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# Comparison of efficacy and adverse effect of Gliclazide, Metformin and Glipizide, Metformin combinations on type 2 diabetes patients

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**ABSTRACT**

The aim of the present study was to compare the effect of Gliclazide+Metformin and Glipizide+Metformin Combinations on Type 2 Diabetes Patients. The percentage reduction in FPG and PPG in Gliclazide Metformin combination and Glipizide+Metformin combination therapy was determined. Percentage reduction in the LIPID PROFILE in Gliclazide Metformin combination and Glipizide+Metformin combination therapy was studied. Adverse effect of Gliclazide+Metformin combination and Glipizide+Metformin combination therapy was compared in the present study.

## 1. INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by elevated bloodglucose levels (hyperglycemia) resulting from defects in insulin secretion, insulin action or both. Insulin is a hormone manufactured by the beta cells of the pancreas, which is required to utilize glucose from digested food as an energy source. Chronic hyperglycemia is associated with microvascular and macrovascular complications that can lead to visual impairment, blindness, kidney disease, nerve damage, amputations, heart disease, and stroke.

Gliclazide is an antidiabetic agent belongs to the class sulfonylurea derivatives. Gliclazide selectively binds to sulfonylurea receptors (SUR-1) on the surface of the pancreatic beta-cells. It was shown to provide cardiovascular protection as it does not bind to sulfonylurea receptors (SUR-2A) in the heart. This binding effectively closes the K+ ion channels. This decreases the efflux of potassium from the cell which leads to the depolarization of the cell. This causes voltage dependent Ca++ ion channels to open increasing the Ca++ influx. The calcium can then bind to and activate calmodulin which in turn leads to exocystosis of insulin vesicles leading to insulin release.

Significant quantity of Gliclazide absorbs within one hour and peak plasma levels are reached within 4 hours. Its half-life is 4 hours. Gliclazide undergoes extensive metabolism to several inactive metabolites in human beings, mainly methylhydroxygliclazide and carboxygliclazide. CYP2C9 is involved in the formation of hydroxygliclazde in human liver microsomes and in a panel of recombinant human P450sin vitro. But the pharmacokinetics of gliclazide MR are affected mainly by CYP2C19 genetic polymorphism instead of CYP2C9 genetic polymorphism. It is excreted by Renal and biliary routes approximately 50% each.

Glipizide is an oral rapid- and short-acting anti-diabetic drug from the sulfonylurea class. It is classified as a second generation sulfonylurea, which means that it undergoes enterohepatic circulation. Second-generation sulfonylureas are both more potent and have shorter half-lives than the first-generation sulfonylureas. Glipizide acts by partially blocking potassium channels among beta cells of pancreatic islets of Langerhans. By blocking potassium channels, the cell depolarizes which results in the opening of voltage-gated calcium channels. The resulting calcium influx encourages insulin release from beta cells.

It is metabolized through hepatic CYP2C9 pathway; Major metabolite: cyclohexyl hydroxymethyl derivative (M1) and carboxyl derivative (M2). It is excreted through renal 60% and fecal 40%.

Metformin is a biguanide hypoglycemic agent used in the treatment of non-insulin-dependent diabetes mellitus not responding to dietary modification. Metformin improves glycemic control by improving insulin sensitivity and decreasing intestinal absorption of glucose. Metformin is an anti-hyperglycemic agent, which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to any other classes of oral antihyperglycemic agents. Unlike sulfonylureas, Metformin does not produce hypoglycemia in either

patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia. With Metformin therapy, insulin secretion remains unchanged while fasting insulin levels and daylong plasma insulin response may actually decrease.

## 2. MATERIALS AND METHODS

A total of 100 type 2 diabetic patients were enrolled in the treatment program. A prospective, randomized, interventional study was carried out and compared the efficacy of Gliclazide-Metformin combination and Glipizide-Metformin combination in the treatment of type 2 diabetes mellitus by using the data obtained by the study. The study was conducted over a period of 8 months. A total of 100 type 2 diabetic patients were selected randomly and enrolled for this study. In which 40 patients were taking Gliclazide-Metformin and the remaining 60 patients were with Glipizide-Metformin. Those patients received Gliclazide-Metformin combinations are introduced into the group I, while those patients received the Glipizide-Metformin were introduced in group II. The patients were given instructions on diabetic diet and asked to monitor their blood glucose level, both fasting and postprandial, glycosylated hemoglobin and lipid profile at the initial visit to the hospital. The patient's records were maintained for the next six month after their initial visit to hospital. The patients were observed for weight, height and BMI measurement. The records of age, sex and other possible associated diseases were also maintained. The patients were asked for the determination of FPG, PPG, cholesterol, triglyceride, HDL, LDL and ADR regularly at the interval of 2 months. The HbA1C was examined only before the treatment and after 3 months of treatment.

**Study criteria:**

**Inclusion criteria:** Patients with age more than 30 years of either sex, Glycosylated hemoglobin > 7% and blood sugar level > 140 mg/dl were included in the study.

**Exclusion criteria:** Patients with current insulin therapy or received insulin for more than six weeks in last 3 months, who had known hypersensitivity to Biguanides and sulphonylurea, who were on chronic medication known to affect glucose metabolism were excluded from the study. Also the patients with renal disease or renal dysfunction, with congestive heart failure, hepatic insufficiency, alcoholic person and pregnant and lactating women were excluded from the study.

**Statistical analysis:** The analysis of glycemic parameters and lipid profile was carried out by using the appropriate test. For parametric data, comparisons were made using paired two-tailed t tests.

## 3. RESULTS AND DISCUSSAION

**Glycemic control:** The significant reduction in the fasting plasma glucose were found in Metformin-Glicazide group (P: 0.001) and there were no significant reduction of fasting plasma glucose in Metformin-Glipizide group (P: 0.0014). The reduction in FPG in Metformin-Gliclazide group was significantly greater than (P: 0.001) that in the Metformin-Glipizide group (P: 0.0014).

The Post Prandial Glucose values were significantly reduced in both groups. The significant reduction in PPG in the Metformin-Gliclazide group was significantly greater (P: 0.001) than that in the Metformin-Glipizide group (P: 0.0144).

The HbA1c levels were found to be reduced significantly in patients treated with Metformin-gliclazide (P:0.001) and Metformin-Glipizide (P:0.001).

**Lipid profile**: The total lipid profile parameters have been performed in both group in terms of total cholesterol, serum triglyceride, HDL, LDL and VLDL. A significant reduction in the total cholesterol were found in the Metformin-Gliclazide (P: 0.012) and Metformin-Glipizide group (P: 0.014). A greater significant reduction in the total cholesterol was found in the Metformin-Gliclazide as compare to Metformin – Glipizide group.

There were significant reduction (P: 0.00126) found in the Metformin-Gliclazide group but there were no significant reduction (P: 0.00121) in the Metformin-Glipizide group. So the reduction in triglyceride in the Metformin-Gliclazide group was significantly greater than that in Metformin-Glipizide group throughout the study.

The HDL concentration has found to be increased significantly in the Metformin-Gliclazide (P: 0.001) and Metformin-Glipizide groups (P: 0.001).

The LDL values were significantly reduced in Metformin-Gliclazide group (P: 0.002) but no significant reduction in LDL were found in Metformin-Glipizide group (0.002).

**Table.1.Fasting Glucose Level of Patient in Both Group (Group I vs Group II)**

| Parameter | Gliclazide + Metformin (Mean ± S.D) | | P-Value | Glipizide + Metformin(MEAN ± S.D) | | P-Value |
|---|---|---|---|---|---|---|
| FPG | Initial (mg/dl) | Final (mg/dl) | 0.001 | Initial (mg/dl) | Final (mg/dl) | 0.0014 |
| | 166.25±32.22 | 130.36±25.55 | | 156.45±35.24 | 136.06±32.45 | |

P< 0.001 = extremely statistically significant** P< 0.05 = statistically significant*
Data was analyzed by paired t test. Values are expressed as MEAN±S.D

**Table.2.Post Prandial Glucose Level of Patient in Both Group (Group I vs Group II)**

| Parameter | Gliclazide +Metformin (MEAN ± S.D) | | P-value | Glipizide +Metformin (MEAN ± S.D) | | P-value |
|---|---|---|---|---|---|---|
| PPG | Initial (mg/dl) | Final (mg/dl) | 0.001 | Initial (mg/dl) | Final (mg/dl) | 0.0144 |
| | 245.54±34.25 | 198.56 ±54.82 | | 230.55±52.46 | 218.84±50.42 | |

P< 0.001 = extremely statistically significant ** P< 0.05 = statistically significant *
Data was analyzed by paired t test. Values are expressed as MEAN±S.D

**Table.3.HbA1cLevelof Patient in Both Group (Group I vs Group II)**

| Parameter | Gliclazide +Metformin (MEAN ± S.D) | | P-value | Glipizide +Metformin (MEAN ± S.D) | | P-value |
|---|---|---|---|---|---|---|
| HbA1c | Initial (%) | Final (%) | 0.001 | Initial (%) | Final (%) | 0.001 |
| | 8.84±0.6 | 7.63±0.8 | | 8.84±.05 | 8.22±0.7 | |

P< 0.001 = extremely statistically significant ** P< 0.05 = statistically significant *
Data was analyzed by paired t test. Values are expressed as MEAN±S.D

**Table.4.Total Cholesterol Level of Patient in Both Group (Group I vs Group II)**

| Parameter | Gliclazide +Metformin (MEAN ± S.D) | | P-value | Glipizide +Metformin (MEAN ± S.D) | | P-value |
|---|---|---|---|---|---|---|
| Cholesterol | Initial (mg/dl) | Final (mg/dl) | 0.012 | Initial (mg/dl) | Final (mg/dl) | 0.014 |
| | 191.23±26.24 | 181.14±20.58 | | 198.2±30.35 | 187.74±15.86 | |

P< 0.001 = extremely statistically significant ** P< 0.05 = statisticallysignificant *
Data was analyzed by paired t test. Values are expressed as MEAN±S.D

**Table.5.Serum Triglyceride Level of Patient in Both Group (Group I vs Group II)**

| Parameters | Gliclazide +Metformin (MEAN ± S.D) | | P-value | Glipizide +Metformin (MEAN ± S.D) | | P-value |
|---|---|---|---|---|---|---|
| Triglyceride | INITIAL (mg/dl) | FINAL (mg/dl) | 0.00126 | INITIAL (mg/dl) | FINAL (mg/dl) | 0.00121 |
| | 198.53±32.55 | 185.75±40.7 | | 194.1±38.52 | 182.4±32.45 | |

P< 0.001 = extremely statistically significant ** P< 0.05 = statistically significant t*
Data was analyzed by paired t test. Values are expressed as MEAN±S.D

**Table.6.HDL Level of Patient in Both Group (Group I vs Group II)**

| Parameters | Gliclazide +Metformin, (MEAN ± S.D) | | P-value | Glipizide +Metformin, (MEAN ± S.D) | | P-value |
|---|---|---|---|---|---|---|
| HDL | Initial (mg/dl) | Final (mg/dl) | 0.001 | Initial (mg/dl) | Final (mg/dl) | 0.001 |
| | 40.56±4.26 | 42.01±5.34 | | 41.75±4.43 | 42.24±4.65 | |

P< 0.001 = extremely statistically significant ** P< 0.05 = statisticallysignificant *
Data was analyzed by paired t test. Values are expressed as MEAN±S.D

**Table.7.LDL Level of Patient in Both Group (Group I vs Group II)**

| Parameter | Gliclazide +Metformin, MEAN ± S.D | | P-value | Glipizide +Metformin (MEAN ± S.D) | | P-value |
|---|---|---|---|---|---|---|
| LDL | Initial (mg/dl) | Final (mg/dl) | 0.002 | Initial (mg/dl) | Final (mg/dl) | 0.002 |
| | 110.29±34.11 | 104.80±46.56 | | 112.0±30.36 | 107.83±53.82 | |

P< 0.001 = extremely statistically significant ** P< 0.05 = statisticallysignificant *
Data was analyzed by paired t test. Values are expressed as MEAN±S.D

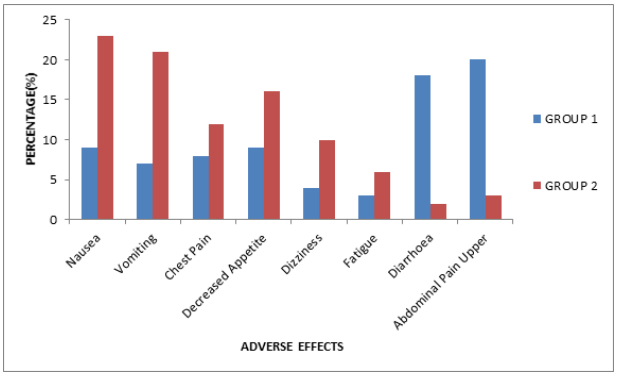


**Figure.1.Comparison of adverse effects Group I and Group II**

**Discussion:** Out of selected 100 patients, 12 patients were in the age group of 31-40 years, 40 patients were in the age group of 41- 50years, 48 patients were in the age group of 51- 60years.

A total of 100 patients were screened and randomized into the two treatment groups. Out of these patients those participate in the study 62 of patients were male, while 38 of patient were female indicating that men were more likely to have type 2 diabetes mellitus.

Out of 100 patients 10 patients were in underweight level(<18), 42 patients were in normal range(18-24) and 48 patients were overweight (>25). This indicating that overweight is one of the risk factors of type 2 diabetes mellitus.

The significant reduction in the fasting plasma glucose were found in Metformin-Glicazide group (P: 0.001) and there were no significant reduction of fasting plasma glucose in Metformin-Glipizide group (P: 0.0014). The reduction in FPG in Metformin-Gliclazide group was significantly greater than (P: 0.001) that in the Metformin-Glipizide group (P: 0.0014).

The Post Prandial Glucose values were significantly reduced in both groups. The significant reduction in PPG in the Metformin-Gliclazide group was significantly greater (P: 0.001) than that in the Metformin-Glipizide group (P: 0.0144).

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The HDL concentration has found to be increased significantly in the Metformin-Gliclazide (P: 0.001) and Metformin-Glipizide groups (P: 0.001).

The LDL values were significantly reduced in Metformin-Gliclazide group (P: 0.002) but no significant reduction in LDL were found in Metformin-Glipizide group (0.002).

It shows that was decreasing the level of cholesterol, TGL, and LDL. The HDL level was also increased.

## 4. CONCLUSION

Our study shows that both combinations such as Gliclazide-Metformin and Glipizide-Metformin reduced the Glycosylated Hemoglobin level, Fasting and post-Prandial plasma glucose. But the Metformin-Gliclazide combination provided superior control of glycemia as compare to the Metformin-Glipizide combination.

Gliclazide-Metformin and glipizide - combination significantly increased the HDL cholesterol levels throughout the study period. Gliclazide-Metformin had low adverse drug reaction compare to the Glipizide- Metformin combination. So the Gliclazide-Metformin combination can be considered as the best combination in patients with increased glycemic control as compare to Glipizide-Metformin combination in type 2 diabetic patient.

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