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Research Article

COMPARATIVE EFFECTS OF METFORMIN IN COMBINATION WITH GLIMEPIRIDE AND GLIBENCLAMIDE ON LIPID PROFILE IN INDIAN PATIENTS WITH TYPE 2 DIABETES MELLITUS

PROF. PRAVINKUMAR V. INGLE*, DR. GOKUL S. TALELE

Assistant Professor, Department of Clinical Pharmacy, R. C. Patel Institute of Pharmaceutical Education & Research, Shirpur 425405, Dhule (Maharashtra), India, [2]Principal, Nashik Gramin Shikshan Prasarak Mandal's, College of Pharmacy[2], Brahma Valley Educational Campus, Trimbak road, Anjaneri, Nashik 422213, Maharashtra, India. Email: prabhu4ever2000@rediffmail.com

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ABSTRACT

Background: Sulfonylurea and metformin is a bastion treatment for type 2 diabetes mellitus in Indian clinical practice, but their possible effects on lipid profile was poorly defined. Since microvascular and macrovascular complications were reduced through strict glycemic and lipid control. The main Objective of this study was to appraise the effects of metformin in combination with glimepiride versus glibenclamide on lipid profile in Indian patients with type 2 diabetes mellitus.

Materials & Methods: A total of 270 diabetic patients were selected for 26 weeks follow up on the basis of inclusion and exclusion criteria, having fasting plasma glucose≥ 140 mg/dl and glycosylated hemoglobin ($HbA_{1}c$) ≥ 7%. Patients were received randomly metformin 1000 mg/day + glimepiride 2 mg/day or metformin 1000 mg/day + glibenclamide 10 mg/day for 26 weeks. The efficacy was measured by comparing the effects on lipid profile (TC, HDL-C, LDL-C, and TG) at the end of study period relative to the baseline.

Results: All the 270 patients enrolled in the study receiving two varied combination treatment had the significant decrease in lipid profile by decreasing their LDL-C and same time increasing the HDL-C.

Conclusion**:** This study was suggesting that combination treatment with metformin plus glimepiride was more effective in improving lipid status of Indian type 2 diabetics than the metformin plus glibenclamide treatment.

Keywords: Type 2 diabetes, Metformin, Glimepiride, Glibenclamide, Lipid profile

INTRODUCTION

Type 2 diabetes and elevated plasma lipid levels are important independent risk factors for cardiovascular disease and coronary heart disease, the choice of an antihyperglycemic agent for patients with type 2 diabetes-in whom abnormal plasma lipid levels are often seen-should take into account effects on lipids control[1]. An estimated 3 of every 4 deaths in patients with diabetes mellitus are attributable to some form of cardiac or vascular disease[2]. Patients with type 2 diabetes are at 2 to 4 fold greater risk for coronary heart disease and stroke[3] and 2 to 8 fold greater risk for heart failure than the general population[4].

Sulfonylureas and metformin are commonly used for the treatment of patients with type 2 diabetes mellitus. The central position of sulfonylureas has been maintained over the years by many international guidelines, including the 1999 guidelines of the International Diabetes Federation (IDF)[5], the 2009 guidelines of the American Diabetes Association (ADA).[6] Glycemic control with monotherapy cannot be maintained in approximately 10% of patients per year requiring the addition of another antidiabetic drug[7,8]. Therefore, type 2 diabetic patients are often treated with a combination of antidiabetic agents. The need to use drugs with different and complimentary mechanisms of action frequently arises in daily clinical practice. There are several reasons to do this: the disease is it self progressive and the therapeutic attempts to achieve and maintain glycemic control often fails in the long term[8-10]. Because of complementary mechanisms of action, combination treatment with metformin plus sulfonylureas is rational and is associated with additive beneficial effect on the glycemic control[11,12]. But the effects on lipids for these varied combinations were poorly described in the Indian clinical practice. So we have selected this combination to assess the effects of these combination treatments on lipid profile in Indian patients with type 2 diabetes mellitus.

We thought this might contribute to existing knowledge and aid and assist the people with diabetes.

MATERIALS & METHODS

Design and data collection

A total of 270 Indian type 2 diabetic patients were enrolled in the study, and selected for follow up, on the basis of inclusion and exclusion criteria. Men and women were eligible to participate in the study if they had uncontrolled type 2 diabetes mellitus, obese/overweight, fasting plasma glucose≥ 140 mg/dl and glycosylated hemoglobin≥ 7.0 % from inpatient and outpatient departments of the hospital. Each patient was interviewed, for their past medication history for diabetes before participation in the study. Patients were included in the study if their diabetes was not adequately controlled by diet, physical activity, and weight reduction alone, or by treatment with single oral hypoglycemic agents.

Those patients taking glibenclamide or glimepiride alone metformin was added to their treatment. Patients taking metformin alone glimepiride or glibenclamide was added randomly to their treatment regimen. Additional exclusion criteria included were type 1 diabetes, a clinically relevant, medical or psychological condition, history of drug or alcohol abuse, pregnancy, breast feeding, renal, hepatic, respiratory insufficiency, hypoxic conditions, acute myocardial infarction, congestive cardiac failure, acute hepatitis, ketoacidosis, disseminated tuberculosis (severe infections), history of adverse reaction to sulfonylureas or metformin, patients taking lipid lowering agents.

All the patients were randomly assigned to receive metformin 1000 mg/day + glimepiride 2 mg/day or metformin 1000 mg/day + glibenclamide 10 mg/day for 26 weeks. Baseline data of selected patients (n = 270) presented in **Table 1.** Data collected were inpatient number, address, age, gender, height (cm), body weight (kg), body mass index (BMI, kg/m^2), date of visit, review on, social status, family history, associated disease/disorder. Patients were not given renewed advice about dietary measures and weight loss at the start of this study. The efficacy was measured by comparing the

effects on lipid profile (TC, HDL-C, LDL-C and TG) at the end of 26 weeks of study period relative to the baseline.

Statistical analysis

Baseline demographic and at the end of study values were summarized using descriptive statistics. Means and mean changes from baseline in TC, TG, HDL-C and LDL-C were calculated, with 95% confidence intervals, for the all patients.

Ethics

The Institutional Human Ethics Committee of R. C. Patel Institute of Pharmaceutical Education & Research, Shirpur-425405, Dhule, Maharashtra, India, approved the protocol of the study.

All the patients were enrolled in the study after explanation of research procedure and at the last by getting their written informed consent.

RESULTS

Demographic and baseline characteristic of patients

A total of 270 patients were selected for followup, and data were presented for all the patients at baseline in (**Table 1).** Metformin in combination with glimepiride versus glibenclamide combination treatment was not having any significant difference at their baseline. At the baseline, patients were treated with monotherapy as glibenclamide, metformin, or glimepiride as an oral hypoglycemic agent. After assigning the two varying combination treatment randomly, the follow up of all the patients were strictly taken.

Effects of combination therapy on lipid profile

After taking two varied combination treatment up to 26 weeks, lipid values were decreased significantly while HDL-C values were increase at the same time. In the present study more significant results on lipid profile were observed in the metformin plus glimepiride group as compared to the metformin plus glibenclamide group. The data are represented in (**Table 2)**.

DISCUSSION

The combination used in the present study was first time assess the effects on lipid profile in Indian type 2 diabetics as concerned with the number of patients. In this present study, treatment with metformin plus glimepiride was associated with statistically significant and durable reductions in total cholesterol, LDL-C, and triglycerides concentrations with a same time increasing HDL-C concentration as compared to the metformin plus glibenclamide combination treatment. At 26 weeks, the overall lipid profile was decrease in the metformin plus glimepiride treatment as compared to the metformin plus glibenclamide combination treatment. These reductions occurred rapidly and lasted for the end of the study period.

Table 1: Baseline Characteristics of Patients (n = 270)

	Metformin plus Glimepiride (n=135)	**Metformin plus Glibenclamide (n=135)**
Sex		
Male/ Female	79/56	75/60
Age (year, Mean, SD)	47	45
BMI (kg/m^2)[c]	28.7 ± 4.1	28.2 ± 4.6
Duration of diabetes (years)[c]	4.7 ± 2.1	4.9 ± 2.8
Serum lipid levels (mg/dL) mean (SD)		
Total cholesterol (mg/dL)	187 ± 19.58	176 ± 17.87
Triglycerides (mg/dL)	179 ± 23.52	168 ± 31.88
HDL (mg/dL)	34.92 ± 5.76	35.65 ± 5.65
LDL (mg/dL)	103.87 ± 11.62	98.76 ± 10.44

Data expressed as Mean ± S.D. TC: Total Cholesterol; TG: Triglycerides; HDL: High- density lipoprotein; LDL: low-density lipoprotein.

Table 2: Patients Reaching Lipid Control Goals at End of 26 Weeks (n = 270)

	Metformin plus Glimepiride (n=135)	**Metformin plus Glibenclamide (n=135)**
Serum lipid levels (mg/dL) mean (SD)		
Total Cholesterol (mg/dL)	157 ± 27.77	155 ± 29.69
Triglycerides (mg/dL)	137 ± 31.29	130 ± 32.41
HDL (mg/dL)	40.34 ± 7.31	37.11 ± 8.39
LDL (mg/dL)	67.53 ± 29.52	74.42 ± 32.74

Data expressed as Mean ± S.D. TC: Total Cholesterol; TG: Triglycerides; HDL: High-density lipoprotein; LDL: low-density lipoprotein.

The tight glycemic control and reduction of elevated lipid levels are primary goals in the prevention of cardiovascular complications in type 2 diabetics. Poor glycemic controls in type 2 diabetes associated with hyperlipidemia are independent risk factors for cardiovascular events. Thus, an ideal antidiabetic agent would improve both glycemic control and dyslipidemias. The lipid effects of metformin plus glibenclamide were already studied[1] but there is a lack of knowledge between the comparative statements of the two combination treatment. Oral antidiabetic agents have differing effects on plasma lipid profiles. Sulfonylureas and alpha-glucosidase inhibitors are generally regarded as having no unique lipid-lowering effects beyond those associated with improved glycemic control[14-17]. Finally, there is evidence to suggest that metformin may lower triglyceride and LDL-C levels independent of improvements in glycemic control. In a study in patients achieving inadequate glycemic control with sulfonylurea therapy, a switch to metformin monotherapy reduced TG and LDL-C levels by 7 % and 5 %, respectively[18]. Glimepiride as a newer generation sulfonylureas detected to have nitric oxide inducing property in human coronary artery endothelial cells.[19] It is generally accepted that nitric oxide plays an important role in regulating normal vascular function and confers protection against the development and progression of atherosclerosis. Recently, 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) have been also reported to induce nitric oxide production in endothelial cells and to show atheroprotective effects independently of their lipid lowering effects[20].

However in this present study we have also got the beneficial effect on the total cholesterol, LDL-C, and triglycerides by combining the metformin plus glimepiride combination treatment. In accordance with the new American Diabetes association guidelines, a sulfonylurea combined with metformin constitutes an attractive option in the clinical practice[21].

CONCLUSION

This study was suggesting that combination treatment with metformin plus glimepiride was more effective in improving lipid status of Indian type 2 diabetics than the metformin plus glibenclamide treatment.

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