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Original Research Article

Comparative study of control of hyperglycemia and dyslipidemia between two treatment-groups of diabetic patient (Metformin Monotherapy and Metformin + Glimepiride Combination)

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Abstract

Aim: The aim of the study is to examine whether the combination of metformin+ glimepiride is superior to metformin mono therapy to treat the newly diagnosed type 2 DM patients to control the HbA1C and dyslipidaemia in terms of LDL, total cholesterol, TG etc.

Materials and Methods: A Prospective randomised study with four groups. The control comprises of 60 healthy volunteers. 120 newly diagnosed type 2 DM cases (Group 1) were enrolled in the study. These 120 patients were randomised into two groups; Group 2 with 60 patients to receive Metformin and Group 3 with 60 patients to receive Metformin + glimepiride combination. Both the Group 2 and Group 3 have received the same hypolipidemic and antihypertensive drugs.

Results: After about 4 years of treatment, in Group 2 and Group 3, FPG, HbA1C% and lipid profile were improved significantly ($p< 0.05$) than the values before treatment started. Group 3 patients (metformin + glimepiride) had slightly better glycaemic control (P=0.85) than Group 2 patients (metformin only). Group 3 patients had also better control over Cholesterol and LDL level, LDL-C/HDL-C, TC/HDL-C than Group B patients.

Conclusion: Metformin and Glimepiride combination therapy improves HbA1c, LDL-C, HDL-C more effectively. However, Group 2 patients had shown better AIP than Group 3 patients.

Keywords: Monotherapy, Combination therapy, Glycaemic control, Dyslipidemia, Atherogenesis.

Introduction

Type 2 DM is the most common form of diabetes occurring in the adult population. Metformin is one of the primary drugs to be prescribed to the newly diagnosed patients as monotherapy along with diet and life style modification.[1] When metformin alone is not sufficient to control hyperglycemia with optimum dose, Sulfonylureas or DPP-4 inhibitors are added. Sometimes monotherapy with sulfonylurea or DPP-4 inhibitors are started in newly diagnosed patients. The combined regimens[2] like metformin + Sulfonylurea or metformin + DPP-4 inhibitors etc. are started when adequate glycemic control is not achieved with a single agent. Dyslipidemia[3] with premature atherosclerotic cardiovascular disease is a dreadful complication to be seen in patients suffering from type 2 DM. Patients are prescribed antilipidemic drugs like statin, fibrates etc. along with oral hypoglycemics ± insulin. OHA like metformin lowers the plasma LDL or TG modestly itself[4] Again, metformin lowers plasma lipid and glucose synergistically with statins[5] specially those patients who respond well to metformin therapy measured by > 1% reduction of HbA1c after 3 months.[6] In this prospective clinical study, it was tried to evaluate whether metformin + glimepiride combination therapy is superior over metformin monotherapy[7,8] to lower HbA1c and lipid profile. The parameters like BMI, FPG, HbA1c, cholesterol, LDL-C, HDL-C, VLDL-C, TG, LDL-C/HDL-C ratio, TC/HDL-C ratio, AIP (log TG/HDL-C)[9,10] etc. were measured at frequent interval in each groups and analysed to compare the efficacy between monotherapy and combination therapy.

Materials and Methods

It is an open label randomised prospective study. At first 120 newly diagnosed type 2 DM patients were included in the study. For comparison of clinical and laboratory parameters healthy volunteers were enrolled and designated as CONTROL.

The Control Group comprises of 60 healthy volunteers with mean age of 40.15±8.18 (SD) years. The age of 120 newly diagnosed type 2 DM cases i.e GROUP 1, was 53.65±4.45 (SD) years. These 120 patients were randomised into two equal groups; Group 2 with 60 patients to receive Metformin only and Group 3 with 60 patients to receive Metformin + glimepiride combination.

Group 2 (average age 54.29±3.47 years) patients were periodically evaluated over mean 2.81±0.92 years of treatment with Metformin and anti lipidemic drug. Group 3 consists of 60 patients also with average 53.7±2.69 (SD) years of age were treated with Metformin+ Glimepiride for average 3.12±1.06 years and evaluated at regular basis. Both the Group 2 and Group 3 have received the same hypolipidemic drug and antihypertensive drugs. Blood parameters like HbA1C (primary endpoint)[11], FPG, LDL, total cholesterol, TG etc. (secondary endpoint) were

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http://doi.org/ 10.18231/j.ijcaap.2019.019

periodically evaluated along with BP, BMI, ECG, renal function etc.[12,13]

Statistical Evaluation

The continuous data were represented in mean ± SD. The comparison between two mean was analysed by using student's t-test. ANOVA test was applied to analyse the difference between more than two means.[14,15] P value < 0.05 was considered to be statistically significant. EXCEL software was used for statistical analysis.

Results

The healthy volunteers had expectedly much better clinical profile and blood parameters than Group 2 and Group 3 patients. Mean BMI of the control group measured to be 23.16±2.87 Kg/M^2. Mean BMI of the newly diagnosed type 2 diabetes cases 27.15±3.66 Kg/M^2.

Group 2 who are on treatment with metformin have mean BMI 25.98±3.37 Kg/M^2 with mean duration of treatment of 4.11±1.12 years.

Group 3 who are treated with mean duration of 4.17±1.10 years with both metformin and glimepiride found to have mean BMI of 26.38±3.89 Kg/M^2. FPG of the control group was measured to be 84.06±7.02 mg/dl. In the newly diagnosed cases(Group 1) FPG were found to be 216±41.4 mg/dL which was improved both in Group 2 and Group 3 with the mean FPG 125.28±23.4 mg/dl and 138.6±22.84 mg/dl respectively.

Control group has within normal% HbA_1C i.e mean 4.35 ± 0.63. In newly diagnosed cases initial mean% HbA_1C was 9.39 ± 1.24. Expectedly, the mean% HbA_1C of Group 2 (on Metformin only) was reduced to 7.40 ± 1.84 whereas in Group 3 (to receive both Metformin and Glimepiride) it dropped down to mean% HbA_1C of 7.09 ± 1.02.

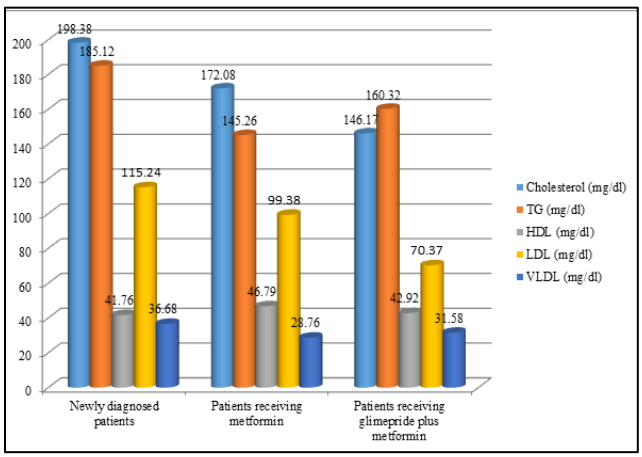

Fig. 1: LIPID profile of newly diagnosed type 2 dm patients before & after treatment with comparison between monotherapy & combined therapy

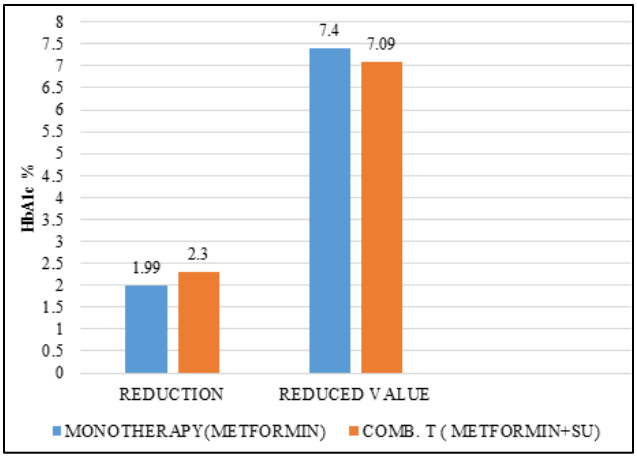

Fig. 2: Comparison of reduction of hba1c values with monotherapy & combination therapy

LIPID Profile

The cholesterol of different groups were measured, that of Control was 156.99 ±34.42 mg/dl. (mean±SD). Before treatment in newly diagnosed cases, the mean cholesterol was 198.38±44.47 mg/dl, after 4 years treatment with dyslipidemic drugs, mean cholesterol in Group 2 was reduced to 172.08±55.68 mg/dl and in Group 3 it was reduced to 146.17±49.88 mg/dl respectively. Greater reduction of plasma cholesterol was noted in Group 3 patients.(Gr 3: 52.21 mg/dl vs Gr 2: 26.3 mg/dl). As earlier mentioned, both the groups were treated with same dyslipidemic drug.

The patients to receive combination therapy had shown better improvement in LDL profile than their peers to receive only metformin. In newly diagnosed patients before the treatment (Group 1) the mean LDL was measured to be 115.24±34.42 mg/dL. In the Group 2 patients with metformin therapy the mean LDL was reduced to 99.38±47.18 mg/dL and for Group 3 patients there was much greater improvement to be 70.37±49.11 mg/dL. The mean LDL of the control was found to be 69.61±18.17 mg/dL.

However, greater reduction of initial plasma values of HDL, VLDL and triglyceride are observed in monotherapy group than combination treatment group which is not commensurated with the findings of LDL or Total cholesterols. In the untreated patients i.e Group 1, at their diagnosis mean triglyceride was 185.12±85.92 mg/dl. In group 2 after 4 years of treatment the TG was reduced to 145.26±62.89 mg/dl and group 3 to have 160.32±51.37 mg/dl respectively. The mean triglycerides of Control group was found to be 120.46±39.86 mg/dl.

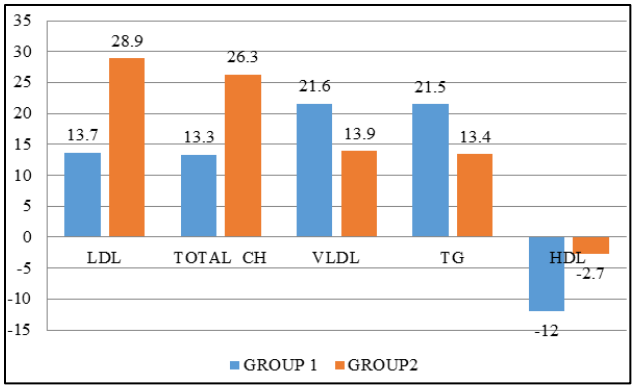

Fig. 3: Comparative changes of lipid profile between mono (group 1) & combination treatment (group 2).

The mean HDL of control group was measured to be 54.14±11.99 mg/dL. In newly diagnosed group i.e. Group 1, the mean HDL was found to be 41.76±6.19 mg/dL. In Group 2 patients treated with Metformin only the mean HDL was measured to be 46.79±7.35 mg/dL. Mean HDL was found to be 42.92±6.57 mg/dL in case of Group 3 patients who were treated with metformin + SU combination.

The mean VLDL was measured to be 23.86±3.47 mg/dL in control groups. The mean VLDL values were measured to be 36.68±7.34 mg/dL for Group 1, 28.76±5.41mg/dL for Group 2 and 31.58±4.63 mg/dL for Group 3 respectively.

Other atherogenic lipid profile like LDL-C/ HDL-C, TC/HDL-C were better controlled with combination therapy. From same baseline value of 2.75, LDL-C/HDL-C was reduced to 2.1 in monotherapy, whereas in combination therapy the ratio was reduced to 1.63. TC/HDL-C was reduced from same baseline value 4.7, to 3.7 in monotherapy and 3.4 in combination therapy respectively. However, AIP (Atherogenic index of Plasma) was reduced more in monotherapy (0.49), than combination therapy (0.57) from the same base line value of 0.64.

Discussion

HbA1c has been taken as the primary endpoint of hypoglycemic efficacy. Reduction of glycated haemoglobin is proportional to the reduction of CVS risk and other macrovascular as well as microvascular complications.[16,17] As described before, 2.3% reduction of HbA1C (statistically significant $p < 0.001$) was observed in Group 3 patients with combination therapy from initial value of 9.39±1.24. In monotherapy i.e Group 2 patients 1.99% reduction was observed from initial value of 9.39±1.24. (also statistically significant $p < 0.001$). However, the difference between two reductions with monotherapy and combination therapy is not statistically significant ($p= 0.85$) i.e it can not be said that superiority of combination therapy to reduce HbA1C is statistically significant than monotherapy.

In our study, statin was used as primary dyslipidemic drug. However, metformin lowers specially LDL-C and total cholesterol apart from synergistic action with statin to improve hyperglycemia and dyslipidemia. Metformin lowers lipid profile by i. increasing insulin sensitivity, therefore reduces lipolysis and lipoprotein precursors to TG/VLDL synthesis in liver, ii. Improving hyperglycemia reduces irreversible glycation of LDL and hastens removal from body iii. inducing weight loss augments dyslipidemia correction.[18]

Along with greater reduction of HbA1c, greater reduction of LDL-C, cholesterol, LDL/HDL etc. were observed in two treatment groups. Since both the groups were having same dyslipidemic drugs, there is obvious positive corelation between glycemic control (HbA1c level) and dyslipidaemia correction.[19,20] Hyperglycaemia induces glycation of lipoproteins, particularly low-density lipoproteins (LDL), preventing the recognition of apoprotein B by the specific receptor leading to reduced clearance from plasma and favouring the accumulation of LDL in macrophages and their oxidation leading to atherosclerosis[21] Therefore, correction of chronic hyperglycemia with reduced biomarker HbA1c, also reduces lipoprotein glycation, leads to efficient removal from plasma and normalisation of LDL level.

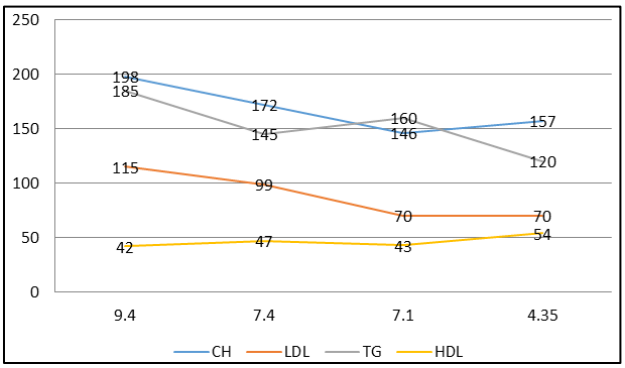

Fig. 4: Relation of reduction in lipid profile with HbA1c%

LDL-C and TC reduction were proportionate to reduction of glycosylated Hb%. [in combination therapy, 24.5% reduction of HbA1c% and in monotherapy 21.2% reduction.] Reduction of LDL value in case of monotherapy was 15.86 mg/dl and in case of combination therapy the reduction is 44.87 mg/dl. The difference in reduction of LDL between two groups of patients by is statistically significant (p value< 0.001).

Table 1: comparative changes (Δ) of different parameters between Monotherapy and Combination therapy group after 3 years of treatment

Parameter	Monotherapy (group 2)	%	Combination Therapy (group 3)	%	P value
ΔHbA1C	-1.99	-21.2	-2.3	-24.5	0.85
ΔLDL	-15.86	-13.7	-44.87	-38.9	<0.001
ΔTG	-39.86	-21.5	-24.8	-13.4	>0.1
ΔCHOLESTEROL	-26.3	-13.3	-52.21	-26.3	<0.01
ΔVLDL	-7.92	-21.6	-5.1	-13.9	<0.01
ΔHDL	+5.03	+ 12	+1.16	+ 2.7	<0.01

In case of Cholesterol, the reduction was 26.3 mg/dl in monotherapy whereas it is 52.21 mg/dl in case of combination therapy. The difference in reduction between two groups is statistically significant (p value < 0.001).

However in case of TG and VLDL, in case of monotherapy greater reduction was observed than the combination therapy. VLDL was reduced by 7.92 mg/dl in case of monotherapy whereas it was reduced by 5.1 mg/dl in combination therapy and the difference in reduction is statistically significant (p value < 0.01). TG was reduced by 39.86 mg/dl in case of monotherapy whereas it was reduced by 24.8 mg/dl in combination therapy and the difference of reduction was not significant (p value > 0.01).

There was greater increase in HDL value observed in case of monotherapy (5.03 mg/dl) than the combination therapy (1.16 mg /dl) and the difference in increase is statistically significant(p value < 0.01).

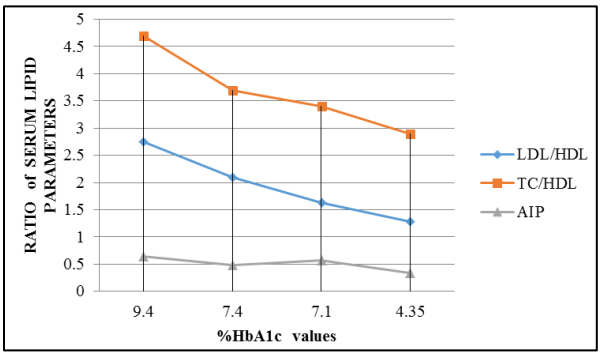

Fig. 5: Relation of LDL/HDL, TC/HDL and AIP with HbA1c

Normal Value: LDL/HDL = 1-1.5 TC/HDL = 2.5 -3.5 TG/HDL=
AIP (Atherogenic Index of Plasma)= LOG (TG/HDL)= 0.2 – 0.5

Mixed response in glycemic and lipid profile due to glimepiride

On Glimepiride addition, mixed favourable outcome in lipid and glycemic profile was observed.

The group 3 patients treated with both metformin and glimepiride had better glycemic (HbA1c) control (though FPG is worse) and TC, LDL-C control. However the TG, VLDL and HDL, AIP (greater AIP in glimepiride+ group) profile was worse than the group 2 patients. One of the possible reason for elevated TG and VLDL in Group 3 patients due to increased TG synthesis in liver due to intake of Sulfonylurea (Glimepiride). Since the patients were newly diagnosed DM 2, they have β cell reserve. On receiving glimepiride, there was increased insulin concentration in plasma.[22] The glucose control was satisfactory but the hypertriglyceridemia was prevailed by increased plasma insulin level in circulation due to induction of the enzyme AcylcoA carboxylase[23] and Fatty acid synthase enzyme complex in hepatocytes and intestine.[24] Besides, depressed lipoprotein lipase in circulation can not remove TG but in adipose tissue un-inhibited hormone sensitive lipase (due to insulin resistance) degrades ester to release more free fatty acids supply to liver for TG synthesis.[25] Again increased free fatty acid worsened the insulin resistance state, consequently increased CETP action transfers TG in exchange of cholesterol to LDL and HDL. These newly formed TG rich LDL and HDL lipoproteins are better substrate to hepatic lipase action to produce small dense atherogenic LDL & HDL particles.[26]

The newly diagnosed DM type 2 patients remain in a state of insulin resistance. Insulin resistance is started either before or along with onset of reduction of beta cell mass during the pathogenesis. However, there is no grown resistance against Insulin action observed to the triglyceride and VLDL synthesis.[25] The relatively increased level of VLDL, TG and AIP are observed along with FPG level than the monotherapy group. The increased insulin resistance observed in Group 3 patients probably due to adverse CVS effect of glimepiride.[27,28] Thus increased CVS risk with more atherogenic lipid profile with sulfonylurea use[29] has been observed in this study.

Conclusion

Those patients who received two drugs had better HbA1c reduction (though statistically not significant) than monotherapy. The two drug regimen was not superior over monotherapy to reduce HbA1c% and both the regimens were highly efficacious to reduce hyperglycemia. LDL-C, TC, LDL/HDL and TC/HDL were better corrected (p<0.01) in combination therapy than metformin only group. These reductions of LDL and total cholesterol were proportional to HbA1c reductions. Those patients to receive SU showed relatively elevated parameters like AIP, FPG, VLDL, TG suggestive of worsened insulin resistance and increased atherogenecity presumably due to adverse CVS effects of sulfonylurea.

Abbreviation used
AIP = Atherogenic index of plasma.
CETP = Cholesterol ester transfer protein.

Conflict of Interest
None.

Source of Funding
None.

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How to cite this article: Bhattacharyya S, Mukherjee B. Comparative study of control of hyperglycemia and dyslipidemia between two treatment- groups of diabetic patient (Metformin Monotherapy and Metformin + Glimepiride Combination). *Int J Comprehensive Adv Pharmacol* 2019;4(3):91-5.