



An Open-Label, Prospective, Observational Study of Effects of Metformin versus Metformin Plus Glimepiride on Plasma Lipid Profile in Type II Diabetes Mellitus patients in a Tertiary Care Teaching Hospital In Kolkata

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Abstract

Introduction: Diabetes is considered a global epidemic affecting more than 8% of adult population worldwide. Insulin resistance contributes to the characteristic dyslipidemia associated with Type 2 DM. So by controlling glycemic level, these drugs in combination or alone also may affect plasma lipid parameters. Metformin and Glimepiride are most commonly prescribed anti-diabetic agent.

Methodology: It was a prospective, parallel group, observational study. In group 1 and group 2 patients received metformin monotherapy and metformin and glimepiride combination therapy, respectively. Doses were adjusted at regular follow-ups by them with an aim to achieve euglycemia. Fasting blood glucose, HBA1C and lipid parameters were assessed at the initiation of therapy and after 3 months.

Results: A total 84 patients completed the study. Group 1 included 44 patients and rest belonged to group 2. However, statistically significant reduction of median triglycerides (TG) & LDL was noted in both groups. There was significant rise in median HDL level within both groups. But after 3 months at follow-up, HDL cholesterol is statistically significantly higher in group 2 compared to group 1. There was no between group difference in respect to median triglyceride and LDL changes. Present study also showed statistically significant median decrease of fasting blood sugar (FBS) and HBA1C from baseline after 3 months of treatment in both groups.

Conclusion: The results of the present study showed that metformin monotherapy as well as metformin and glimepiride combination therapy had beneficial effects on lipid profile in addition to glycemic control. The beneficial effects of these drugs on lipid profile were reassuring in situations where due to various reasons statins cannot be prescribed or cannot be afforded by the patients of type 2 diabetes mellitus.

Keywords: Type II Diabetes, Dyslipidemia, Metformin, Glimepiride, Efficacy.

Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders characterized by hyperglycemia. DM causes secondary pathophysiological changes in multiple organ systems, leading to complications that cause immense suffering of the patient and increased burden on health care system. According to International Diabetes Federation (IDF), about 451 million people worldwide are suffering from Type II DM in 2017.¹ In India; the prevalence of Type II DM reached 72 million as speculated by IDF.² The hallmarks of type 2 diabetes are hyperglycemia, insulin resistance and insulin deficiency, and it is increasingly recognized that insulin resistance contributes to the characteristic dyslipidemia associated with type 2 DM.³ Diabetic dyslipidemia is characterized by reduced high density lipoprotein (HDL), increased triglycerides (TG), increased very low density lipoprotein (VLDL) and postprandial lipemia. A number of agents of different modes of action are available to improve glycemic control. Sulfonylurea drugs improve glucose levels by stimulating insulin secretion by the pancreatic beta cells. Glimepiride, a member of the sulfonylurea class, is one the most popular among them nowadays. Biguanides, of which metformin is used now, reduces glucose levels primarily by decreasing hepatic glucose production and by increasing insulin action in muscle and fat.⁴ Metformin by reducing gluconeogenesis and AMPK mediated action, complement the actions of glimepiride (if administered in combination), by inducing and maintaining improvements in insulin resistance, the abnormal lipid profile associated with type 2 DM and other cardiovascular risk factors.⁵ Study has shown that lipid and glucose homeostasis are interrelated. So by controlling glycemic level these drugs in combination or alone also may affect plasma lipid parameters⁶. Metformin as monotherapy or as combination with glimepiride is the most commonly prescribed anti-diabetic medication. So this proposed work was conducted to investigate

the effects of, metformin alone vs combination of glimepiride and metformin, on lipid profile in type 2 DM patients who will not be receiving any hypolipidemic agent in addition. In spite of a detailed thorough search among published literatures we found very few studies which assessed the effect of Metformin monotherapy versus Metformin plus Glimepiride combination on plasma lipid profile in Type II Diabetes Mellitus patients especially among Indian population. Hence the present study was carried out in Diabetic clinic at R G Kar Medical College, Kolkata to find out any effect on plasma lipid profile of these two drugs in Type II DM patients.

Aims & Objectives

- 1) To see the effects of metformin on lipid profile, if any.
- 2) To see the effects of glimepiride and metformin combination on lipid profile, if any.
- 3) To compare the above effects if present and whether the effects are beneficial or harmful.

Methodology

It was a prospective, parallel group, observational study. The estimated sample size was set to be 100 in two groups. The participants of the study were patients attending Diabetes Clinic of either sex, of all ages, of established type 2 DM going to start metformin monotherapy or glimepiride plus metformin combination therapy. In group 1, patients received metformin monotherapy. In group 2, those who were going to start metformin and glimepiride combination therapy, were included. Patients were screened for the following inclusion & exclusion criteria before recruitment. Inclusion Criteria were patients of Type 2 DM, Male or Female of all ages and going to start metformin monotherapy or combination of metformin & glimepiride for the management of Type II diabetes mellitus. Exclusion Criteria were Type 1 DM, Renal impairment, Hepatic impairment, Coronary Heart Disease, Congestive Cardiac Failure, H/O Cerebral Infarct or Hemorrhage, TIA, Serum LDL \geq 160mg/dl,

TG>=400mg/dl, HDL<=30mg/dl, Severe persistent asthma or COPD, Patients already on Hypolipidemic medications, Pregnant and Breastfeeding mother. The patients were followed up for one year. The medicines were prescribed by the physicians of diabetes clinic in R.G. Kar Medical College & Hospital. Doses were adjusted at regular follow-ups by them with an aim to achieve euglycemia. Lipid parameters were assessed at the initiation of therapy and after 3 months. Fasting blood sugar and glycosylated hemoglobin were measured simultaneously at the initiation of therapy and after 3 months. Data were analyzed by SPSS V22.0 software. Categorical data were analyzed by Chi-Square test. Numerical data were analyzed by Wilcoxon Signed Rank Test and Mann Whitney U Test. P value less than 0.05 were considered to be significant. This study was conducted in accordance with the Declaration of Helsinki Principles. The study was started only after obtaining permission from the Institutional

Ethics Committee. Informed consent was taken from each subject before inclusion into the study.

Results & Analysis

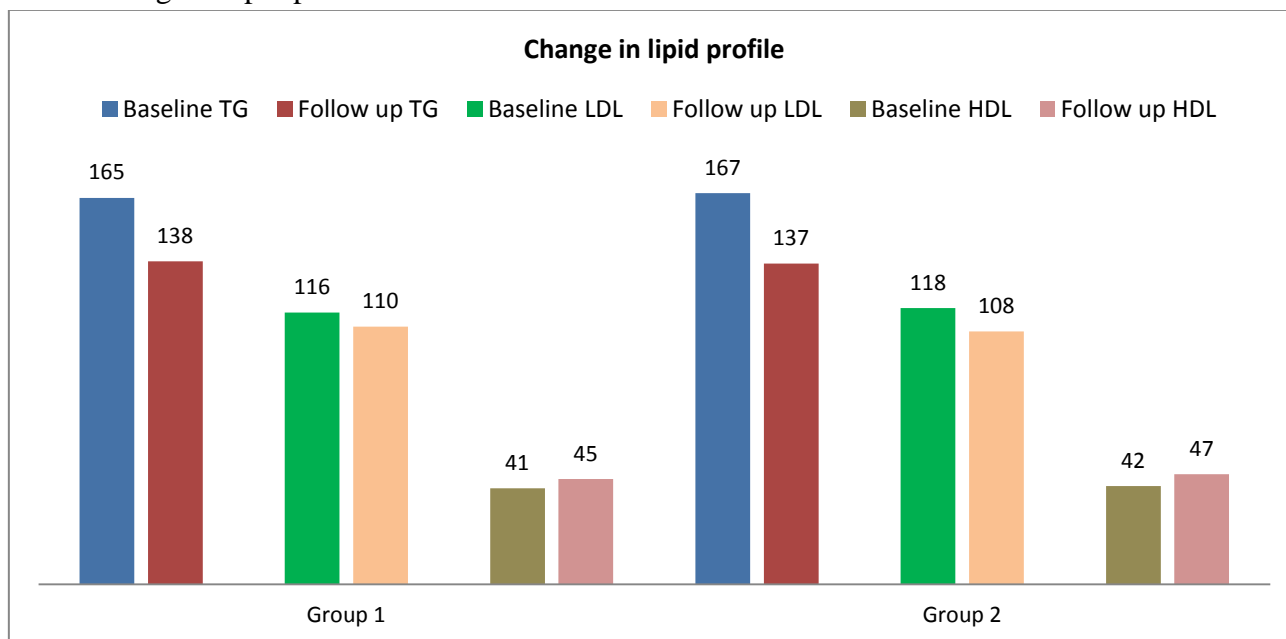
A total of 100 patients were included, whereas 84 patients were available for follow up. Group 1 included 44 patients and rest belonged to group 2. Table 1 showed the demographic profile of the patients. There was no statistically significant difference in age (Mann Whitney U Test) and sex (Chi Square Test) across groups.

Table 1: Patients’ demographic Profile

Characteristics		Group 1	Group 2
Gender	Male	23	22
	Female	21	18
Age	Median (Interquartile range)	49(43.50, 51)	46(42.25, 55.25)

Now, figure 1 shows the median levels of serum triglyceride (TG), LDL and HDL in two groups at baseline and after 3 months follow up.

Figure 1: Change in lipid profile



At baseline, these two groups were comparable in respect to TG, LDL and HDL levels as there was no statistically significant difference in median values as found in Mann Whitney U test (P> 0.05). However, statistically significant (Wilcoxon Signed Rank Test) median reduction of

triglycerides was noted within group 1 as well as in group 2. Similar result was obtained in respect to median LDL level. There was significant rise in median HDL level within both groups. But after 3 months at follow-up, HDL cholesterol is statistically significantly (Mann Whitney U Test)

higher in group 2 compared to group 1. Hence there was more increase of HDL in group 2 after 3 months of treatment as compared to group 1.

Table 2: Comparative evaluation of Fasting Blood Sugar {Median (Interquartile range) in mg/dl} levels in group 1 and group 2

Duration in months	Group 1	Group 2
baseline	141.50 (135, 146)	172 (166.25, 177.75)
3 months follow-up	109 (105, 113)*	110 (104.25, 115.75)*

*p<0.05, as compared to baseline values (Wilcoxon signed rank test)

Present study also shows statistically significant median decrease of fasting blood sugar (FBS) from baseline after 3 months of treatment in both groups.

Table 3: Comparative evaluation of Glycosylated hemoglobin (HbA1c) {Median (Interquartile range) in mg/dl} levels in group 1 and group 2

Duration in months	Group 1 {Median (Interquartile range) in mg/dl}	Group 2 {Median (Interquartile range) in mg/dl}
Baseline	7.7 (7.5, 7.8)	8.3 (8.3, 8.475)
Follow-up	6.4 (6.225, 6.6)*	6.5 (6.125, 6.7)*

*p<0.05, as compared to baseline values (Wilcoxon signed rank test)

Present study also shows statistically significant median decrease of HBA1C from baseline after 3 months of treatment in both groups. However, present study also shows FBS and HbA1c levels were statistically significantly (Mann Whitney U Test) higher in group 2 than group 1 at baseline. But after 3 months at follow-up, the distribution of FBS and HbA1c were comparable across both the groups. It is evident that group 2 patients enjoyed better reduction of FBS and HBA1C level than metformin monotherapy group.

Discussion

Present prospective parallel group study was conducted with an aim to compare the effects of metformin monotherapy and metformin and glimepiride combination therapy on lipid parameters in addition to glycemic control in patients with type 2 diabetes. In the present study, statistically significant median reduction of triglycerides (TG) and LDL and elevation of HDL

with metformin monotherapy is found, which is in line with the observation made by Mughal M.A., et al. (2000).⁷ Likewise, statistically significant median reduction of triglycerides (TG) and LDL and raise of HDL with metformin and glimepiride combination therapy is found, which is in line with Sen S, et al. (2013)⁸ and Ingle P.V., et al. (2011).⁹ The present study shows that FBS and HbA1c have been statistically significantly reduced below target levels as per American Diabetes Association (ADA) 2015 guidelines, indicating that both metformin monotherapy, as well as metformin and glimepiride combination therapy groups had effective glycemic control. The present study shows that distribution of triglyceride, LDL cholesterol, are same across both group 1 and group 2 at baseline and after 3 months at follow-up, indicating there is no difference in effect on these lipid parameters, among metformin monotherapy and metformin and glimepiride combination therapy. This finding is in line with that of Zhang F., et al. (2013)¹⁰. But HDL cholesterol though has same distribution in both groups at baseline, after 3 months at follow-up HDL cholesterol is significantly higher in group 2 compared to group 1. This indicates that metformin and glimepiride combination therapy is more effective in increasing HDL cholesterol. This finding is in contrast to the finding of Zhang F., et al. (2013)¹⁰ who found metformin and sulfonylurea (including glimepiride) combination therapy has the disadvantage of decreasing HDL cholesterol compared to metformin monotherapy. This contrast finding may be explained on the ground that Zhang F., et al. (2013)¹⁰ consists of a multi-centric, meta-analysis of randomized controlled trials. Moreover it mainly included Chinese population. The present study is an observational study and has been done on a small study population (purposive sampling technique). It is mainly done on a Bengalee and some non-Bengalee Indian population residing at north Kolkata and north 24 parganas. So there is genetic, geographical, lifestyle including food

habit variation, all of which can have contributed to the contrast outcome regarding HDL cholesterol change. However, the rise of HDL in group 2 and group 1 was 5mg/dl and 4mg/dl respectively. Though it was statistically significant but clinical significance was uncertain.

Conclusion

The present study had limitations. It was an observational study and not a randomized controlled trial. Blinding was not done. It has been done on a small number of subjects with the sampling been done by purposive sampling technique. Moreover lipid and glucose homeostasis being interlinked, the changes in lipid levels must have been influenced by changes in glucose level in the study. But in this setting with the present study design and statistical analysis done, the effect of glycemic control on lipid profile could not be ascertained. The results of the present study showed that metformin monotherapy as well as metformin and glimepiride combination therapy have beneficial effects on lipid profile in addition to glycemic control. The beneficial effects of these drugs on lipid profile were reassuring in situations where due to various reasons statins cannot be prescribed or cannot be afforded by the patients of type 2 diabetes mellitus.

Acknowledgement: We are thankful to all the patients, staffs of Deptt of Pharmacology and Medicine and Biochemistry of R.G Kar Medical College, Kolkata for their valuable support.

Conflict of interest: None

Financial disclosure: None

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