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A Prospective Study to Analyse the Metabolic Effect of Metformin with Glimepiride on Type 2 Diabetic Patients of North India.

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ABSTRACT

Background: Diabetes Mellitus is a leading disease of developing countries and its incidence is increasing day by day. Among Oral Hypoglycemic agents, Metformin is still the best treatment choice for type 2 diabetes mellitus. Metformin is associated with improvements in lipoprotein metabolism, including decreases in LDL-C, fasting and postprandial TGs, and free fatty acids. **Methods:** This prospective study was carried out on Type 2 Diabetic patients attending the Diabetic clinic at Teerthanker Mahaveer Medical College & Research Center, Moradabad. Only those patients were included who were not adequately controlled with a stable dose of metformin monotherapy. A total of 125 patients were enrolled in the study taking Glimepiride plus Metformin. The patients received therapy of metformin 500mg three times daily & glimepiride 5mg twice daily. **Results**: Out of the 125 patients enrolled in the study, only 82 patients completed the study. Out of 82 patients, 49 were males and 33 females. There was a significant reduction ($p<0.05$) of FPG as compared to baseline. The (PPBS) was reduced from 275.95 ±63.599 (mg/dl) to 167.04±27.084 (mg/dl) at 12 weeks and141.36±31.064(mg/dl) at 24 weeks (mg/dl). There was a significant reduction ($p<0.05$) of Hb1Ac, TC, TAG, LDL, VLDL, UA, SGOT as compared to baseline but no significant rise in HDL was seen as compared to baseline. **Conclusion:** Significant improvement in fasting blood sugar (FBS), Postprandial blood sugar (PPBS), Lipid profile and Glycosylated hemoglobin as compared to baseline.

Keywords: Glimepiride, Metformin, Type 2 Diabetes Mellitus, Metabolic Syndrome.

INTRODUCTION

Metformin is still the best treatment choice for type 2 diabetes mellitus. Metformin is associated with improvements in lipoprotein metabolism, including decreases in LDL-C[1], fasting and postprandial TGs, and free fatty acids.[2] It may have a neutral effect on body weight of patients with T2DM when compared to diet or may limit or decrease the weight gain experienced with sulfonylureas[3], TDZ[4], insulin.[5,6]

Modest weight loss with metformin has been observed in subjects with IGT.[7-9] However, a meta-analysis of overweight and obese non-diabetic subjects, found no significant weight loss as either a primary or as secondary outcome. [10]

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Past studies comparing the efficacy between metformin with sulfonylureas showed that metformin was significantly better in controlling HbA1c, FPG, BMI, LDL and TG.[11-14] It was also known by the previous studies, that Glimepiride is a better Sulphonylureas in treating T2DM.[15–19] Some meta-analytic studies found that metformin was not significantly better than glimepiride, particularly in controlling HbA1c, FPG and BMI. These studies supported that both metformin and glimepiride was effective in treating T2DM for glycemic control. Metformin performed better than glimepiride in management of BMI and lipid metabolism indices but the advantages of metformin were only significant in short follow-up periods.

Even for treating the patients who were not responding to conventional (non-glimepiride) sulfonylureas, glimepiride and metformin were equivalent in glycemic control. This finding could not be achieved by comparing sulfonylureas (including glimepiride) as a group with metformin. Metformin and glimepiride were not significantly different in glycemic control of T2DM, suggesting

that glimepiride would be a good choice second to metformin in the monotherapy of T2DM.

The previous studies revealed that glimepiride plus metformin combination significantly reduced the glycosylated postprandial glucose level and serum cholesterol level during the course of treatment.

Nathan et al[20] reported that the expected percentage decrease in HbA1c levels is 1.0% to 2.0% with metformin monotherapy, 1.0% to 2.0% with sulfonylureas (SUs), 0.5% to 1.0% with glinides, 0.5% to 0.8% with α-glucosidase inhibitors (α-GI), 0.5% to 1.4% with Thiazolidinediones (TZD) and 0.5% to 0.8% with DPP-4 inhibitors. Monotherapy with metformin or SU exhibits a stronger reduction of HbA1c levels than a DPP-4 inhibitor alone. However, metformin is associated with side effects such as GI symptoms and is contraindicated in patients with renal insufficiency. The major side effects of SUs are hypoglycemia and weight gain. In patients receiving treatment with SUs, the incidence of hypoglycemic episodes has been reported to be 17.6% per year.[21] Side effects appear to be more frequently seen with metformin or SUs than with Sitagliptin

MATERIALS AND METHODS

This study was carried out at Teerthanker Mahaveer Medical College & Research Center, Moradabad for the consecutive newly diagnosed diabetic patients > 40 (40-70) years of age attending the Diabetic clinic and diagnosed with Type 2 diabetes using the standard diagnostic criteria in effect at the inception of the study. In this prospective study, patients were included with a history of T2DM not adequately controlled with a stable dose of metformin monotherapy. A total of 125 patients were enrolled in the study taking Glimepiride plus Metformin. The patients received therapy of metformin 500mg three times daily & glimepiride 5mg twice daily.

Diagnosis of Diabetes: Diagnosis of the patients suffering from type 2 diabetes mellitus was made on the basis of clinical assessment and diagnostic tests as per the ADA Guidelines. According to ADA, the fasting plasma glucose (FPG), 2 hours post meal blood glucose, random blood sugar is reliable and convenient test to identity diabetes in asymptomatic subjects.

Parameters measured: The patients were advised follow up at 12 weeks and 24 weeks. At each visit patients were evaluated for glycemic parameters and biochemical parameters. The glycemic parameters included analysis of Fasting plasma glucose, post prandial plasma glucose and glycosylated hemoglobin. The biochemical analysis included lipid profile – total cholesterol, serum triagylcerides level, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotin-protein and very low density lipoprotein estimation. The safety analysis was performed by measuring serum creatinine, serum uric acid level, SGOT and SGPT level at 12 weeks and 24 weeks. The follow up of those patients continued for six months and blood samples for various estimation withdrawn at base line 3 month and 6 months of the study.

Statistical Analysis: Data was analysed using SPSS version 17.

RESULTS

Out of the 125 patients enrolled in our study, only 82 patients completed the study [Table 1]. Out of 82 patients 49 were males and 33 were females. Mean age of group is 56.13±12.47 years, Mean weight was 71.18±10.99 Kilogram (Kg), Mean Fasting blood sugar (FBS) was found to be 70.83±9.82 (mg/dl), Mean Postprandial blood sugar (PPBS) was 275.95±63.60 (mg/dl), Mean Total cholesterol (TC) was 204.09±40.25 (mg/dl), Mean Triglyceride (TG) is167.87±58.42 (mg/dl), Mean Low Density Protein (LDL) is 124.06±33.70 (mg/dl). Mean Very Low Density Protein (VLDL) was 138.14±44.63 (mg/dl), mean HDL is 48.25±9.69 (mg/dl) mean UA was 4.29±1.06 (mg/dl), mean SC is 0.89±0.23 (mg/dl), mean SGOT is 37.25±6.99 (IU/L) and mean SGPT is 40.98±14.50 (IU/L) [Table 1].

There was a significant reduction ($p<0.05$) of FPG as compared to baseline. The (PPBS) was reduced from 275.95 ±63.599 (mg/dl) to 167.04±27.084 (mg/dl) at 12 weeks and141.36±31.064 (mg/dl) at 24 weeks (mg/dl) [Table 1].

There was a significant reduction ($p<0.05$) found in cases of Hb1Ac, TC, TAG, LDL, VLDL, UA, SGOT as compared to baseline but there was no significant rise in HDL as compared to baseline.

DISCUSSION

T2DM is a chronic metabolic disorder & has high prevalence in India. T2DM is characterized by a long asymptomatic period of hyperglycemia and many individuals with T2DM have complications even at the time of diagnosis. Hyperglycemia is associated with number of microvascular and macrovascular complications, which are significant cause of morbidity & mortality among diabetes subjects.

This study was undertaken to assess the differential effect on glucose and lipid parameters of glimepiride plus metformin in patients suffering from type 2 diabetes and metabolic syndrome. Our study found that there was significant improvement in fasting plasma glucose, Postprandial blood glucose, cholesterol profile, and HbA1c at 12 weeks and 24 weeks as compared to baseline. At 12 weeks' significant improvement was observed

Table 1: Metabolic parameters at baseline, 12 and 24 weeks.

S.N	Parameters	Baseline (Mean ±SD)	12 Weeks	24 Weeks
1	Age (years)	56.13±12.47	-	-
2	Weight(Kilogram)	71.18±10.99	-	-
3	Fasting Blood Sugar (FBS (mg/dl)	185.07±49.04	116.23±14.526*#	107.09±18.747*
4	Postprandial Blood Sugar (PPBS) (mg/dl)	275.95±63.60	167.04±27.084*	141.36±31.064*
5	Glycosylated Hemoglobin (Hb1Ac) (mmol/mol)	8.99±1.36	7.602±.8103*#	6.741±.7596*
6	Total Cholesterol (TC) (mg/dl)	204.09±40.25	168.50±31.184*#	148.45±30.669*
7	Serum Trigylcerides (TG) (mg/dl)	167.87±58.42	139.98±38.257*	121.18±29.756*
8	Low Density Lipoprotein (LDL) (mg/dl)	124.06±33.70	98.07±26.517*	80.95±29.366*
9	Very Low Density Lipoproteins (VLDL) (mg/dl)	28.10±14.427	21.96±9.077*#	17.71±5.742*
10	High Density Lipoprotein (HDL) (mg/dl)	48.25±9.69	48.50±9.519	49.56±12.949
11	Serum Uric Acid (UA) (mg/dl)	4.29±1.06	4.16±0.915*	4.134±.9067
12	Serum Creatinine (SC) (mg/dl)	0.89±0.23	0.831±.2413	0.8302±.21519
13	Aspartate Aminotransferase (SGOT) (IU/L)	37.25±6.99	34.89±6.423*#	34.86±6.997*
14	Alanine transaminase (SGPT) (IU/L)	40.98±14.50	37.63±9.245*#	37.63±9.245*#

p>0.05 as compared to other group using student unpaired 't' test
*p<0.05 within group by using student paired 't' test
#p<0.05 as compared to other group using student unpaired 't' test

after taking metformin and glimepiride in Fasting glucose level, HbA1c, Total Cholesterol (TC), Very Low Density Lipoprotein (VLDL). Both the therapies were well tolerated by the patients.

In a Similar study conducted by Likhar, et.al.[15] at 18 week, revealed that patients who were metformin alone and with inadequate glycemic control, receive glimepiride demonstrated that after 18 weeks, it had significant reduction in HbA1C. The results of our study are quite similar to this study as there was a significant decrease in glycosylated hemoglobin in glimepiride treated patients at 12 weeks but our study differs from this study as we assessed the patients for a period of 24 weeks and we also estimated the lipid parameters which were significantly better in glimepiride group at 12 weeks.

Another similar study done by Khan A et.al.[24] to compare the metabolic effects of the drugs, metformin and glimepiride showed significant favourable results in FBS, PPBS, and HbA1c at the completion of the study period. The results are quite similar to our study as our study found that both the groups had significant improvement in fasting plasma glucose, Postprandial plasma glucose, and (HbA1c) at 12 weeks and 24 weeks as compared to baseline. But improvement was better in glimepiride group at 12 weeks in our study.

A prospective, open-labeled, multicentric study over 12 weeks done in 2013 by Lister SC[8] to evaluate the efficacy and tolerability of glimepiride and metformin combination in those T2DM patients who had uncontrolled glycemic control with metformin after 12 weeks glimepiride and metformin combination treatment showed significant improvement in HbA1c, FPG, and post prandial blood glucose as HbA1C, FPG and ,PPBG were significantly reduced from baseline value at the end of the treatment. Lipid profile is also improved in this study results of this study shows that glimepiride and metformin combination have good glycemic control and better tolerability. The results of this study is very much similar to our study as in our study HbA1c and FBS were significantly reduced at 12 weeks and lipid profile were improved but the results are dissimilar from our study in that PPBS was not significantly reduced at 12 weeks.

At the end of the study, both liver functions test and renal functions tests remained unaltered statistically and within normal clinical range. Hypoglycemia and other adverse events were numerically more in metformin and glimepiride group.

The results of this study are quite similar to our study as in our study also there was significant reduction in FPG, PPBG, HbA1C, TC, TAG, LDL, VLDL and HDL was increased from baseline value.

There are certain limitations in our study, the sample size is small, a large sample size could have given different results. The time period for enrollment of patients was only one year and patients had to be followed up for duration of 6 months so it would have not been feasible if the sample size was large.

CONCLUSION

Based on the findings of the present study it's possible to conclude: it had significant improvement in fasting blood sugar (FBS), Post-prandial blood sugar (PPBS), Lipid profile, and Glycosylated hemoglobin as compared to baseline. At 12 weeks' Significant improvement in following parameters: Fasting blood sugar (FBS), Glycosylated Hemoglobin (HbA1c), Total Cholesterol (TC), Very Low Density Lipoprotein (VLDL).

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