Research article

An open label, Prospective study to compare the effect of fixed dose combination of Metformin and Pioglitazone versus fixed dose combin-ation of Metformin and Gliclazide on Lipid Profile parameters in Type-II diabetes patient

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Abstract

Objective: To evaluate and compare the effect of Fixed Dose combination of metformin and pioglitazone versus metformin and Gliclazide on lipid profile parameters in Type-II diabetes patients with deranged Lipid Profile.

Methods: Patients (n=60) of type-2 Diabetes with deranged lipid profile parameters consisting of 31 males and 29 females between 35-59 yrs were studied. They were divided into two groups of 30 each. Group-I: Metformin +Pioglitazone and Group-II: Metformin +Gliclazide. Each patient was assessed for a period of 16 weeks. Lipid profile parameters were assessed before study and at the end of the study. Statistical analysis was carried out by using paired 't' test for comparing the effect of Metformin + Pioglitazone, and Metformin+ Gliclazide on lipid profile parameters before and after therapy. For comparing between groups after the therapy ANOVA (Analysis of Variance) test was applied.

Results: There were significant reduction in the studied lipid profile parameters in both groups after 16 weeks of therapy ($P<0.05$). The inter-group comparison showed that the combination: Metformin +Pioglitazone (FDC) group has more significant ($P<0.05$) effect on the Serum Triglycerides (TG), High density lipoprotein cholesterol (HDL-C) while the combination: Metformin +Gliclazide has more significant ($P<0.05$) effect on Low density lipoprotein cholesterol (LDL-C).

Key Words: Metformin, Pioglitazone, Gliclazide, Lipid profile, Serum Triglycerides, High density lipoprotein cholesterol (HDL-C), Low density lipoprotein cholesterol (LDL-C).

Introduction

Diabetes mellitus (DM) is one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago.[1] In 1936, the distinction between type 1 and type 2 DM was clearly made.[2] Type 2 DM was first described as a component of metabolic syndrome in 1988.[3] It is characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.[4] It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million.[5]In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million).[6,7]People living with type 2 DM are more vulnerable to various complications, which often lead to their premature death. Peripheral resistance to insulin along with hepatic overproduction of glucose and impairment of secretion of insulin are the core abnormalities that characterize type-2 diabetes. Resistance to insulin plus compensatory hyperinsulinemia predisposes the persons to variety of abnormalities; these include high levels of plasma triglycerides (TG), low levels of high density lipoprotein cholesterol (HDL-C),

hypertension, and coronary heart disease. These complications will lead to development of obesity, hypertension & dyslipidemia. Cardiovascular disease accounts for approximately 75% of deaths among patients with diabetes. There is growing body of evidence to show that hyperglycemia and dyslipidemia are connected with this excess cardiovascular risk.[8,9] Present study was carried out to assess the effect of a fixed dose combination of metformin + pioglitazone versus metformin + Gliclazide on lipid profile parameters like total Serum cholesterol, TG, HDL-C, LDL-C and VLDL in type-2 diabetes mellitus patients.

Material and Methods:

The present study was carried out in Department of Medicine at MVP's. Medical College and Hospital, Nashik.

Study Design:

It was an open labeled, parallel, randomized and single centre study in patients with type-2 diabetes with dyslipidemia.

Study Population:

Patients (n=60) of either sex, with type-2 Diabetes having deranged lipid profile parameters consisting of 31 males and 29 females between 35-59yrs, attending the Out Patient Department (OPD) of Medicine at MVP's. Medical College and Hospital, Nashik. Were enrolled for the study.

Study Duration:

The duration of anti-diabetic therapy was 4 months.

lnclusion criteria:

1) Patients with Type-2 diabetes with obesity not controlled on diet and exercise.

2) Patients with deranged lipid profile parameters.

3) Patients not on any hypolipidemic drugs.

4) Patients having lipid levels above the low risk desirable lipid levels were studied.

In diabetic patient low risk desirable lipid levels are as follows: [10]

Serum Cholesterol <200 mg/dl

Serum Triglyceride <150 mg/dl

HDL- Cholesterol >40 for men &> 50mg/dl for women

LDL- Cholesterol <100 mg/dl

Exclusion criteria:

l) Patients with type-l Diabetes.

2) Patients requiring insulin for glycemic control or had history of ketoacidosis.

3) Patients with rapidly progressive retinopathy, neuropathy nephropathy.

4) Patients with myocardial infarction, hepatic or renal insufficiency and patients with anemia.

5) Patients allergic to study drugs.

6) Pregnant and lactating female.

Procedure: The Institutional Ethicsl Committee approved study protocol. Patients were explained in detail about the study pattern and related hazards. Informed written consent was obtained from the patients. Those included under-went all baseline investigations like liver function tests, kidney function tests, blood sugar level, Lipid profile, fundoscopy,and complete blood count. All the investigations were repeated at the end of the study period. Each patient was assessed for a period of 16 weeks.Enrolled patients were randomly divided into two groups of thirty each

Group-I: Metformin +pioglitazone

Group-II: Metformin+gliclazide

Dosage Schedule:

GROUPS	DRUGS	DOSES	DURATION
GROUP - I	Fixed dose combination of Metformin +Pioglitazone	Metformin 500 mg and Pioglitazone 15mg	4 months
GROUP - II	Fixed dose combination of Metformin + gliclazide	Metformin 500 mg and 80mg gliclazide	4 months

Each patient in respective group was provided free samples for fifteen days and was asked to visit to diabetic clinic for follow up and for collection of drugs.

At each follow up visit, patients were assessed for glycemic control, history pertaining to adverse drug effect of the therapy was asked. All patients were given advice about diet and exercise.

Semi-autoanalyser method: Patients were asked to come fasting in diabetic clinic, venous blood sample were collected in plain bulb. The collected blood samples were centrifuged by centrifuge machine at 10,000 rpm for 10 min and serum was separated .The separated serum was analyzed for Lipid profile parameters like serum cholesterol ;serum Triglycerides; HDL-Cholesterol using concentration linear mode of semi autoanalyser.

Statistical Analysis: Statistical analysis was carried out by using paired' test for comparing the effect of Metformin +pioglitazone and Metformin +gliclazide on lipid profile parameters before and after therapy. For comparing between groups after the therapy ANOVA (Analysis of Variance) test was applied.

Result:

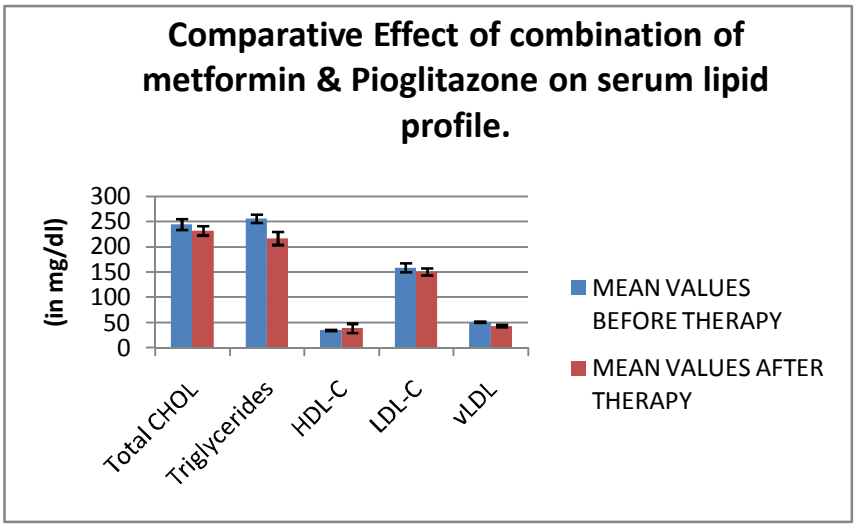
All (30) patients in each group completed the study. In the Metformin+gliclazide group,26 patients remained on starting dose .In the four patients dose were up titrated to twice a day. Table –I shows baseline s & after therapy lipid levels in both groups. There was reduction in all lipid parameters after the treatment in both groups. But significant reduction was seen in serum TG, VLDL and significant increase in HDL-C was reported in Metformin +Pioglitazone group where as significant reduction in only LDL-C was reported in Metformin +Gliclazide group.

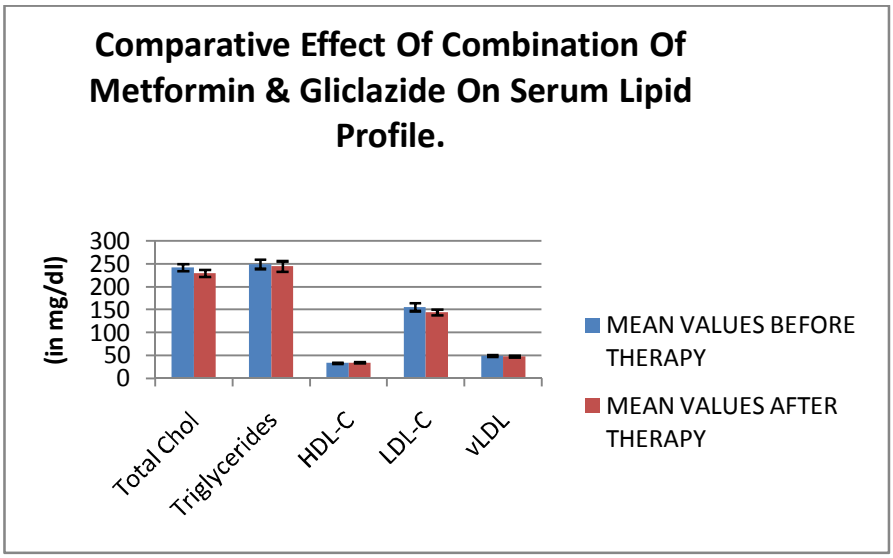
Table No.1

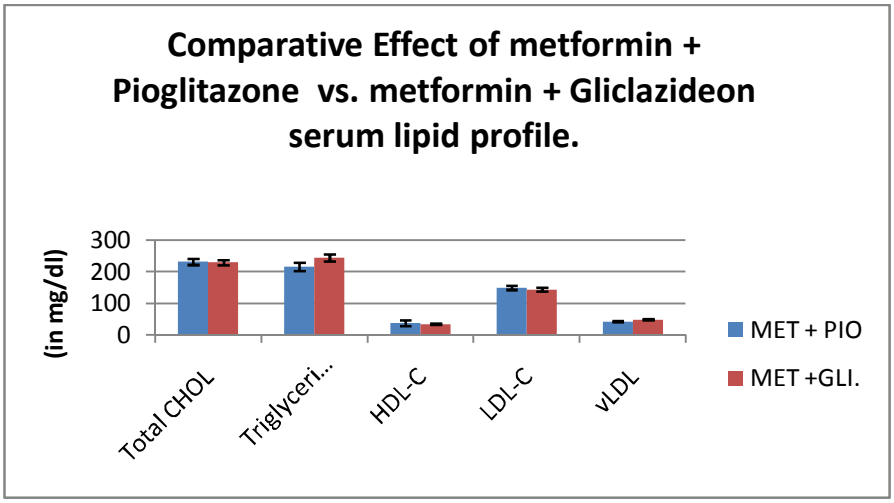
Comparative Effect of fixed dose combination of metformin+ Pioglitazone & metformin+ Gliclazide on serum lipid profile before and after therapy.

Lipid Profile Parameter (mg %)	MEAN VALUES BEFORE THERAPY		MEAN VALUES AFTER THERAPY	
	MET + PIO	MET +GLI.	MET + PIO	MET +GLI.
CHOL	244.49± 11.107	242.62 ± 8.178	232.19± 9.295	230.12 ± 8.168
TG	256.00 ± 8.178	250 ±10.11	216**.74 ± 12.816	245±11.67
HDL-C	34.93 ± 1.232	34.23±1.212	38*.79 ± 9.24	35.13±1.232
LDL-C	158.63 ± 8.989	156.61±8.82	150.61 ± 6.851	144*.54±6.25
VLDL	50.93 ± 1.56	50 ± 2.25	43*.35 ± 2.625	49±20.33

- * **= P<0.05** = Statistically Significant.
- ** **= P<0.001** = Statistically Highly Significant.
- **MET+PIO** = Fixed Dose combination of metformin+ Pioglitazone
- **MET +GL** = Fixed Dose combination of metformin+ Gliclazide
- **CHOL** = Serum Cholesterol
- **TG** = serum triglyceride
- **HDL-C** =High Density Lipoprotein Cholesterol
- **LDL-C** = Low Density Lipoprotein Cholesterol
- **VLDL** = Very Low Density Lipoprotein







Discussion:

It was mentioned by Misra A & et al that Indians are genetically predisposed to the development of coronary artery disease due to dyslipidemia and low levels of high density lipoproteins. [11]These determinants make Indians more prone to development of the complications of diabetes at an early age (20-40 years) compared with Caucasians (>50 years) and indicate that diabetes must be carefully screened and monitored regardless of patient age within India[11]

The etiology of diabetes in India is multifactorial and includes genetic factors coupled with environmental influences such as obesity associated with rising living standards, steady urban migration, and lifestyle changes. Individuals with diabetes are at high risk for cardiovascular disease, lipid disorders are common among these individuals and development of effective therapy for hyperlipidemia is

important.[12]Oral hypoglycemic agents have significantly enriched the therapeutic armentarium with novel compounds. For the process of evolution many new molecules have been invented while the far reaching benefit of certain old drugs has been rediscovered. The best example is Biguanides especially metformin recommended by FDA having beneficial effect in type-2 diabetes with obesity and insulin resistance.[13]

The Thiazolidinediones (TZDs) are potent agonists of the peroxisome proliferator-activated receptor-γ (PPAR-γ). PPAR-γ receptor activation increases glucose and lipid uptake, increases glucose oxidation, decreases free fatty acid concentration and decreases insulin resistance.[14] PPAR-γ receptor activation also stimulates adiposite differentiation resulting in more and smaller fat cells .[15]Visceral fat either does not change significantly [15] or decreases [16,17] Hepatic fat is significantly decreased with improvements in glycaemic control and correction of dyslipidemia. [18] Intramyocellular lipids significantly decrease, along with an improvement in lipid profile parameters, blood pressure and endothelial function. Thus pioglitazone improved the insulin resistance and glycemic control as well as improvement in lipid profile parameters, blood pressure and endothelial function.[19]

Sulphonylureas are widely used to treat type 2 diabetes because they stimulate insulin secretion by pancreatic beta-cells.[20] Hypoglycemia and weight gain are the main related inconveniences.[21] Gliclazide is a second generation sulphonylurea, causes less hypoglycemia than chlorpropamide and glibenclamide. Thiazolidinediones and sulfonylurea's exert opposing effects on β-cell functionality over time. β-cell stress is reduced with thiazolidinedione therapy, but enhanced with sulfonylurea therapy.[22]

In the present study, we found that 16 weeks therapy with metformin +Gliclazide and metformin +pioglitazone was equally effective in improving glycemic control, a result that supports data from previous studies .[20-24] However, The present study showed that the results of fixed dose combination of metformin 500mg +Pioglitazone 15mg showed significant improvement in lipid levels i.e. significant reduction in serum TG, VLDL, and significant increase in HDL-C while fixed dose combination of metformin 500mg +gliclazide 80 mg showed only significant reduction in LDL-C. Other lipid parameters are decreased but not significantly. Simultaneously when the intergroup comparison was done, its showed that Fixed dose Combination therapy of metformin +pioglitazone has much more beneficial and significant effect on serum lipid levels like serum TG & HDL-C than metformin+giclazide ($p<0.05$).These findings of our study are similler to the findings of D.J.Betteridge & et al.[25]

Since there is strong association with low HDL-C, elevated TG's and higher risk of coronary heart disease patients with type-2 diabetes, both metformin and pioglitazane improved glycemic control as well as insulin resistance and lipid profile suggesting that metformin + pioglitazone reduce the cardiovascular risk for patients with type-2 diabetes. Despite the lack of long-term clinical trials of the fixed-dose combination of pioglitazone and metformin in the management of cardiovascular risk factors, the evidence of a possible effect of pioglitazone on proinflammatory markers, adipocytokines, and procoagulative state supports its use in the treatment of metabolic syndrome.

Conclusion:

Diabetic patients are often treated with multiple drugs, and may require a more practical and

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convenient therapeutic regimen, which can be provided by a fixed-dose combination. The fixed dose Combination of metformin+pioglitazone has beneficial effect on serum lipid levels in addition to well glycemic control. Therefore these drugs in combination may be preferred while treating the patients of type-2 diabetes with obesity and deranged lipid profile. More studies are needed on the potential economic impact of fixed-dose combination treatment with pioglitazone and metformin, andLarge-scale, long-term clinical trials will provide clear evidence of the potential preventive effects on macro- and microvascular complications of type 2 diabetes.

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