazone group (P < 0.01). The percentage change in various parameters among the different groups are displayed as under in Figure 1.

**FIGURE 1: Percentage change in various parameters among different groups:**




Rosiglitazone (3 mg/kg) after 04 weeks of treatment significantly increased ALT levels while the effect on AST and serum bilirubin were not significant.

**TABLE 2: Effect of Rosiglitazone on liver function tests:**

| PARAMETER | BASE LINE | AFTER ROSIGLITAZONE |
|---|---|---|
| AST (SGOT) (IU/L) | 22 ± 1.93 | 26.9 ± 2.32 |
| ALT (SGPT) (IU/L) | 35.2 ± 2.13 | 42.8 ± 3.32 * |
| SERUM BILIRUBIN (MG/DL) | 0.637 ± 0.056 | 0.719 ± 0.059 |

All values represent mean ± SEM.

* P<0.05 as compared to Base line values

**DISCUSSION:**

Interplay between progressive insulin resistance and beta cell failure is the currently accepted theory for the aetiopathogenesis of Type II diabetes mellitus. In fact insulin resistance is the antecedent abnormality and is the major contributing factor to the development of Type II diabetes mellitus and most patients with NIDDM nearly always have an element of insulin resistance. [7]

The study was conducted in a rodent model of insulin resistance- the high fructose fed rats. Male Wistar albino rats fed on a high fructose fed diet have been reported to develop hyperglycemia, hypertriglyceridemia and elevated levels of free fatty acids. This change in parameters is consistent with the development of insulin resistant diabetes in the rats and is symptomatically similar to clinical insulin resistance. [8,9]

The study was conducted in a group of forty rats that were made insulin resistant diabetic by feeding a high fructose diet for 04 weeks. The fructose content was 600 gms per 1000 gms of the diet and provided 60% of the total caloric intake. These rats were used to study the effect of various treatment modalities.

Rosiglitazone (3 mg/kg body weight), after 04 weeks of daily treatment produced a significant decrease in serum glucose (30%) ($P<0.001$), serum triglycerides (33%) ($P<0.001$), serum free fatty acids (42%) ($P<0.01$) and blood haemoglobin (20%) ($P<0.05$) and an increase in body weight (8%) when compared to control. Our observations are in agreement with the known effects of rosiglitazone in the literature. [10,11] However the extent of lowering of parameters in some cases are different. The effects of rosiglitazone on Serum glucose, triglycerides and free fatty acids are possibly due to its well-known insulin sensitizing action. The fall in haemoglobin can be explained by the increase in plasma volume and the dilutional effect of glitazones. [12] The cause of increase in body weight is not clear. However an effect on adipogenesis and increased appetite have been implicated. [13]

Metformin (300mg/kg/day) also decreased serum glucose (18%) ($P<0.05$), serum triglycerides (27%) ($P<0.01$), and free fatty acids (17%). Fall in weight with metformin was significant when compared to rosiglitazone group ($P< 0.01$). This is in agreement with the known beneficial actions of metformin [14,15], though the extent of lowering of various parameters is significantly less than rosiglitazone. The animals on metformin had a lowering of body weight (7%) when compared to Control. This effect has been attributed to the anorexic effect of metformin. [16]

When Rosiglitazone was combined with Metformin there was greater lowering of biochemical parameters viz. serum glucose (42%) , serum triglycerides (47%) and FFA (55%) . The effects on serum glucose, triglycerides and free fatty acids were significant when compared to metformin group ($P< 0.001$, 0.05 and 0.01 respectively). Effects of combination therapy on haemoglobin levels were significant compared to rosiglitazone group ($P<0.05$). The additive effects seen with rosiglitazone and metformin can be explained by the different mechanisms of action of the two drugs. While Rosiglitazone acts mainly by increasing insulin sensitivity in target organs such as adipose tissue and muscle, Metformin acts primarily by decreasing endogenous hepatic glucose production. The adverse effects like increase in body weight and lowering of haemoglobin that were seen with rosiglitazone were significantly less during therapy with the combination, viz blood haemoglobin (1%) and body weight (2%). The observations were in agreement with the previous observations. [17]



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The co-administration of Metformin and Rosiglitazone, may offer a great advantage in providing additive effect on serum glucose, triglycerides and free fatty acids. The combination was also useful in reversing the adverse effects of rosiglitazone on body weight and blood haemoglobin.

The effects of Rosiglitazone on liver function tests were mixed. There was a general tendency towards elevation of serum bilirubin and liver enzymes, though only in case of ALT, was the increase statistically significant. It seems likely that Rosiglitazone does have some adverse effect on liver function and is not entirely free from hepatotoxicity.

**CONCLUSION:**

In view of the above-mentioned observations, it has been concluded that Rosiglitazone seems to be more effective than Metformin in treatment of insulin resistant diabetes. The combined administration of Rosiglitazone and Metformin is much more effective in controlling the insulin resistant diabetic state with minimum adverse effects on blood haemoglobin and body weight. Use of Rosiglitazone was associated with a mild adverse effect on liver function and a gain in body weight. Hence it is recommended to perform regular liver function tests to guard against the possibility of hepatotoxicity.

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