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ORIGINAL RESEARCH

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

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Abstract

Background: Type II diabetes mellitus (T2DM) owes its pathological origin to inappropriate secretion of insulin, due to defective islet cell function or beta cell mass. The present study was conducted to evaluate the efficacy of metformin-rosiglitazone therapy in patients with type II diabetes mellitus.

Materials & Methods:90 type II DM patients of both genderswere randomized into 2 groups of 45 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.Glycosylated haemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and β-cell function, compared between baseline and week 26 in both groups.

Results: Group I had 25 males and 20 females and group II had 23 males and 22 females. In group I and group II, the mean FPG (mg/dl) at baseline was 178.2 and 190.4 and at 26 weeks was 116.4 and 120.6. The mean HbA1C (%) level at baseline was 9.1 in group I and 8.9 in group II and at 26 weeks was 5.8 in group I and 5.6 in group II. The difference was significant (P< 0.05). In group I and group II at baseline and at 26 weeks, the mean TC (mmol/L) was 5.34 and 5.20 and at 26 weeks was 5.48 and 5.96. The mean HDL (mmol/L) level was 1.16 and 1.20 and at 26 weeks was 1.22 and 1.34. The mean LDL (mmol/L) at baseline was 3.06 and 2.98 and at 26 weeks was 3.14 and 3.48. The mean TG (mmol/L) level at baseline was 2.76 and 2.54 and at 26 weeks was 2.79 and 2.63. The mean TC- HDL ratio (mmol/L) at baseline was 4.87 and 4.63 and at 26 weeks was 4.80 and 4.81 respectively. The difference was significant (P< 0.05).

Conclusion: Combination treatment with once-daily met form in-rosiglitazone improves glycemic control, insulin sensitivity, and β-cell function more effectivelythantreatmentwithmetforminalone.

Key words: Diabetes mellitus, metformin, Rosiglitazone maleate

Introduction

Type II diabetes mellitus (T2DM) owes its pathological origin to inappropriate secretion of insulin, due to defective islet cell function or beta cell mass. Continuous consumption of calories-rich meals, junk food and sedentary lifestyle have culminated into an epidemic of diabetes projected to afflict around 300 million people across the globe by 2020.[1] Defective insulin secretion leads to various metabolic aberrations in T2DM, spanning from hyperglycemia due to defective insulin-stimulated glucose uptake and upregulated hepatic

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glucose production, along with dyslipidaemia, which includes impaired homeostasis of fatty acids, triglycerides, and lipoproteins. 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 hydrochloride promotes glucose lowering by reducing hepatic glucose production and gluconeogenesis and by enhancing peripheral glucose uptake.[4]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.[5] Because both metformin and Rosiglitazone maleateact by different mechanisms,theircombinedusemaybeindicated in patients whose disease ispoorlycontrolledwithamaintenancedose of metformin.[6]The present study was conducted to evaluate the efficacy of metformin-rosiglitazone therapy in patients with type II diabetes mellitus.

Materials & Methods

The present study comprised of 90 type II DM patients of both genders. The consent was obtained from all enrolled patients.

Data such as name, age, gender etc. was recorded. Patients were randomized into 2 groups of 45 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.Glycosylated haemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and β-cell function, compared between baseline and week 26 in both groups. Data thus obtained were subjected to statistical analysis. P value < 0.05 was considered significant.

Results

Table I Distribution of patients

Groups	Group I	Group II
Drugs	metformin plus placebo	metformin plus rosiglitazone
M:F	25:20	23:22

Table I shows thatgroup I had 25 males and 20 females and group II had 23 males and 22 females.

Table II Comparison of parameters

Parameters	Variables	Group I	Group II	P value
FPG (mg/dl)	Baseline	178.2	190.4	0.01
	26 weeks	116.4	120.6	
HbA1C (%)	Baseline	9.1	8.9	0.02
	26 weeks	5.8	5.6	

Table II, graph I shows that in group I and group II, the mean FPG (mg/dl) at baseline was 178.2 and 190.4 and at 26 weeks was 116.4 and 120.6. The mean HbA1C (%) level at baseline was 9.1 in group I and 8.9 in group II and at 26 weeks was 5.8 in group I and 5.6 in group II. The difference was significant (P< 0.05).

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Graph IComparison of parameters

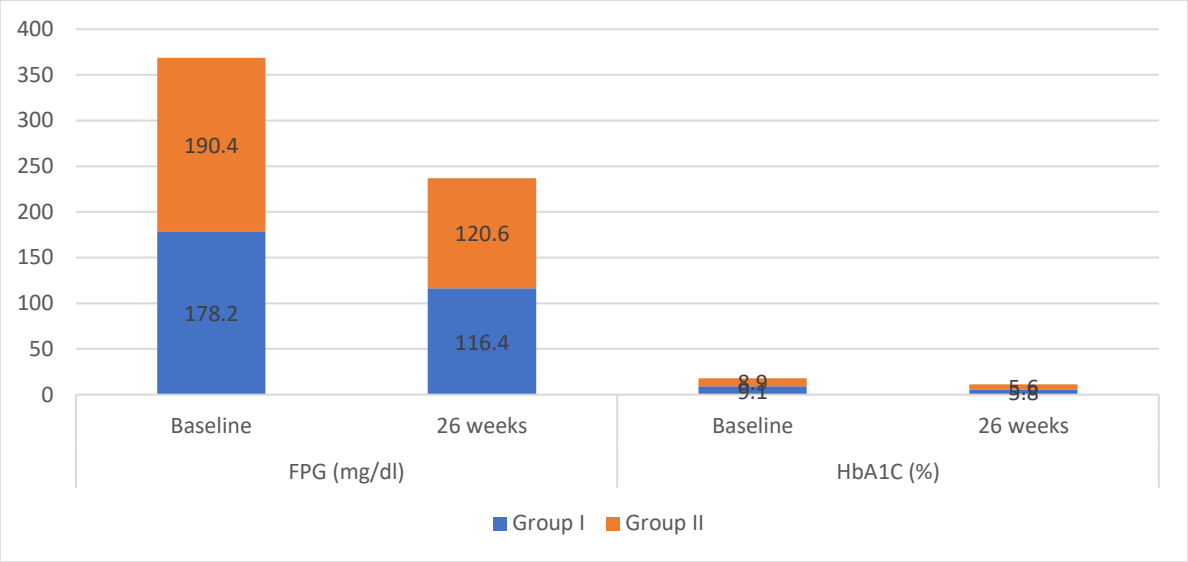

Table III Comparison of lipid profile

Parameters	Variables	Group I	Group II	P value
TC (mmol/L)	Baseline	5.34	5.20	0.05
	26 weeks	5.48	5.96	
HDL (mmol/L)	Baseline	1.16	1.20	0.03
	26 weeks	1.22	1.34	
LDL (mmol/L)	Baseline	3.06	2.98	0.01
	26 weeks	3.14	3.48	
TG (mmol/L)	Baseline	2.76	2.54	0.12
	26 weeks	2.79	2.63	
TC- HDL ratio (mmol/L)	Baseline	4.87	4.63	0.17
	26 weeks	4.80	4.81	

Table III, graph II shows that in group I and group II at baseline and at 26 weeks, the mean TC (mmol/L) was 5.34 and 5.20 and at 26 weeks was 5.48 and 5.96. The mean HDL (mmol/L) level was 1.16 and 1.20 and at 26 weeks was 1.22 and 1.34. The mean LDL (mmol/L) at baseline was 3.06 and 2.98 and at 26 weeks was 3.14 and 3.48. The mean TG (mmol/L) level at baseline was 2.76 and 2.54 and at 26 weeks was 2.79 and 2.63. The mean TC- HDL ratio (mmol/L) at baseline was 4.87 and 4.63 and at 26 weeks was 4.80 and 4.81 respectively. The difference was significant (P< 0.05).

Discussion

Diabetes mellitus (DM) is emerging as an epidemic worldwide and is a global public health problem. Diabetes mellitus (DM) is currently taking its place of the most threat to human health within the 21st century.[5] Diabetes has become a major health issue in South-East Asia. Together these abnormalitiesconfoundeffortstotreatdiabetesbecause most antidiabetic agents tar-get only 1 underlying cause of the disease.[8] Approximately 50% of patientstreatedwithmonotherapyrequireadditional therapy to achieve target glycosylated hemoglobin (HbA_{1c}) levels 3yearsafterdiagnosis.[9,10]The present study was conducted to evaluate the efficacy of metformin-rosiglitazone therapy in patients with type II diabetes mellitus.

We found that group I had 25 males and 20 females and group II had 23 males and 22 females. Fonseca et al[11]evaluated the efficacy of metformin-rosiglitazone therapy in patients

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whose type 2 diabetes is inadequately controlled with metformin alone.Three hundred forty-eight patients aged 40 to 80 years with a mean fasting plasma glucose level of 12.0 mmol/L (216 mg/dL), a mean glycosylated hemoglobin level of 8.8%, and a mean body mass index of 30.1 kg/m2 were randomized.Patients were assigned to receive 2.5 g/d of metformin plus placebo (n = 116); 2.5 g/d of metformin plus 4 mg/d of rosiglitazone (n = 119); or 2.5 g/d of metformin and 8 mg/d of rosiglitazone (n = 113) for 26 weeks.Glycosylated hemoglobin levels, fasting plasma glucose levels, insulin sensitivity, and β-cell function improved significantly with metformin-rosiglitazone therapy in a dose-dependent manner. The mean levels of glycosylated hemoglobin decreased by 1.0% in the 4 mg/d metformin-rosiglitazone group and by 1.2% in the 8 mg/d metformin-rosiglitazone group and fasting plasma glucose levels by 2.2 mmol/L (39.8 mg/dL) and 2.9 mmol/L (52.9 mg/dL) compared with the metformin-placebo group (P<.001 for all). Of patients receiving 8 mg/d of metformin-rosiglitazone, 28.1% achieved a glycosylated hemoglobin level of 7% or less. Dose-dependent increases in body weight and total and low-density lipoprotein cholesterol levels were observed (P<.001 for both rosiglitazone groups vs placebo). The proportion of patients reporting adverse experiences was comparable across all groups.

We found thatin group I and group II, the mean FPG (mg/dl) at baseline was 178.2 and 190.4 and at 26 weeks was 116.4 and 120.6. The mean HbA1C (%) level at baseline was 9.1 in group I and 8.9 in group II and at 26 weeks was 5.8 in group I and 5.6 in group II. Orbayet al[12]determined 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 aminotransferase (ALT) and aspartate aminotransferase (AST) levels greater than 2.5 times the upper limit of the reference range. This study confirms that the addition of rosiglitazone (4 mg/day) to sulphonylurea and metformin treatment for patients with type 2 diabetes improves glycemic control, is safe, and generally well tolerated.

We observed that in group I and group II at baseline and at 26 weeks, the mean TC (mmol/L) was 5.34 and 5.20 and at 26 weeks was 5.48 and 5.96. The mean HDL (mmol/L) level was 1.16 and 1.20 and at 26 weeks was 1.22 and 1.34. The mean LDL (mmol/L) at baseline was 3.06 and 2.98 and at 26 weeks was 3.14 and 3.48. The mean TG (mmol/L) level at baseline was 2.76 and 2.54 and at 26 weeks was 2.79 and 2.63. The mean TC- HDL ratio (mmol/L) at baseline was 4.87 and 4.63 and at 26 weeks was 4.80 and 4.81 respectively.Zinman Bet al[13] in their study 207 patients with impaired glucose tolerance were randomly assigned to receive combination rosiglitazone (2 mg) and metformin (500 mg) twice daily or matching placebo for a median of 3·9 years. 103 participants were assigned to rosiglitazone and metformin, and 104 to placebo; all were analysed. 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%]; p<0·0001). The relative risk reduction was 66% (95% CI 41–80) and the absolute risk reduction was 26% (14–37), yielding a number needed to treat of 4 (2·70–7·14). 70 (80%) patients in the treatment group regressed to normal glucose tolerance compared with 52 (53%) in the placebo group (p=0·0002). Insulin sensitivity decreased by study end in the placebo group (median −1·24, IQR −2·38 to −0·08) and remained unchanged with rosiglitazone and metformin treatment (−0·39, −1·30 to 0·84; p=0·0006 between groups).

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Conclusion

Authors found that combinationtreatmentwithonce-dailymetformin-rosiglitazoneimprovesglycemiccontrol,insulinsensitivity,andβ-cellfunctionmoreeffectivelythantreatmentwithmetforminalone. In patients whose fundamental responsibility is insulin resistance, such a combination promotes the exhilarating possibility of treating diabetes by targeting the underlying cause of the disease, rather than conventional approach of stimulating insulin secretion.

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