Section: Medicine

Original Research Article

EFFICACY OF METFORMIN-ROSIGLITAZONE THERAPY IN PATIENTS WITH TYPE II DIABETES MELLITUS

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Abstract

Background: To assess efficacy of metformin-rosiglitazone therapy in patients with type II diabetes mellitus. **Materials and Methods:** Eighty- four patients with type II DM of both genders were divided into 2 groups of 42 each. Group I received 2.5 g/d of metformin plus placebo and group II received 2.5 g/d of metformin plus 4 mg/d of rosiglitazone for 26 weeks. All were subjected to assessment of glycosylated haemoglobin, fasting plasma glucose, insulin sensitivity, and β-cell function, at baseline and at 26 weeks in both groups. **Result:** Group I had 25 males and 17 females and group II had 23 males and 19 females. The mean TC (mmol/L) was 5.31 and 5.28 at baseline and 5.45 and 5.92 at 26 weeks. The mean TG (mmol/L) level at baseline was 2.78 and 2.56 and at 26 weeks was 2.72 and 2.61. The mean HDL (mmol/L) level was 1.17 and 1.25 and at 26 weeks was 1.24 and 1.36. The mean LDL (mmol/L) at baseline was 3.08 and 2.96 and at 26 weeks was 3.18 and 3.42. The mean TC- HDL ratio (mmol/L) at baseline was 4.85 and 4.65 and at 26 weeks was 4.81 and 4.84 in group I and group II respectively. The difference was significant (P< 0.05). The mean HbA1C level at baseline was 9.2% in group I and 8.7% in group II and at 26 weeks was 5.9% in group I and 5.4% in group II. The mean FPG at baseline was 180.2 mg/dl and 192.4 mg/dl and at 26 weeks was 118.4 mg/dl and 121.6 mg/dl. The difference was significant (P< 0.05). **Conclusion:** It was found that combination treatment with once-daily metformin- rosiglitazone improves glycemic control, insulin sensitivity, and β-cell function more effectively than treatment with metformin alone.

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterized by high blood sugar levels. Hyperglycemia occurs due to increase in high blood sugar levels by a deficiency in insulin action or secretion or both. It may lead to disturbances in the metabolism of lipid, carbohydrates, and protein. Among DM the prevalence of type 2 or non-insulin dependent diabetes mellitus (NIDDM) increasing significantly in South Asian population, especially in developing country like India.[1]

The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. Several pathogenic processes are involved in the development of diabetes.[2] Long term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; autonomic neuropathy causing gastrointestinal, genitourinary and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease.[3]

Metformin acts primarily at the liver by reducing glucose output and secondarily by augmenting glucose uptake in the peripheral tissues, chiefly muscle.[4] These effects are mediated by the activation of an upstream kinase, liver kinase B1 (LKB-1), thus regulating the downstream kinase adenosine monophosphatase co-activator, transducer of regulated CREB protein 2 (TORC2), leading to its inactivation which consequently down regulates transcriptional events that promote synthesis of gluconeogenic enzymes.[5]

Rosiglitazone maleate, a member of the thiazolidinedione class of antidiabetic agents that was recently approved by the US Food and Drug Administration, targets insulin resistance by binding to the transcription factor peroxisome proliferator-activated receptor-γ, promoting synthesis of glucose trans- porters and activating adipocyte differentiation.[6] We performed this study to assess

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the efficacy of metformin-rosiglitazone therapy in patients with type II diabetes mellitus.

MATERIALS AND METHODS

After considering the utility of the study and obtaining approval from ethical review committee, we selected eighty- four patients with type II DM of both genders. Patients' consent was obtained before starting the study.

Data such as name, age, gender etc. was recorded. Patients were divided into 2 groups of 42 each. Group I received 2.5 g/d of metformin plus placebo and group II received 2.5 g/d of metformin plus 4 mg/d of rosiglitazone for 26 weeks. All were subjected to assessment of glycosylated haemoglobin, fasting plasma glucose, insulin sensitivity, and β-cell function, at baseline and at 26 weeks in both groups. The results were compiled and subjected for statistical analysis using Mann Whitney U test. P value less than 0.05 was set significant.

RESULTS

Group I had 25 males and 17 females and group II had 23 males and 19 females. [Table 1]

Table 1: Patients distribution

Groups	Group I (42)	Group II (42)
M:F	25:17	23:19

Table 2: Assessment of lipid profile

Parameters	Variables	Group I	Group II	P value
TC (mmol/L)	Baseline	5.31	5.28	0.04
	26 weeks	5.45	5.92	
TG (mmol/L)	Baseline	2.78	2.56	0.02
	26 weeks	2.72	2.61	
HDL (mmol/L)	Baseline	1.17	1.25	0.04
	26 weeks	1.24	1.36	
LDL (mmol/L)	Baseline	3.08	2.96	0.05
	26 weeks	3.18	3.42	
TC- HDL ratio (mmol/L)	Baseline	4.85	4.65	0.94
	26 weeks	4.81	4.84	

The mean TC (mmol/L) was 5.31 and 5.28 at baseline and 5.45 and 5.92 at 26 weeks. The mean TG (mmol/L) level at baseline was 2.78 and 2.56 and at 26 weeks was 2.72 and 2.61. The mean HDL (mmol/L) level was 1.17 and 1.25 and at 26 weeks was 1.24 and 1.36. The mean LDL (mmol/L) at baseline was 3.08 and 2.96 and at 26 weeks was 3.18 and 3.42. The mean TC- HDL ratio (mmol/L) at baseline was 4.85 and 4.65 and at 26 weeks was 4.81 and 4.84 in group I and group II respectively. The difference was significant (P< 0.05) [Table 2].

Table 3: Assessment of parameters

Parameters	Variables	Group I	Group II	P value
HbA1C (%)	Baseline	9.2	8.7	0.02
	26 weeks	5.9	5.4	
FPG (mg/dl)	Baseline	180.2	192.4	0.05
	26 weeks	118.4	121.6	

The mean HbA1C level at baseline was 9.2% in group I and 8.7% in group II and at 26 weeks was 5.9% in group I and 5.4% in group II. The mean FPG at baseline was 180.2 mg/dl and 192.4 mg/dl and at 26 weeks was 118.4 mg/dl and 121.6 mg/dl. The difference was significant (P< 0.05) [Table 3].

DISCUSSION

Diabetes mellitus (DM), commonly known as diabetes is an endocrinal disorder in which there are elevated blood sugar levels over a long period. The common symptoms of high blood sugar are frequent urination, increased thirst, and increased hunger.[7] However, diabetes can cause many complications also if left undertreated.[8] Some of the complications are diabetic ketoacidosis and hyperosmolar hyperglycemic state.[9] Rapid socioeconomic development and demographic changes, along with increased susceptibility for Indian individuals, have led to the explosive increase in the prevalence of diabetes mellitus in India over the past four decades.[10,11] We performed this study to assess the efficacy of metformin-rosiglitazone therapy in patients with type II diabetes mellitus.

Our results showed that group I had 25 males and 17 females and group II had 23 males and 19 females. Orbay et al,[12] assessed the efficacy and safety of adding rosiglitazone to a combination of glimepiride and metformin therapy with insufficiently controlled type 2 diabetes. Mean HbA1c levels decreased significantly from 7.54 +/- 0.9% to 6.57 +/- 0.7% (p < 0.001) at 26th week. FPG levels fell from 169.39 +/- 37.8 mg/dl to 135.69 +/- 28.0 mg/dl (p < 0.001), respectively. Insulin levels decreased from 19.60 +/- 9.8 U/L to 14.66 +/- 11.6 U/L (p = 0.026) at 26th week. No one experienced elevations of alanine

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aminotransferase (ALT) and aspartate aminotransferase (AST) levels greater than 2.5 times the upper limit of the reference range.

Our results showed that the mean TC (mmol/L) was 5.31 and 5.28 at baseline and 5.45 and 5.92 at 26 weeks. The mean TG (mmol/L) level at baseline was 2.78 and 2.56 and at 26 weeks was 2.72 and 2.61. The mean HDL (mmol/L) level was 1.17 and 1.25 and at 26 weeks was 1.24 and 1.36. The mean LDL (mmol/L) at baseline was 3.08 and 2.96 and at 26 weeks was 3.18 and 3.42. The mean TC- HDL ratio (mmol/L) at baseline was 4.85 and 4.65 and at 26 weeks was 4.81 and 4.84 in group I and group II respectively. Zinman B et al,[13] studied 207 patients with impaired glucose tolerance who received combination rosiglitazone (2 mg) and metformin (500 mg) twice daily. 103 subjects received rosiglitazone and metformin, and 104 received placebo. Vital status was obtained in 198 (96%) participants, and medication compliance (taking at least 80% of assigned medication) was 78% (n=77) in the metformin and rosiglitazone group and 81% (n=80) in the placebo group. Incident diabetes occurred in significantly fewer individuals in the active treatment group (n=14 [14%]) than in the placebo group (n=41 [39%]). The relative risk reduction was 66% and the absolute risk reduction was 26%, yielding a number needed to treat of 4. 70 (80%) patients in the treatment group regressed to normal glucose tolerance compared with 52 (53%) in the placebo group. Insulin sensitivity decreased by study end in the placebo group and remained unchanged with rosiglitazone and metformin treatment.

Our results showed that the mean HbA1C level at baseline was 9.2% in group I and 8.7% in group II and at 26 weeks was 5.9% in group I and 5.4% in group II. The mean FPG at baseline was 180.2 mg/dl and 192.4 mg/dl and at 26 weeks was 118.4 mg/dl and 121.6 mg/dl. Wang et al,[14] determined the safety and effectiveness of rosiglitazone in inadequately controlled type 2 diabetes patients with NAFLD. Type 2 diabetes patients with inadequate control on insulin secretagogues and metformin were enrolled. Patients were treated for 24 weeks with rosiglitazone, 4-8 mg daily. Out of a total of 68 patients, 60 (88.2%) completed the study treatment without serious adverse events. Treatment in two (2.9%) patients was discontinued due to elevated AST or ALT levels to more than three times the upper limit of normal, and noncompliance or loss of follow-up in six (8.8%) patients. Of the 60 patients who completed the study treatment, mean fasting plasma glucose, A1C, fasting plasma insulin, mean ALT and homeostasis model assessment for insulin resistance were all significantly reduced. Normal AST and ALT levels were achieved and maintained for at least three consecutive measurements and through to the end of the study period in 20 (33.3%) patients. Weight increased by a mean of 2.6 +/- 2.4 kg ($p < 0.001$).

CONCLUSION

It was found that combination treatment with once-daily metformin- rosiglitazone improves glycemic control, insulin sensitivity, and β-cell function more effectively than treatment with metformin alone.

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