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RESEARCH ARTICLE

EFFECT OF INTERACTION BETWEEN METFORMIN AND GLIMIPERIDE ON GLYCOSYLATED HAEMOGLOBIN AND LIPID PROFILE IN STRESS INDUCED TYPE 2 DM

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ABSTRACT

The aim of the present study is to evalutae the effect of metformin in combination with Glimepiride and in patient with type 2 Diabetes Mellitus.The research is carried out to study the effect of metformin when it is given in combination on glycaemic control in patient with type 2 Diabetes Mellitus. Patients with Glycosylated Hemoglobin more than 6.5% were included in the study. 30 animal in five group were randomly assigned for treatment based on metformin and glimepiride in a dose of 200 mg/kg and 17.5 mg/kg for 21 weeks. The comparisons were conducted between these five groups for HbA1C, FPG, PPG and lipid profile. On week 21, the significant reductions in HbA1c were found in drug treated groups but the patients treated with metformin and glimepiride resulted in significantly greater reductions in HbA1C . Also the greater significant reductions were observed in case of FPG, total cholesterol, serum triglyceride and LDL cholesterol in patient with metformin and glimepiride treated group.

Key word: Metformin, glimiperide, Diabetes, hypoglycemic agent, safety

Abbreviation

FPG-Fasting plasma glucose, PPG-post prandial glucose, LDL-Low density lipoprotein, HDL-High density lipoprotein, HbA 1 c-Glycocylated haemoglobin, NCD-Non Communicable Disease

INTRODUCTION

It is a chronic metabolic disorder which is characterized by hyperglycemia, hyperlipaemia, glycosuria, negative nitrogen balance and sometimes ketonemia that may lead to long term complication in a form of diabetic retinopathy, diabetic nephropathy, diabetic neuropathy and diabetic fetopathy or it is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized, producing hyperglycemia resulting from a defect in

I. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)

A. Immune-mediated
B. Idiopathic

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Other specific types of diabetes

IV Gestational diabetes mellitus

Two features of the current classification of DM diverge from previous classifications. First, the terms *insulin-dependent diabetes mellitus* (IDDM) and *non-insulin-dependent diabetes mellitus* (NIDDM) are obsolete. Since many individuals with type 2 DM eventually require insulin treatment for control of glycemia, the use of the term NIDDM generated considerable confusion. A second difference is that age is not a criterion in the classification system. Although type 1 DM most commonly develops before the age of 30, an autoimmune beta cell destructive process can develop at any age. It is estimated that between 5 and 10% of individuals who develop DM after age 30 years have type 1 DM. Although type 2 DM more typically develops with increasing age, it is now being diagnosed more frequently in children and young adults, particularly in obese adolescents.

A total of 57 million deaths occurred in the world during 2008; 36 million (63%) were due to NCDs, principally cardiovascular diseases, diabetes, cancer and chronic respiratory diseases. Nearly 80% of these NCD deaths (29 million) occurred in low- and middle-income countries. NCDs are the most frequent causes of death in most countries in the Americas, the Eastern Mediterranean, Europe, South-East Asia, and the Western Pacifi c. In the African Region, there are still more deaths from infectious diseases than NCDs. Even there, however, the prevalence of NCDs is rising rapidly and is projected to cause almost three-quarters as many deaths as communicable, maternal, perinatal, and nutritional diseases by 2020, and to exceed them as the most common causes of death by 2030. WHO projections show that NCDs will be responsible for a significantly increased total number of deaths in the next decade. NCD deaths are projected to increase by 15% globally between 2010 and 2020 (to 44 million deaths). The greatest increases will be in the WHO regions of Africa, South-East Asia and the Eastern Mediterranean, where they will increase by over 20%. In contrast, in the European Region, WHO estimates there will be no increase. In the African Region, NCDs will cause around 3.9 million deaths by 2020. The regions that are projected to have the greatest total number of NCD deaths in 2020 are South- East Asia (10.4 million deaths) and the Western Pacific (12.3 million deaths) .Nearly 26 million Americans have diabetes, according to new estimates from the Centers for Disease Control and Prevention (CDC). In addition, an

estimated 79 million U.S. adults have prediabetes, a condition in which blood sugar levels are higher than normal, but not high enough to be diagnosed as diabetes. Prediabetes raises a person's risk of type 2 diabetes, heart disease and stroke.

Diabetes affects 8.3 percent of Americans of all ages, and 11.3 percent of adults aged 20 and older, according to the National Diabetes Fact Sheet for 2011. About 27 percent of those with diabetes—7 million Americans—do not know they have the disease. Prediabetes affects 35 percent of adults aged 20 and older.

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. Type 2 diabetes is caused by two primary metabolic defects: progressive β-pancreatic cell dysfunction and insulin resistance. 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 ispresent5. 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.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. When the lifestyle modification, diet and exercise fails to maintain the adequate glycaemic control, oral hypoglycemic agents are introduced as a treatment approach.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 A1C concentration of 6.5%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; _ -glucosidase inhibitors – intestinal enzyme inhibitors that slow carbohydrate absorption; and meglitinides – rapid but short-acting, nonsulphonylurea secretagogues.The goal levels of diabetes related parameters during treatment is given. 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.

METFORMIN

Salient feature of Metformin pharmacological profile are-

- It is a drug of choice for Type 2 DM.
- It suppresses hepatic gluconeogenesis and glucose output, increases peripheral utilization of glucose and inhibits glycogenolysis.
- It shows less hypoglycemia in comparision to others as a ADR.
- It also causes Lactic acidosis,Vit B12 deficiency and abdominal discomfort as ADR

GLIMIPERIDE

- It is a third generation sulfonyl urea which is a insulin secretagogue.
- It increases insulin secretion by blocking ATP sensitive K-channel
- Hpoglycemia and weight gain as a ADR is a major problem.
- It is usually given in combination with metformin.

MATERIALS AND METHODS

Animals

Wistar albino rats (150–170 g) were obtained from Central Animal Facility,Jamia Hamdard and kept at 25±1 °C, 55±5% humidity alongwith 12 h light/dark cycle. The animals were given standard pellet diet (Lipton rat feed, Ltd., Pune) and water ad libitum throughout the experimental period. The experiment was approved by the 'Institutional Animal Ethics Committee'. Both the drug pioglitazone and vitamin E were administered orally.

Table 1: Details of animal used for this study

Animal	Rat (Rattus Norvegicus)
Strain	Wistar
Weight	150mg
Gender	Male
Total time duration	Six month
Standard drug	Metformin and Glimiperide
Total no. of animal per group	Six
Work place	Pharmacology research lab, IEC Group of Institution, Gr Noida
Total no.of animal	30
Total no. of group of animal	Five

Experimental Framework

30 Wistar rats of either sex is taken.It is divided into 5 groups with 6 rats in each group.The experimental study was carried out under controlled condition.Rat is procured from animal house ,CMJ university ,Meghalay.The rat was maintained on pellet feed and water *ad libitum* until the time of experiment.Animal was kept overnight fasting before the day of experiment. Diabetes was induced by stress . The drugs (metformin and glimiperide) was given to group for 21 weeks.Glimperide is given in a dose of 17.5 mg/day and metformin 200 mg/day.

Table 2: Drugs with their trade name

Drug	Trade name
Metfoprmin	Glyciphage
Glimiperide	Glimi

 ISSN: 2250-1177 CODEN (USA): JDDTAO

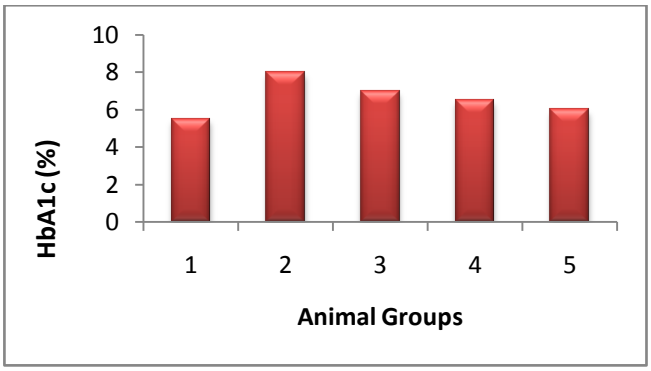
TREATMENT SCHEDULE

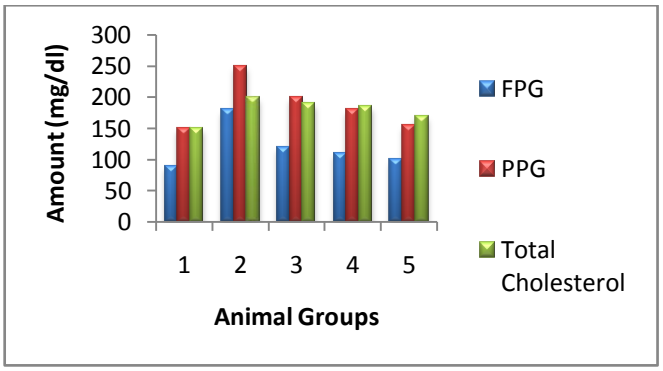
Table 3: Number of groups with their treatment schedule is presented below.

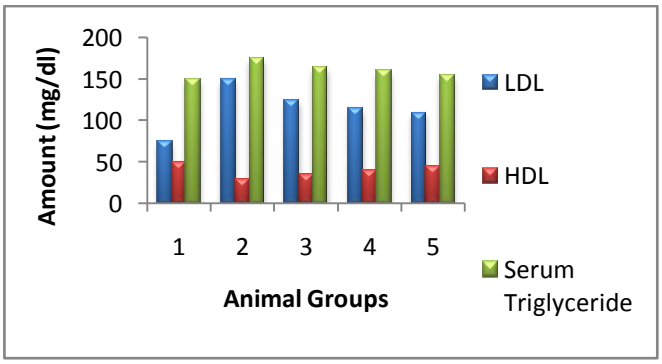
Group	Animal	Drugs,route of administration,dose
1	Normal control	No drug
2	disease control	Stress
3	Glimeperide control	Glimiperide(17.5 mg/kg,oral) in diabetic rat
4	Metformin control	Metformin(200mg/kg/day,Oral)in diabetic rat+HFD+stress
5	Glimeperide + metformin control	Glimiperide(17.5mg/kg,oral)+Metformin(200 mg/kg/day,Oral) in diabetic rat

RESULTS

Animal group		Parameter							
		Body weight (Kg)	HbA1c (%)	FPG (mg/dl)	PPG (mg/dl)	Total Cholesterol (mg/dl)	Serum Triglyceride (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
1	Normal control	**150**	**5.5**	**90**	**150**	**150**	**150**	**50**	**75**
2	Disease control	**175**	**8.0**	**180**	**250**	**200**	**175**	**30**	**150**
3	Glimeperide control	**160**	**7.0**	**120**	**200**	**190**	**165**	**35**	**125**
4	Metformin control	**155**	**6.5**	**110**	**180**	**185**	**160**	**40**	**115**
5	Glimeperide + metformin control	**152**	**6.0**	**100**	**155**	**170**	**155**	**45**	**110**







Glycemic control

It is seen in the that those group who is under the treatment of Metformin and glimiperide have better poat prandial and fasting glycemic control while it is moderate in Metformin and least in glimiperide teated group.The untreated group i.e disease control have very high level of blood glucose.

Glycosylated hemoglobin: - During the study there were significant differences were found in initial and final values of HbA1C levels of both groups. Though the HbA1C level was found to be reduced more significantly (P: 0.0001) patients treated with Metformin-glimepirideThe glycosylated hemoglobin was found to be reduced.

Total Cholesterol

It is seen in the that those group who is under the treatment of Metformin and glimiperide have lowest level of total cholesterol.while it is moderate in Metformin and higher in glimiperide teated group.The untreated group i.e disease control have very high level of blood cholesterol.

Effects on Triglycerides

It is seen that those group who is under the treatment of Metformin and glimiperide have lowest value of triglycerides, while it is moderate in Metformin and higher

in glimiperide teated group.The untreated group i.e disease control have very high level of blood glucose.Although even combination of Metformin and glimiperide treated group have more blood triglyceride in comparision to normal control.

Effects on HDL

It is seen that Metformin and glimiperide treated group have lower level while it is moderate in Metformin and lesser in glimiperide teated group.The untreated group i.e disease control have highest level of HDL.

Effects on LDL

It is seen in the that those group who is under the treatment of Metformin and glimiperide have lower level while it is moderate in Metformin and higher in glimiperide teated group.The untreated group i.e disease control have very high level of serum LDL.

DISCUSSION

A conventional 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 DM as its primary mechanism of action, with the requirement of poor glycaemic control as an indication for the addition of a second oral agent. During the study it has been found that type 2 diabetes is more pronounced at the age of 44.26 ± 1.5yrs. while 58% of patients were found to be at the greater risk of hypertension or other cardiovascular complication. Treatment with metformin-glimepiride orally simultaneously targets insulin resistance and insulin deficiency of type 2 diabetes, which may account for the greater effects on glycaemia. Indeed,metformin-glimepiride therapy produced greater mean changes from baseline in HbA1C.The greater mean changes from the baseline in case of fasting plasma glucose were found. But the statistical analysis using one way ANOVA followed by Dunnet test concludes that the drug treated group metformin glimiperide 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. Furthermore, 29.41% of patients receiving metformin-glimepiride therapy attained a final HbA1c of <6.0%. These results demonstrate that treatment with metformin-glimepiride was efficacious in improving glycaemia by achieving therapeutic goals for HbA1C and fasting plasma glucose in patients with type 2 diabetes.

The reductions in the blood sugar level were found 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.Cardiovascular disease is 2–3 times commoner in diabetics than in non-diabetics. Known risk factors are such as raised cholesterol, hypertension,, abdominal obesity, hyperinsulinemia, and degree of glycaemic control only partly explain the increased risk. In the present study more than 58% of patients were at the greater risk of cardiovascular diseases. 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 double combination to be prescribed in patients with increased cholesterol and triglyceride concentration.

CONCLUSION

From the data in results and discussion the present study concludes that the combinations of Metformin and glimepiride reduce the Glycosylated Hemoglobin level,fasting and post-prandialplasma glucose level significantly.. While the significant reduction in the total cholesterol,triglyceride and LDL cholesterol was also observed in the Metformin and glimepiride combination. It also significantly increased the HDL cholesterol levels . So the Metformin and glimepiride combination can be considered as the best possible two drug combination in patients with altered lipid profile.

ACKNOWLEWDGEMENT

We are grateful to Committee, research laboratory, CMJ University for their valuable advice, support and encouragement.

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