

# BENEFICIAL EFFECTS OF TRIPLE DRUG COMBINATION OF ROSIGLITAZONE WITH GLIBENCLAMIDE AND METFORMIN IN TYPE 2 DIABETES MELLITUS PATIENTS ON INSULIN THERAPY

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## ABSTRACT

The thiazolidinediones are a class of anti-diabetic medication that enhances the action of insulin in the muscle, liver and adipose tissue. Data has been lacking on their use in combination with both sulfonylurea and metformin among patients of type 2 diabetes who are on insulin therapy secondary to failure of routine oral hypoglycemic drugs in controlling their diabetes. The objective of this study was to determine the effects of rosiglitazone in combination with sulphonylurea and metformin on diabetes control in patients being treated with insulin due to secondary failure of oral hypoglycemic agents.

151 consecutive type 2 diabetes patients (mean age 56.49 years) attending 4 centers in Mumbai, who were being treated with insulin were selected. They were switched on to triple drug combination of glibenclamide 5mg, metformin 500mg and rosiglitazone 4 mg along with insulin. Study participants were required to have type 2 diabetes mellitus for at least 5 years. Patients were excluded if they had any of the following: serum creatinine concentration greater than 1.5 mg/dl, alanine aminotransferase (ALT) level more than 2 times the upper limit of normal, symptomatic angina, cardiac insufficiency or history of myocardial infarction.

Rosiglitazone 4 mg once a day with glibenclamide 5mg and metformin 500mg given three times daily, significantly decreased hemoglobin A<sub>1c</sub> level from 12.4±1.87% to 7.79±0.41% (p<0.001), average fasting blood glucose from 194.8±73.7 mg/dl to 124.06±26.14 mg/dl (p<0.01) Average post prandial blood glucose from 256.24±41.36 to 162.32±14.33 mg/dl(p<0.01). At 6 months, 49% of patients did not need to be continued on insulin. The total insulin requirement in 151 patients was reduced by 73.37%. There were no significant side effects and hepatic transaminoferases were within acceptable levels. Average weight gain was 1.88±1.93kg. Significant hypoglycemia was observed in 11.26% (17 patients) with none requiring hospitalization.

In conclusion, triple oral drug therapy with rosiglitazone, glibenclamide and metformin can be safely used in type 2 diabetes patients receiving insulin with significantly improved metabolic control. With this combination it was possible to significantly reduce the insulin dose or discontinue insulin therapy in a large number of patients.

**KEY WORDS** : Type 2 diabetes; Combination therapy; Insulin; Rosiglitazone; Metformin; Glibenclamide.

## INTRODUCTION

Type 2 diabetes mellitus is characterized by the presence of insulin resistance with concomitant or eventual beta cell dysfunction. Resistance to insulin-stimulated glucose uptake is present in most patients with this disease (1). Treatment is aimed at reducing blood glucose levels to normal or near-normal values (2, 3). Diet and exercise are the first treatments of choice for patients with type 2 diabetes mellitus. However, when they do not achieve adequate blood glucose control (4) initiation with oral anti-diabetic therapy is then advocated.

First-line monotherapy typically begins with sulfonylurea (an insulin secretagogue) or metformin (which inhibits hepatic gluconeogenesis) (5). When monotherapy fails, these agents are frequently prescribed in combination (6). However, when patients continue to experience suboptimal control on maximum doses of these drugs, insulin injection therapy has to be started (7, 8).

Thiazolidinediones are a class of peroxisome proliferator-activated receptor- drugs that, unlike sulfonylureas and metformin, stimulate increased peripheral glucose disposal and reduce insulin resistance in the muscle, liver, and adipose tissue (9-12). Studies have shown that rosiglitazone used as monotherapy or in combination with sulfonylurea and metformin improves glucose control (13-15). The addition of an insulin-sensitizing agent, such as rosiglitazone, to complement the insulin-stimulatory and hepatic glucose-suppressive

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effects of sulfonylurea and metformin has been considered an attractive therapeutic alternative to insulin. However, the use of triple drug combination of rosiglitazone, sulphonylurea and metformin in patients already on insulin therapy has not been studied. Whether a thiazolidinedione would be efficient at a stage of the disease when  $\beta$ -cell secretion is failing (16) remains to be demonstrated. The current study with triple drug therapy was under taken to see it's effect in glycemic control in patients of type 2 diabetes mellitus who were already on insulin.

## METHODS

**Patients:** 151 consecutive type 2 diabetes patients (mean age, 56.49 years) males 69 and females 82 attending 4 centers in Mumbai, who were being treated with insulin were selected. They were switched on to triple drug combination of glibenclamide 5mg t.i.d, metformin 500mg t.i.d and rosiglitazone 4 mg O.D along with insulin. Only subjects with duration of type 2 diabetes mellitus of at least 5 years duration and who were being treated with insulin were included in the study.

The exclusion criteria included any patients with any cardiac abnormality, including history of symptomatic angina, cardiac insufficiency or history of myocardial infarction or an abnormal ECG. Patients with known renal failure or increased S. creatinine levels  $>1.5$  mg/dl. Patients with SGOT/SGPT more than 2 times the upper limit of normal and patients having more than 60 ml alcohol/day.

**Study Design:** 151 patients who met the inclusion criteria had their base line ECG, fasting and post prandial blood sugars, HbA<sub>1c</sub>, SGOT, SGPT, creatinine and lipid profile done. They were then treated with rosiglitazone 4 mg/d and glibenclamide 5mg, metformin 500mg three times a day in addition to insulin. They were advised to repeat their plasma glucose every three weeks and report for follow-up. They were educated regarding hypoglycemia and were to report it telephonically if they experienced it before their follow-up date.

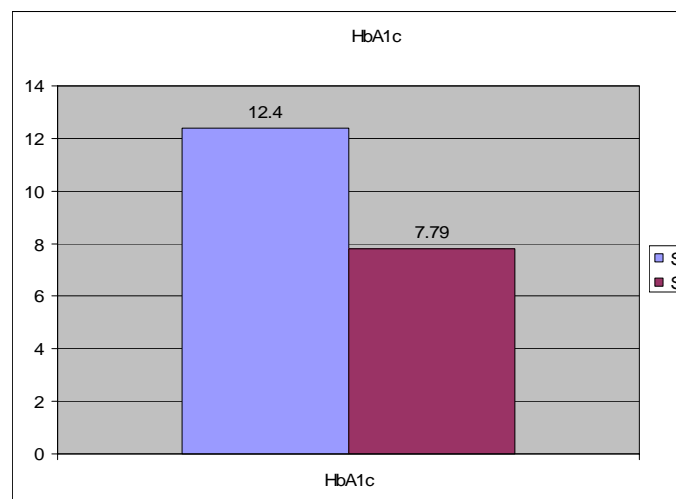
Fasting and postprandial plasma glucose level and biochemical measures of safety, including chemistry tests (SGOT, SGPT), hematological tests, were performed at 3-weekly intervals throughout the study. Self-monitoring of blood glucose was encouraged, if the patients had glucose meters. At every follow-up if the plasma glucose levels reduced, the insulin doses were appropriately reduced. Some patients who experienced hypoglycemia before the follow-up date were telephonically instructed to reduce their insulin doses.

Once the patient was off insulin, and continued to show a fall in plasma glucose levels, glibenclamide was periodically reduced. The rosiglitazone and metformin was continued in full doses except in a few patients who could not tolerate full doses of metformin. Repeat measurements of Hemoglobin A<sub>1c</sub> levels were done at 3 months and six months.

## RESULTS

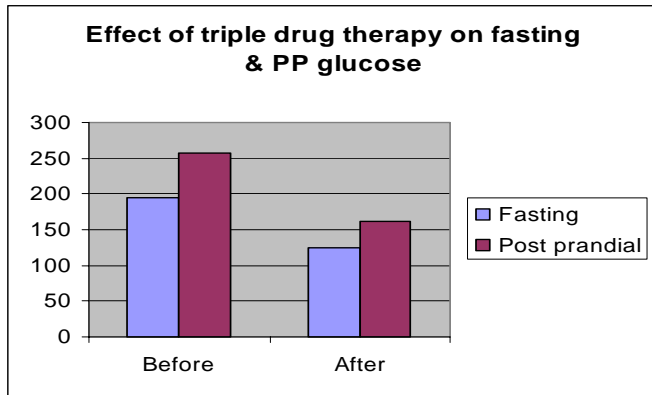
151 patients who had complete records of follow-up and completed six months of triple drug therapy were analyzed. 17 patients (11.26%) experienced significant hypoglycemia with none requiring hospitalization. These patients were those who did not stick to follow-up schedules. Most patients reporting hypoglycemia, at any time, reported only one occurrence.

**Fig 1: HbA<sub>1c</sub> Pre and Post Trial.**



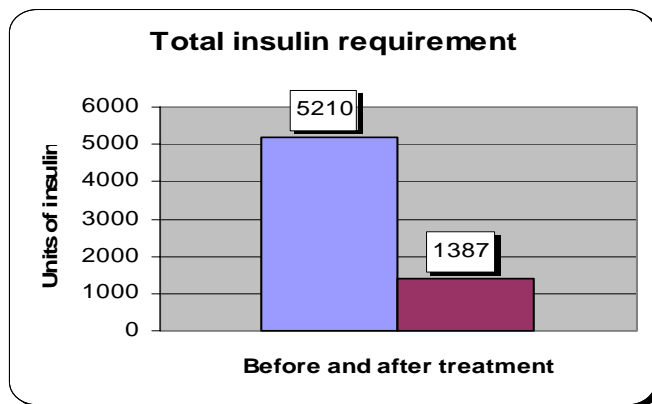
Mean values for hemoglobin A<sub>1c</sub>, fasting and postprandial glucose and insulin requirement decreased significantly from baseline during the course of therapy for 6 months. The combination therapy at the end of 6 months significantly increased the proportion of patients achieving treat-to-target hemoglobin A<sub>1c</sub> levels compared to earlier therapy. The average HbA<sub>1c</sub> in 151 patients was reduced from  $12.4 \pm 1.87\%$  to  $7.79 \pm 0.41\%$  a reduction of 36.35% ( $p < 0.001$ ) (Fig 1 and Table 1). Among 58 males the reduction was 39.16% compared to 35.32% in 82 female patients. The average fasting plasma glucose levels reduced from  $194.8 \pm 73.7$  mg/dl to  $124.06 \pm 26.14$  mg/dl a reduction of 36% ( $p < 0.01$ ). The average postprandial plasma glucose levels reduced from  $256.24 \pm 41.36$  mg/dl to  $162.32 \pm 14.33$  mg/dl a reduction of 36.65% ( $p < 0.01$ ) (Fig 2 and Table 1).

**Fig 2: Effect of Triple Drug Therapy on Fasting and Post Prandial Glucose**



The total insulin being taken by 151 patients prior to starting triple drug therapy was 5210 units /day. After 6 months of therapy the requirement of insulin dropped to 1387 units/day, a reduction of 73.37%. Further in 74 (49.01%) patients, insulin therapy was totally discontinued (Fig 3 and Table 1).

**Fig 3: Insulin Usage Pre and Post Trial**



**Table1: Effect of Triple Drug Combination on Fasting and Post Prandial Glucose, HbA<sub>1c</sub> and Insulin usage.**

Fasting mg/dl	Postprandial-mg/dl	HbA <sub>1c</sub> %	Insulin dose-units/day
194.8 ± 73.70	256.24 ± 41.36	12.4 ± 1.87	5210
124.06 ± 26.14	162.32 ± 14.33	7.79 ± 0.41	1387

Mean body weight at baseline and 6 months was 67.45±0.87 kg and 69.33±11.70kg. There was an increase of 1.88±1.93 kg after 6 months.

Triple drug therapy was well tolerated throughout the study. No patients withdrew from the study because of elevated ALT levels. Symptoms associated with hypoglycemia were reported by 17 patients with none

requiring hospitalization. No patient required intervention other than a snack or beverage. Many reports of hypoglycemic symptoms were associated with missed meals.

## DISCUSSION

Patients with type 2 diabetes mellitus are often treated according to a stepped progression, starting with a regimen of nutrition counseling and exercise and progressing to monotherapy with a sulfonylurea, metformin, or acarbose. As hyperglycemia worsens, combinations of oral agents are often required. When a combination of a sulfonylurea and metformin cannot achieve the treatment goals, insulin injections must be initiated (2, 3).

Addition of an insulin-sensitizing agent, such as rosiglitazone, to complement the insulin-stimulatory and hepatic glucose-suppressive effects of sulfonylurea and metformin has been considered an attractive therapeutic alternative to insulin. The triple drug combination could work synergistically in reducing insulin resistance, thereby reducing the requirements of insulin significantly. However, the use of triple drug combination of rosiglitazone, glibenclamide and metformin in patients already on insulin therapy has not been studied. Our study provides evidence, supporting use of a triple drug therapy of glibenclamide 5mg, metformin 500mg and rosiglitazone 4 mg in patients of type 2 diabetes as a therapeutic means of improving glycemic control in patients with inadequate glycemic control despite treatment with insulin.

The triple drug therapy method used in this study demonstrated early and sustained reductions in fasting glucose levels, followed more slowly by similar reductions in hemoglobin A<sub>1c</sub> levels. Inclusion criteria were specifically designed to test the effects of triple drug therapy in patients on insulin therapy. Patients with cardiac or renal compromise were strictly not included.

The 73.37% reduction in total insulin dose paralleled the reductions in glucose and hemoglobin A<sub>1c</sub>. These findings suggest that the triple drug therapy is quite effective in improving insulin-mediated glucose utilization through increased insulin sensitivity.

The patients gained 1.88 kg SD ± 1.93, which may be explained in part by a decrease in glycosuria secondary to improved glycemic control and resultant caloric retention. Rosiglitazone and glibenclamide are also known to contribute to weight gain.

17 patients reported occurrences of symptomatic hypoglycemia with none requiring hospitalization. This happened in patients who did not stick to follow-up schedules as advised. Rosiglitazone is capable of reducing glucose levels when used in combination with an insulin secretagogue and metformin, timely decrease in concurrent insulin therapy is warranted to avoid severe hypoglycemia or sustained activity-limiting hypoglycemic episodes.

With respect to hepatic events, the SGOT/SGPT levels showed marginal variations but never enough to warrant discontinuation of therapy as none of the patients had levels greater than 2.5 times the normal.

Our study shows that a triple drug combination of rosiglitazone, glibenclamide and metformin is effective and well tolerated and can be safely used in type 2 diabetes patients receiving insulin with significantly improved metabolic control. With this combination it is possible to significantly reduce the insulin dose or discontinue insulin therapy in a large number of patients. The addition of a rosiglitazone also offers an alternative to patients with inadequate glycemic control despite treatment with full doses of a sulfonylurea and metformin. The triple drug combination could help a good proportion of such patients to reach target levels of hemoglobin A<sub>1c</sub> and allow postponement of insulin therapy.

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