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COMPARATIVE STUDY OF EFFECTS OF COMBINATION OF METFORMIN + GLIMEPIRIDE VS METFORMIN + GLIMEPIRIDE + PIOGLITAZONE IN TYPE 2 DIABETES MELLITUS PATIENTS.

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ABSTRACT

Metformin belongs to biguanides, Glimepiride is a second-generation sulfonylurea, Pioglitazone belongs to thiazolidinediones type of oral hypoglycaemic drugs. A prospective randomized open labelled parallel study was conducted in Type II Diabetes Mellitus patients. One group received Metformin and Glimepiride (M+G) where as another group received Metformin, Glimepiride and Pioglitazone (M+G+P) for 12 weeks. Baseline investigations were carried out before and after the study. The data was statistically analysed using students 'T' test. M+G+P group showed a significant fall ($p < 0.05$) in fasting and post prandial blood glucose , giycosylated haemoglobin ($p < 0.05$), significant rise ($p < 0.05$) in high density lipoprotein, better patient compliance and follow up compared to M+G group. There was no significant difference in triglycerides, low density lipoprotein levels in both the groups. Gastrointestinal side effects were more in M+G group while pedal oedema, hypoglycaemic episodes were more in M+G+P group.

KEY WORDS: Metformin, Glimepiride, Pioglitazone, blood glucose, Giycosylated haemoglobin, High density lipoprotein.

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INTRODUCTION

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. India now has more than 50 million people with type 2 diabetes [2]. Diabetes mellitus can be controlled effectively by life style modifications like weight reduction, exercise, diet alterations [3]. If these measures prove ineffective, then pharmacological therapy becomes necessary. The presently available drugs are Sulfonylureas, Biguanides, Meglitinides, Thiazolidinediones, Alpha glucosidase inhibitors, Incretin-based drugs, Dipeptidyl Peptidase-IV inhibitors, and Amylin analogs [4, 5]. Patients are first put on monotherapy. If glucose and HbA1c levels are uncontrolled by monotherapy, life threatening complications can occur. So, now a days to prevent complications associated with uncontrolled diabetes double or triple drug therapy is used [6, 7]. Metformin works by suppressing glucose production by the liver [8] - by reducing gluconeogenesis and glycogenolysis [9], reducing the absorption of glucose from the intestine and by increasing insulin action in muscle and fat which are mediated by activation of the cellular kinase AMP-activated protein kinase (AMP kinase) [10].Glimepiride is a second-generation sulfonylurea primarily activating specific sulfonylurea receptors (SURs) on pancreatic β-cell membrane [11, 12].When sulfonylureas are bound to SURs, ATP-sensitive potassium channels close, thus resulting in an augmented trans-membrane calcium flux and insulin release from β-cells. Among sulfonylureas, only glimepiride is internalized in the cell and is able to stimulate both first and second phases of insulin secretion [13, 14, 15]. Thiazolidinediones like Pioglitazone interact with a group of nuclear receptors, known as peroxisome proliferator activated receptors-γ (PPAR-γ). Activation of PPARγ affects both glucose and fat metabolism [16]. As a PPAR-γ agonist, Pioglitazone reduces insulin-resistance by enhancing the effect of insulin on peripheral tissues [17].

MATERIALS AND METHODS

This was a randomised parallel group, open labelled comparative study done in accordance with the Declaration of Helsinki and guidelines of ICH-GCP. The protocol was approved by the NTR University of Health Sciences, Vijayawada, Andhra Pradesh and prior permission was also taken from the Institutional Ethics Committee. The sample size was 100 patients. They were randomly allocated to two groups with 50 patients each. The criteria for selecting the patients included patients of both the genders aged between 30 - 60 years with Type 2 Diabetes Mellitus non responsive to Metformin monotherapy with Hb A1c – 6.5 % to 11 % attending medical outpatient department in the general hospital . The exclusion criteria included patients with diabetes, aged < 30 years and > 60 years, patients with diabetes with Hb A 1c < 6.5 % & > 11%, type 1 diabetes patients who are on insulin, latent autoimmune diabetes of adulthood, drug or toxin-induced diabetes, diabetes associated with other conditions like hypertension, history of acute metabolic complications such as diabetic ketoacidosis or hyperosmolar non ketotic coma within 3 months before screening, current therapy with any oral anti-diabetic drugs or previous use in the 4 weeks other than sulfonylureas or Metformin (8 weeks in case of thiazolidinedione) before screening, concomitant treatment prohibited during the study period, any oral anti-diabetic drugs other than study medication, insulin therapy over 7 days consecutively or intermittently in order to treat acute metabolic decompensation or systemic infection, systemic corticosteroids or large dose of inhaled steroids, renal, hepatic disease, cardiovascular disease, pregnant or lactating females, drug or alcohol abuse, hypersensitivity to Glimepirides, or Metformin, night-shift workers and treatment with any investigational product in the last 3 months.A written informed consent was obtained from all the patients after a detailed explanation prior to enrolment. The patients were randomly assigned in two groups. For one group of patients, tablets containing fixed combination

of Metformin [500mg] and Glimepiride [1mg] (M+G) and for the next group, tablets containing fixed combination of Metformin [500mg], Glimepiride [1mg] and Pioglitazone [15 mg] (M+G+P) were prescribed. Patients were advised to take one tablet orally once daily with the first main meal of the day. The patients were followed for every 4 weeks throughout the study period. In all visits, clinical examination and history including symptoms, blood glucose (fasting, post prandial), adverse effects were estimated. Lipid profile and HbA1c (glycosylated haemoglobin) were estimated before therapy and at 3 months. Compliance regarding the medication consumption was assessed by the pill count method where 30 pills were given every 4 weeks. The patient has to show the remaining pills. Laboratory investigations done were fasting blood sugar, post prandial blood sugar using glucose oxidase and peroxidase method, lipid profile by standard enzyme procedures (triglycerides, HDL, LDL) and HbA1c by radioimmunoassay.The blood sample was drawn under aseptic conditions in fasting state. Estimation was done using a semiauto analyser at the central laboratory.

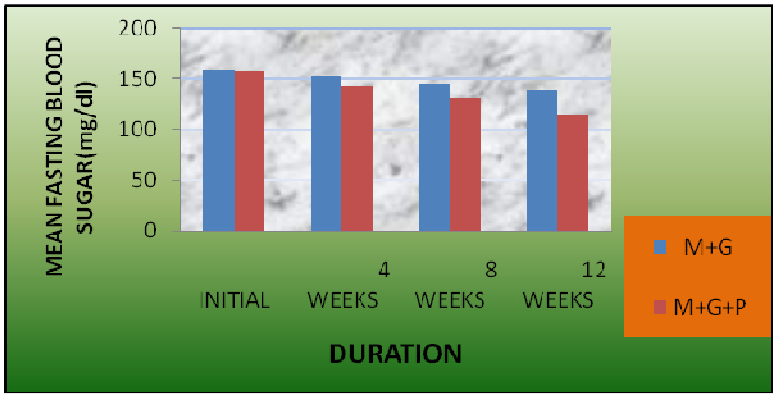
RESULTS AND DISCUSSION

Out of 100, the patients who completed the study were 96. Four patients lost follow up. In (M+G) group out of 47 patients, 23 were males and 24 were females. In (M+G+P) group out of 49 patients, 19 were males and 30 were females. In total, males constituted 44% and females were 56% of the study population. Maximum numbers of patients were aged between 51-55 years and minimum numbers of patients were aged between 30-35 years. Baseline investigations were carried out before and after the study. The data was statistically analysed using students paired “t” test.

P <0.05 was considered statistically significant.

1. Blood sugar

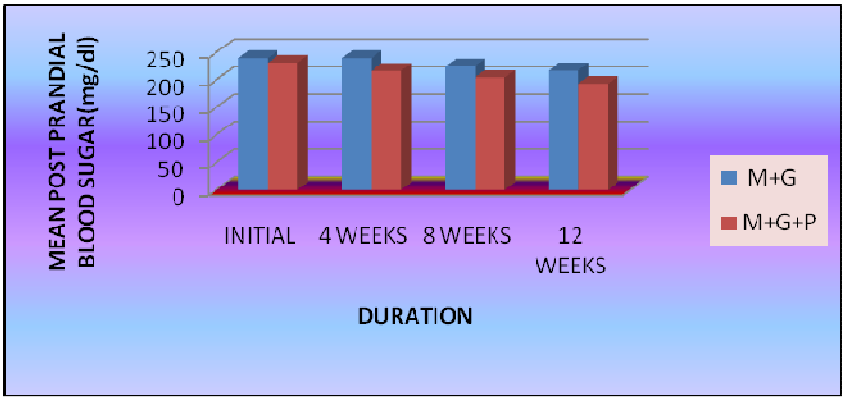
Graph 1
Fasting blood sugar



M+G → Metformin + Glimepiride, M+G+P → Metformin + Glimepiride + Pioglitazone

Initially there was no significant difference in the mean fasting blood sugar values between both study groups ($p > 0.05$). Gradually the Metformin + Glimepiride + Pioglitazone group showed greater fall in mean fasting blood sugar compared to Metformin + Glimepiride group by the 12 weeks of the study period ($p < 0.05$).

Graph 2
Post prandial blood sugar

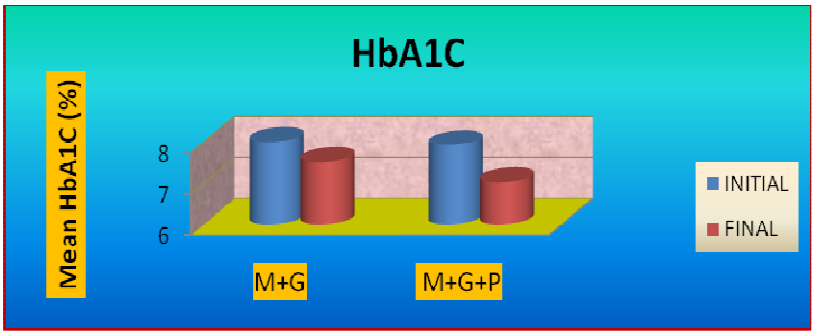


M+G → Metformin + Glimepiride, M+G+P → Metformin + Glimepiride + Pioglitazone

Initially there was no significant difference in the mean post prandial blood sugar values between both study groups ($p > 0.05$). Gradually the Metformin + Glimepiride + Pioglitazone group showed greater fall in mean post prandial blood sugar compared to Metformin + Glimepiride group by 12 weeks of study period ($p < 0.05$).

2. Glycosylated haemoglobin

Graph 3
Glycosylated haemoglobin (HbA1C)

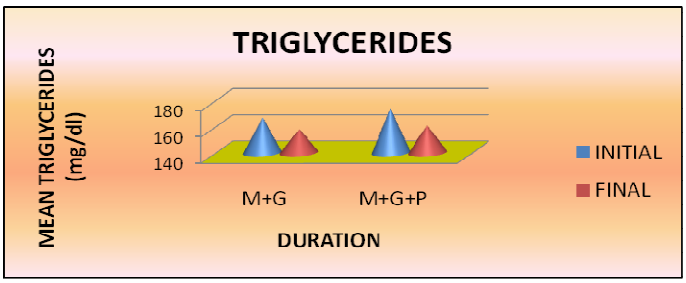


M+G → Metformin + Glimepiride, M+G+P → Metformin + Glimepiride + Pioglitazone.

The initial mean glycosylated haemoglobin values were similar in both groups ($p > 0.05$). There was a significant fall of mean glycosylated haemoglobin in the Metformin + Glimepiride + Pioglitazone group compared to Metformin + Glimepiride group by the end of the study period ($p < 0.05$).

3. Lipid profile

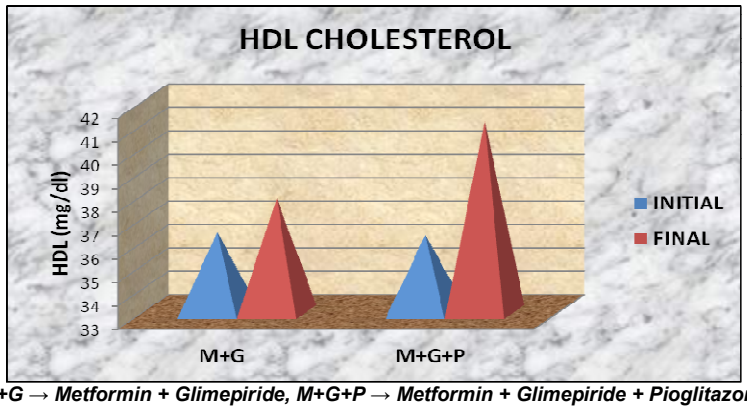
Graph 4
Triglycerides



M+G → Metformin + Glimepiride, M+G+P → Metformin + Glimepiride + Pioglitazone

There was no significant difference ($p > 0.05$) in the mean triglyceride values between both the study groups initially and at the end of the study period.

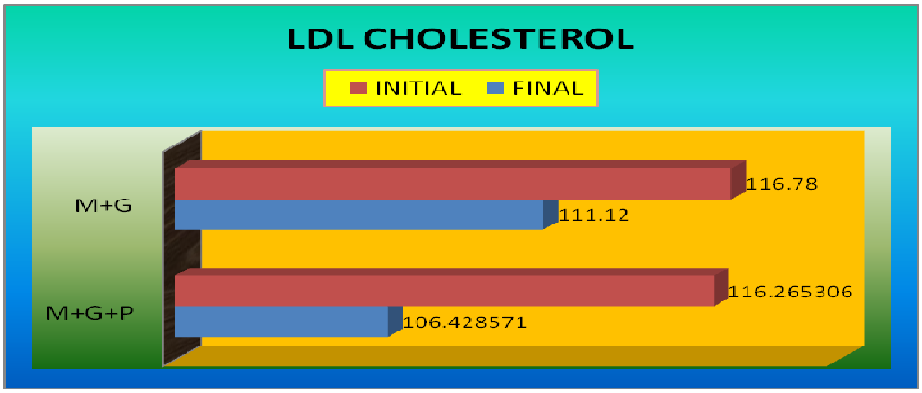
Graph 5
High density lipoprotein (HDL) Cholesterol



M+G → Metformin + Glimepiride, M+G+P → Metformin + Glimepiride + Pioglitazone

The initial mean HDL cholesterol values were similar in both groups ($p > 0.05$). There was a significant rise of final mean HDL cholesterol values in the Metformin + Glimepiride + Pioglitazone group compared to Metformin + Glimepiride group ($p < 0.05$).

Graph 6
Low density lipoprotein (LDL) Cholesterol

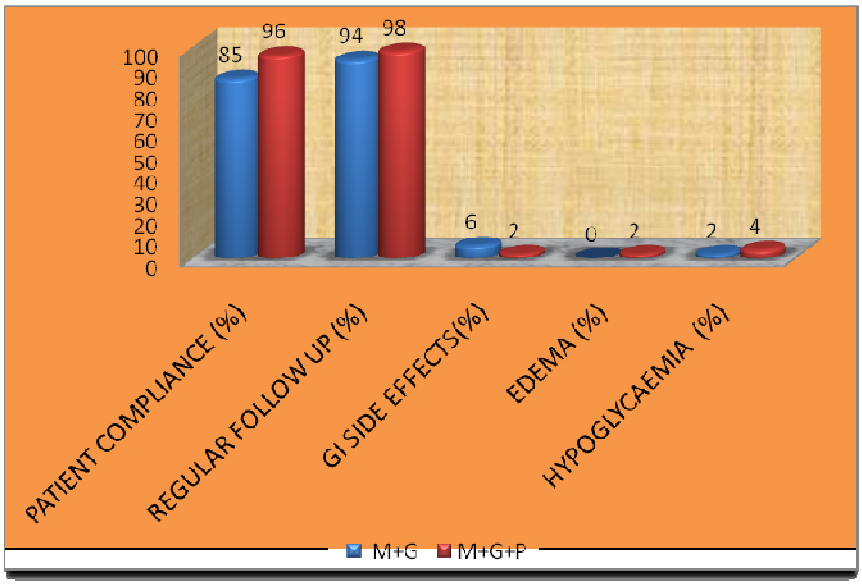


M+G → Metformin + Glimepiride, M+G+P → Metformin + Glimepiride + Pioglitazone

There was no significant difference ($p > 0.05$) in the mean LDL Cholesterol values between both study groups initially and at the end of the study period.

4. Adverse effects

Graph 7
Adverse effects



M+G → Metformin + Glimepiride, M+G+P → Metformin + Glimepiride + Pioglitazone

Metformin + Glimepiride + Pioglitazone group showed better patient compliance, regular follow up, lesser adverse effect profile compared to Metformin + Glimepiride group.

Pioglitazone reduces insulin-resistance by enhancing the effect of insulin on peripheral tissues [18]. It acts mainly on adipose tissue, liver and muscle through activation of PPAR-γ receptors, a nuclear transcription factor, which is activated by its ligand and modulates transcription of genes of proteins involved in metabolism of both glucose and lipids [19].

CONCLUSION

Metformin + Glimepiride + Pioglitazone group showed significant fall ($p < 0.05$) of fasting, post prandial blood glucose, giycosylated haemoglobin ($p < 0.05$) and significant rise ($p < 0.05$) in high density lipoprotein levels, better patient compliance, follow up compared to (M+G) group. There was no significant difference in triglycerides, low density lipoprotein levels in both the groups. Gastrointestinal side effects were more in (M+G) group while pedal oedema, hypoglycaemic episodes were more in Metformin + Glimepiride + Pioglitazone group. Metformin + Glimepiride + Pioglitazone group showed better glycaemic control, favourable lipid profile, higher patient compliance, regular follow up, lesser adverse effect profile compared to Metformin + Glimepiride group.

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CONFLICT OF INTEREST
Conflict of interest declared none.

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