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Comparison of effect of metformin in combination with glimepiride and glibenclamide on glycaemic control in patient with type 2 diabetes mellitus

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Abstract

The aim of the present study is to compare the effect of metformin in combination with Glimepiride and Glibenclamide In patient with type 2 Diabetes Mellitus. Subjects and method: This is an open-label, randomized study carried out to study the effect of metformin when it is given in combination with either glimepiride or glibenclamide on glycaemic control in patient with type 2 Diabetes Mellitus. Patients with Glycosylated Hemoglobin more than 7% were included in the study. 31 patients were randomly assigned for treatment based on metformin-glibenclamide 1000/10 mg tablets or metformin-glimepiride1000/2mg for 12 weeks. The comparisons were conducted between these two groups for HbA_{1C}, FPG, PPG and lipid profile. Result: At week 12, the significant reductions in HbA1c were found in both groups but the patients treated with metformin-glimepiride resulted in significantly greater reductions in HbA_{1C} (-1.4%) than metformin-glibenclamide (-1.2%). Also the greater significant reductions were observed in case of FPG, total cholesterole, serum triglyceride and LDL cholesterole in patient with metformin-glimepiride group. Conclusion: Metformin-glimepiride tablets resulted in significantly greater reductions in HbA_{1C} and fasting plasma glucose compared with metformin plus glibenclamide in patients with type 2 diabetes mellitus.

Keywords: combination therapy, glimepiride, glibenclamide, metformin, type 2 diabetes mellitus.

Abbreviation: CVD: Cardiovascular Disease; DM: Diabetes Mellitus; FPG: Fasting Plasma Glucose; Group I: Metformin plus Glimepiride; Group II: Metformin plus Glibenclamide; GIT: Gastrointestinal Tract; HbA_{1C}: Glycosylated Hemoglobin; HDL:

High Density Lipoprotein; LDL:Low Density Lipoprotein;OHAs:Oral Hypoglycaemic Agents; PPG: Post-prandial Plasma Glucose; SEM: Standard Error mean.

Introduction

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized, producing hyperglycemia resulting from a defect in insulin secretion, insulin action, or both.[1,2] It is an endocrine disorder, more than 100 million (6% of the population) of people world-wide are affected inspite of enormous facilities available to control its growth[3]. Type 2 diabetes is caused by two primary metabolic defects: progressive pancreatic β-cell dysfunction and insulin resistance[4]. β-Cell dysfunction superimposed on insulin resistance leads to hyperglycaemia and subsequently to type 2 diabetes. Typically, at the time of diabetes diagnosis, nearly 50% of β-cell function has been lost and less than 60% of normal insulin sensitivity is present[5]. Diabetes is a chronic illness that requires continuing medical care and patient self-management education to prevent acute complications and to reduce the risk of long-term complications[6].The lifestyle modification, diet and exercise of moderate intensity are used to improve insulin sensitivity and are recommended as an integral part of treatment of Type 2 diabetes[7]. When the lifestyle modification, diet and exercise fails to maintain the adequate glycaemic control, oral hypoglycemic agents are introduced as a treatment approach[4, 5]. Oral Hypoglycemic Agents (OHAs) can be used either alone or in combination with other OHAs or insulin. The Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes recommends a target hemoglobin A_{1C} concentration of 7.0% or less for all patients with diabetes. Currently, there are five major classes of oral antidiabetic agents: sulphonylureas – insulin secretagogues that target β -cell dysfunction; metformin – a biguanide that reduces hepatic glucose production and improves insulin sensitivity, thiazolidinediones – insulin sensitizers that lower peripheral insulin resistance; α -glucosidase inhibitors – intestinal enzyme inhibitors that slow carbohydrate absorption; and meglitinides – rapid but short-acting, non-sulphonylurea secretagogues[9,10].The goal levels of diabetes related parameters during treatment is given in Table No. 1

Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Insulin is indicated in the following situations: 1) when diet and oral hypoglycaemic drugs fail to control hyperglycaemia and achieve therapy targets 2) diabetes during pregnancy when diet alone is inadequate, 3) when oral hypoglycaemic drugs are contraindicated, 4) during stressful conditions such as infection and surgery[1, 2, 9].

Table No. 1 Blood-glucose targets for people with Diabetes.

Parameter	Normal	Goal	Action suggested if
Pre-prandial Fasting Glucose	<110 mg/dl	80-120 mg/dl	<80 or >140 mg/dl
2h postprandial Glucose	<140 mg/dl	<140 mg/dl	>180 mg/dl
Bedtime	<120 mg/dl	100-140 mg/dl	<100 or >160 mg/dl
HbA1c	≤ 6%	< 6.5 %	>8 %

Combination therapy: It is always beneficial to switch over the patients on combination therapy, when there is high secondary failure associated with monotherapy and devastating long term consequence of poor glycemic control. A reasonable goal of treatment is to maintain good glycemic control through combination therapy so as to keep HbA1c value below 7% for a particular patient. Initiation of combination drug therapy at low dosages can minimize the side effects associated with high dose therapy of either agent, yield additive clinical benefits, and possibly curtail cost of treatment. For many drugs, 50% of the dosage needed to achieve the maximal therapeutic effect will produce well over 50% of that effect [2, 11].

Patients and method

This was a single center, open-label, randomized parallel group study conducted at the Indira Gandhi Memorial Hospital, Shirpur. (North Maharashtra Region) The study was approved by the local research ethics committee and all subjects gave written informed consent to participate in the study. Patients with age more than 35 yrs, of either sex, glycosylated hemoglobin > 7% and blood sugar level > 140 mg/dl were included in the study. The written consent was also taken from each patient in local language. 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 are 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 planned to exclude from the study. A total of 31 type 2 diabetic patients were enrolled on a treatment program. 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 three month after their initial visit to hospital. The patients were observed for weight, height and blood pressure measurement. The records of age, sex, family history and other possible

associated diseases were also maintained. The records of the weight and height are helpful for the determination of body mass index. The patients were also interviewed for their initial sign and symptoms. As the patients were recruited for the study they were randomized into two groups according to the treatment they received. Those patients received Metformin-Glimepiride (1000/2 mg/day) combinations were introduced into the group I while those patients received the Metformin-glibenclamide (1000/10 mg/day) were introduced in group II. The patients were asked for the determination of FPG and PPG regularly at the interval of each month. The HbA1C and lipid profile were examined only before the treatment and after 3 months of treatment. The glycosylated hemoglobin determination was carried out by using BIO-RAD Micromat II HbA_{1C} instrument, while FPG, PPG and Lipid profile were determined by using Microplate reader.

Efficacy and safety evaluations

The primary efficacy variable was the change in HbA1C from baseline to 3 month. Secondary efficacy outcomes included changes in fasting plasma glucose, 2-h postprandial plasma glucose and fasting lipid profile levels from baseline to 3 month after randomization of the patient into the study. Safety outcomes included adverse events, particularly hypoglycaemic symptoms. The patients were interviewed and asked for the any type of adverse events throughout the study. The patients were specially asked for the hypoglycaemic symptoms. The daytime hypoglycemic episodes are usually recognized by sweating, nervousness, tremor, and hunger while nighttime hypoglycemia may be without symptoms or manifest as night sweats, unpleasant dreams, or early morning headache.

Statistical analysis

The analysis of Glycosylated hemoglobin and lipid profile was carried out by using the appropriate test. For parametric data, within patient comparisons were made using paired two-tailed t tests and between group comparisons two-tailed unpaired t tests. The FPG and PPG were analyzed by using one way ANOVA followed by Dunnet test.

Results

A total of 31 patients were screened and randomized into the two treatment groups, of whom 28 completed the study successfully. 3 patients, 1 from Metformin-glimepiride group due to withdrawal of consent and 2 patients from Metformin-glibenclamide group were switched to another treatment were excluded from the study. Out of the patients those participated in the study, 48.38% of patients were male while 51.61% of patients were female. A 29.03% of diabetic patients found to be overweight. The patients were categorized as an overweight if their body mass index lies between 25-

9.9 Kg/m^2. 58.06% of patients were found to be having genetic history of diabetes mellitus. The mean age was 49.95 ± 2.032 yrs. in the first group and was 48.27 ± 2.902 yrs. in the second group. The mean duration of diabetes mellitus was 4.4 ± 0.78 and 4.0 ± 0.57 yrs in Group I and Group II respectively. The baseline characteristics of all patients at randomization are summarized in the table 2.

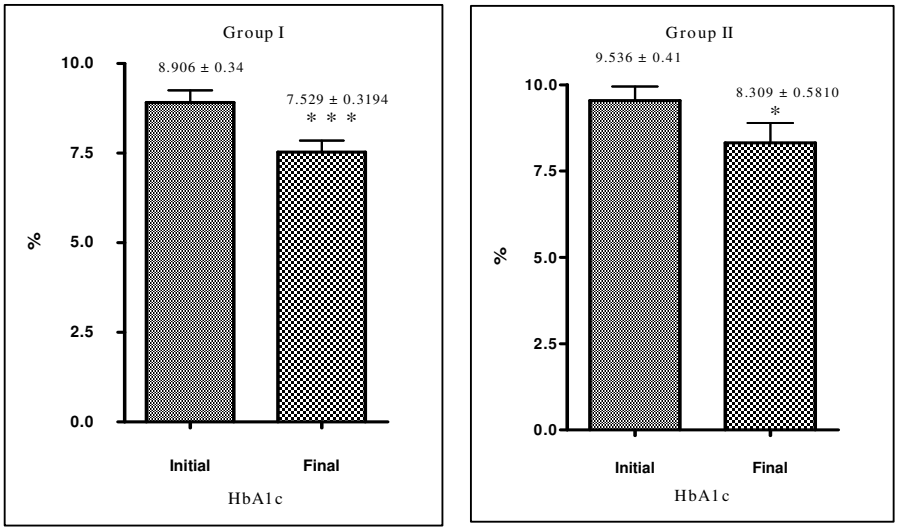
Table No. 2:- The baseline characteristics of all patients at randomization

	Metformin plus Glimepiride	**Metformin plus Glibenclamide**
Sex (Male/Female)	10/8	5/8
Age (yrs)	49.95 ± 2.032	48.27 ± 2.902
Diabetes duration (yrs)	4.4 ± 0.78	4.0 ± 0.57
BMI (Kg/m^2)	23.13 ± 0.5436	23.85 ± 0.5145
HbA1c (%)	8.9 ± 0.34	9.536 ± 0.41
FPG (mg/dl)	181.8 ± 9.49	205.7 ± 27.48
PPG (mg/dl)	240.0 ± 16.65	301.9 ± 38.62
Total Cholesterol (mg/dl)	150.3 ± 6.82	118.5 ± 6.472
Serum Triglyceride mg/dl)	175.4 ± 17.95	114.0 ± 17.55
HDL (mg/dl)	37.92 ± 1.76	36.43 ± 1.58
LDL (mg/dl)	75.31 ± 6.47	67.21 ± 11.23

Glycaemic control

Glycosylated hemoglobin: - During the study there were no significant differences were found in initial and final values of HbA_{1C} levels of both groups. Though the HbA_{1C} level was found to be reduced more significantly (P: 0.0001) patients treated with Metformin-glimepiride, while in the patients treated with Metformin-glibenclamide also reduced HbA_{1C} but less significantly as compare to Metformin-glimepiride treated patient. The glycosylated hemoglobin was found to be reduced by -1.376 ± 0.27 and -1.227 ± 0.48 in Metformin plus Glimepiride and Metformin plus glibenclamide groups respectively.(Shown in fig No.1)

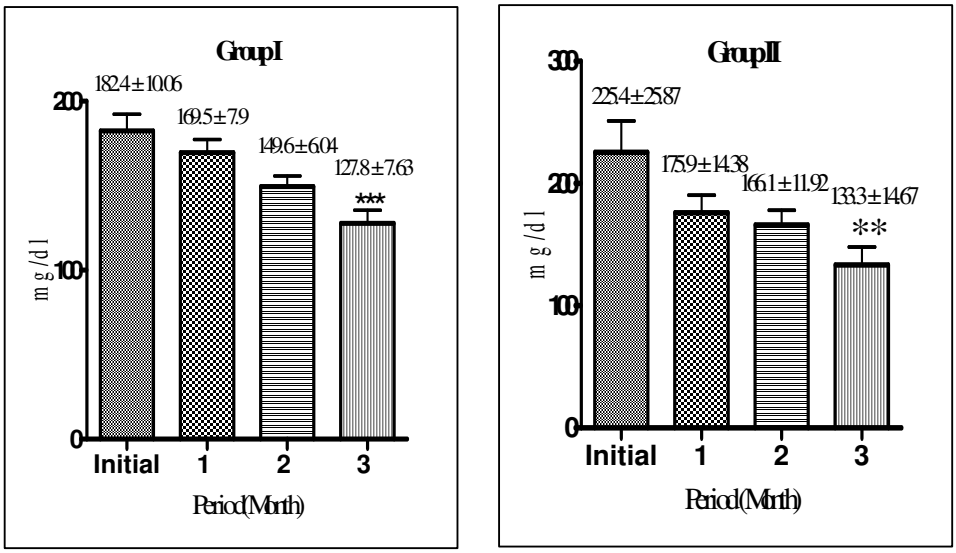
Fig No. 1: Comparison of HbA1c between Group I and Group II



Group I: Metformin plus Glimepiride,Group II: - Metformin plus Glibenclamide.
Data was analyzed by Paired t- test,P<0.001= very significant *** ,
P<0.05 = significant *,Values are expressed as mean ±SEM

FPG AND PPG: - The FPG values were found to be reduced by - 54.59 ± 10.84 mg/dl and - 92.09 ± 24.25 mg/dl in each group I and Group II respectively. The significant reductions in the fasting plasma glucose were found in both groups. The reduction in FPG in the Metformin-glimepiride group was significantly greater than (P: 0.0001) that in the Metformin-glibenclamide group (P: 0.0066) throughout the study. (Shown in Fig No.2)

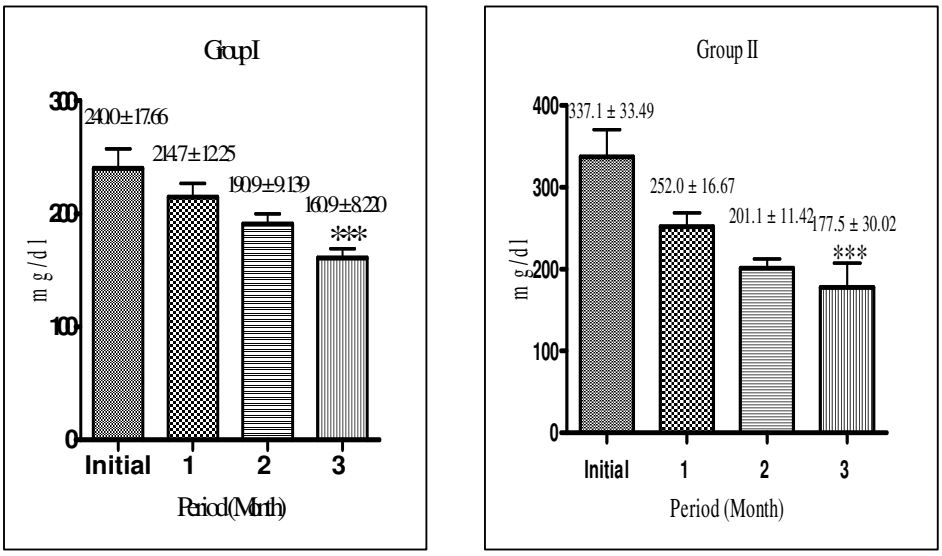
Fig No.2: - Comparison of FPG between Group I and Group.



Data was analyzed by one way ANOVA followed by Dunnet test .
P<0.001=extremely significant *** ,P<0.01= Very significant **,Values are expressed as mean ±SEM

The PPG values were reduced throughout the study period of 3 month by 79.06 mg/dl and 159.64 mg/dl in each group. The PPG values were significantly reduced in both the groups. The significant reduction in PPG in the Metformin-glimepiride group as well metformin glibenclamide group were found similar. (P<0.0001) (Shown in fig No.3)

Fig No.3: - Comparison of PPG between Group I and Group II



Data was analyzed by one way ANOVA followed by Dunnet test
P<0.001= extremely significant ***
Values are expressed as mean ±SEM

Lipid profile

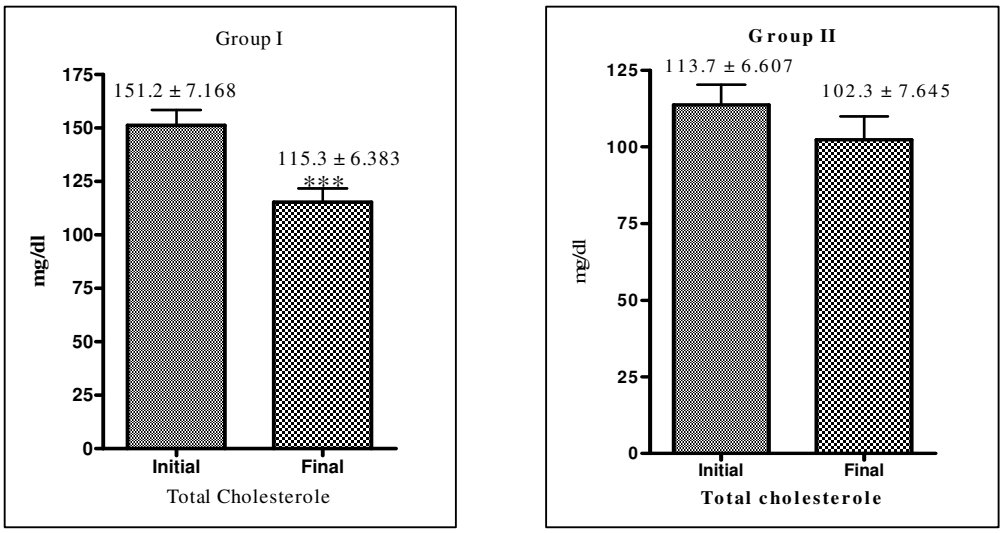
The total lipid profile parameters have been performed in both groups in terms of total cholesterol, serum triglyceride, HDL and LDL.

A significant reduction in the total cholesterol was found in the Metformin and Glimepiride (P<0.0001) as compare to Metformin and Glibenclamide group. The total cholesterol was also reduced in the second group but non-significantly. (Shown in Fig No 4)

There were significant reductions (P: 0.0068) found in the Metformin-Glimepiride group in case of serum triglycerides but there were no changes found in the serum

triglyceride level throughout the study in Metformin-Glibenclamide group.(Shown in Fig No 5)

Fig No.4: -Total Cholesterole Group I Vs Group II

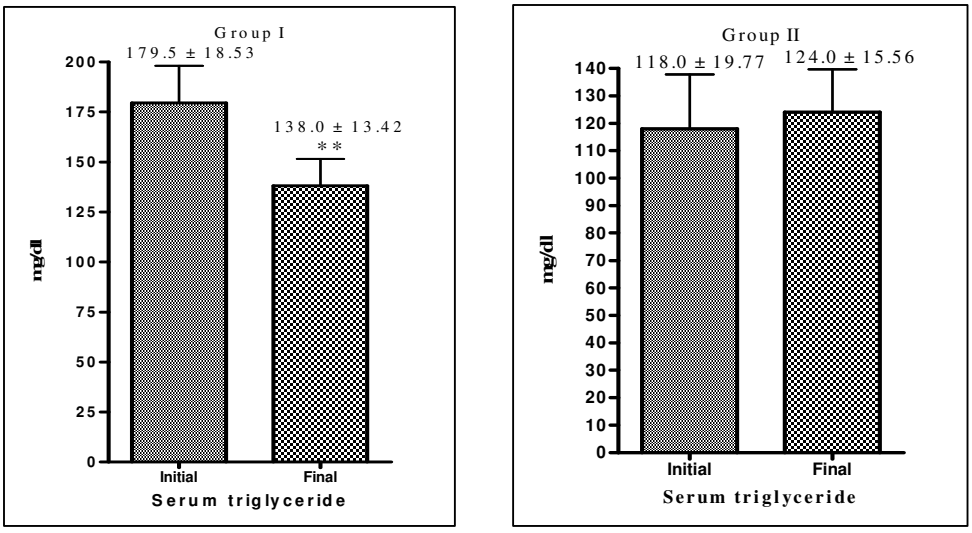


Data was analyzed by Paired t test

P<0.001=extremely significant ***

Values are expressed as mean ±SEM

Fig No.5: - Serum triglyceride Group I Vs Group II



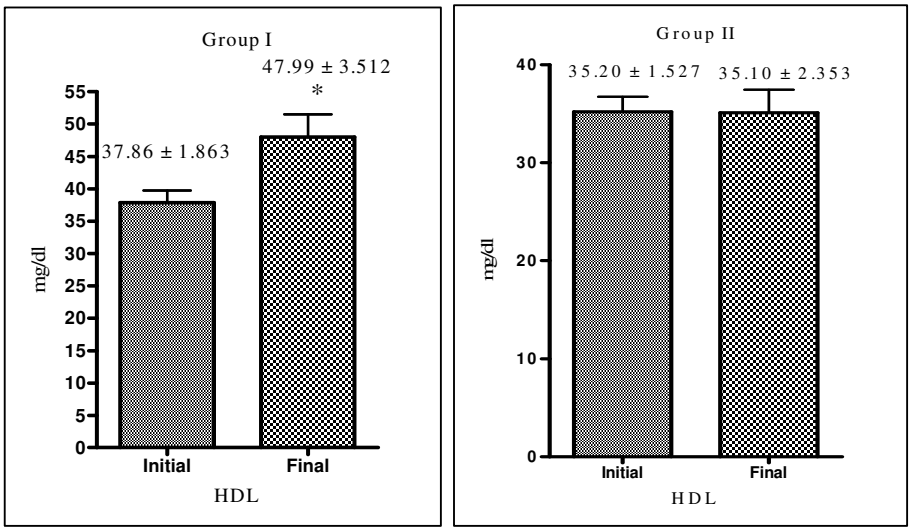
Data was analyzed by Paired t test

P<0.01= very significant ** , Values are expressed as mean ±SEM

The HDL concentration has been found to be increased significantly (P: 0.0190) in the Metformin-Glibenclamide group, however there was no change found in the values of HDL cholesterole in Metformin-glibenclamide group. (Shown in Fig No 6)

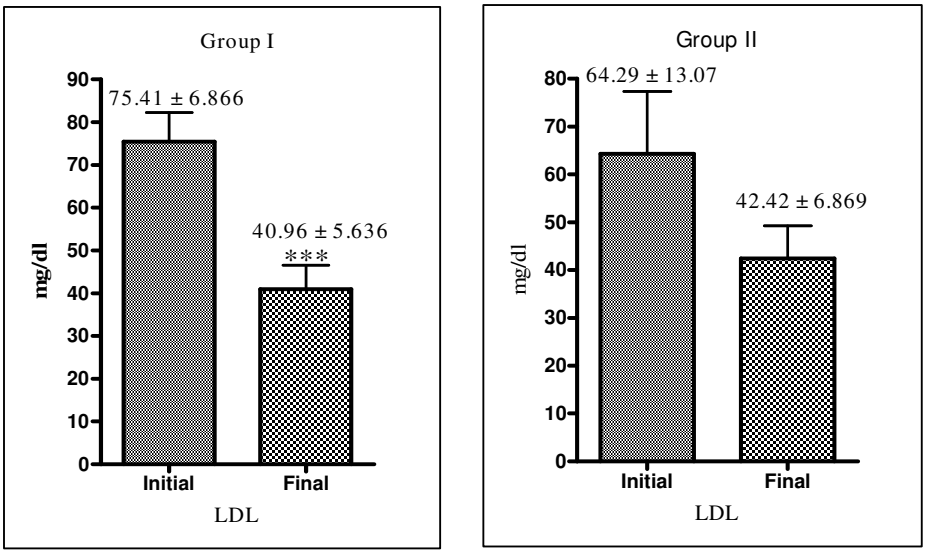
The LDL concentration has been found to be reduced significantly (P<0.0001) in the Metformin-glimepiride group. (Shown in Fig No 7)

Fig No. 6: - HDL concentration Group I Vs Group II



Data was analyzed by Paired t test
P<0.05 = significant *
Values are expressed as mean ±SEM

Fig No. 7: - LDL concentration Group I Vs Group II



Data was analyzed by Paired t test,P<0.001= extremely significant ***

Hypoglycemic and other adverse effect

The patients were interviewed at the end of the study for the detection of any other side effects. No patient complaint about the any type of nausea, vomiting, headache or GIT side effects at the given doses of medication. However when the patients were asked for the hypoglycemic symptoms, 3 patients from each group reported the hypoglycemic symptoms. It means that 17.64% and 27.27% of patients from Group I and Group II reported the hypoglycemic effect.

Discussion

Type 2 diabetes arises in the settings of insulin resistance in muscle, adipose tissue and liver and a progressive decline in pancreatic β -cell function[5]. A traditional stepwise approach to diabetes therapy involves the use of a single oral agent titrated to maximum dosage, each of which targets a single pathological defect of type 2 diabetes as its primary mechanism of action, with the requirement of poor glycaemic control as an indication for the addition of a second oral agent[13]. The aim of our study was to compare the effect on glycemic control, weight gain, and frequency of hypoglycemia in patients receiving metformin in combination with glimepiride or glibenclamide. During the study it has been found that type 2 diabetes affected both the sex equally and mostly it is pronounced at the age of 49.26 ± 1.604 yrs. while 58% of patients were found to be at the greater risk of hypertension or other cardiovascular complication. Treatment with metformin-glibenclamide tablets and metformin-glimepiride tablets simultaneously targets insulin resistance and insulin deficiency of type 2 diabetes, which may account for the greater effects on glycaemia. Indeed, metformin-glimepiride tablet therapy produced greater mean changes from baseline in HbA1C (1.4% for metformin-glimepiride tablets vs. 1.2% for metformin plus glibenclamide). The greater mean changes from the baseline in case of fasting plasma glucose were found (- 92.09 mg/dl) for metformin-glibenclamide (Group II) while for metformin-glimepiride (Group I) it was (-54.59 mg/dl). But the statistical analysis using one way ANOVA followed by Dunnet test concludes that the Group I reduced FPG is more significantly ($P<0.0001$) than Group II. The metformin glibenclamide combinations were prescribed in patients with fasting plasma glucose more than 240.0 ± 16.65 mg/dl. While the better mean reductions were found in the FPG in patients of group II. Furthermore, 29.41% of patients receiving metformin-glimepiride therapy attained a final HbA1c of <7.0%. These results demonstrate that treatment with metformin-glimepiride was more efficacious than with metformin plus glibenclamide in improving glycaemia by achieving therapeutic goals for HbA_{1C} and fasting plasma glucose in patients with type 2 diabetes. The both combination used in the study are of Biguanide (Metformin) and sulphonylurea (Glimepiride and Glibenclamide) category.

The reductions in the blood sugar level were found in both groups due to the synergistic effect. The synergistic effect of both combinations may be due to the different mechanism of action of individual drugs in the both combination. Metformin decreases hepatic glucose production through inhibition of gluconeogenesis and possibly glycogenolysis and improves the peripheral insulin sensitivity.

In diabetic patients there is an increased risk of cardiovascular complications followed by higher morbidity and mortality than in a nondiabetic population with coronary artery disease. Cardiovascular disease (CVD) is 2–3 times commoner in diabetics than in non-diabetics. Known risk factors are such as raised cholesterol, hypertension, smoking, abdominal obesity, hyperinsulinemia, disorders of platelet function and coagulation, and degree of glycaemic control only partly explain the increased risk[14]. In the present study more than 58% of patients were at the greater risk of cardiovascular diseases. The smoker patients were mostly found to the development of hypertension (66.66%). The patients treated with Metformin-glimepiride combination resulted in the significantly reduction in the total cholesterol, serum triglyceride, and LDL cholesterol while helped to increased the HDL cholesterol throughout the study. So this combination can be considered as the best combination to be prescribed in patients with increased cholesterol and triglyceride concentration.

Conclusion

From the assumption described in results and discussion the present study concludes that the both combinations such as Metformin-glimepiride and Metformin glibenclamide reduced the Glycosylated Hemoglobin level, Fasting and post-prandial plasma glucose significantly. But the metformin-glimepiride combination provided superior control of glycaemia as compare to the Metformin-glibenclamide combination. While the significant reduction in the total cholesterol, serum triglyceride and LDL cholesterol was observed in the Metformin-glimepiride combination. It also significantly increased the HDL cholesterol levels throughout the study period of 12 weeks. So the Metformin-glimepiride combination can be considered as the best combination in patients with increased lipid parameters as compare to metformin-glibenclamide combination in diabetic patients.

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