Does add on therapy of Fenofibrate to Statins prevent the glycemic effect of statins and new-onset diabetes?

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INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death worldwide as per the WHO, and it still confers a large economic burden on society. Multiple risk factors have been identified for developing coronary heart disease (CHD). The most understood and discussed risk factors among them are dyslipidemia and diabetes mellitus1. Lipid lowering therapies have been shown to lower the risk of CHD events by 30-40%2. Randomized statin trials have shown that a reduction in LDL-C by 80 mg/dl results in a decrease of coronary artery disease (CAD) by 42% and stroke by 20%. 3

Drugs that are generally used to treat dyslipidemia include fibric acid derivatives, ezetimibe and statins etc. The statins currently forming the mainstay of hypolipidemic drugs have proven mortality and morbidity benefit in both primary and secondary prevention of CHD 4,5 Diabetes is another risk factor commonly recognized as a "coronary heart disease risk equivalent" 6,7. Type 2 diabetes mellitus (T2DM) mostly results from the interaction among genetic, environmental and other risk factors but certain drugs (e.g. glucocorticoids, β-adrenergic agonists and thiazides etc.) may also precipitate diabetes in individuals with insulin resistance.8 On February 28, 2012, the Food and Drug Administration (FDA) added new safety label changes for using the statins because of their potential to increase HbA1c. Recently, an Intervention Trial Evaluating Rosuvastatin (JUPITER) a placebo controlled, primary prevention trial reported a 26% higher incidence of diabetes in the Rosuvastatin Group at1.9 years interim analysis. 9 WHI (Women's Health Initiative) study also suggested an increased risk of New Onset Diabetes Mellitus (NODM) with different statins.10 A meta-analysis of diabetics found that a 1%point increase in HbA1c level confers an 18% risk of CVD .11

It has been recently reported that atorvastatin and rosuvastatin can increase glycemic parameters (FPG, 2 hours PPG, HbA1c) of nondiabetic cohort during 24 weeks of therapy.12 Observational studies and meta-analyses of randomized clinical trials have also revealed a 10–12% increased risk of New Onset Diabetes Mellitus (NODM) associated with statin therapy; the risk has been shown to increase in individuals with features of the metabolic syndrome or prediabetes. Hence statins (atorvastatin and rosuvastatin) although have proven mortality and morbidity benefit in both primary and secondary prevention of CHD but can increase risk of new onset diabetes mellitus by changing glycemic parameters.

Fenofibrate belongs to a class of drugs called fibric acid derivatives, a PPARα (peroxisome proliferator activated receptor-α) agonist used in the treatment of dyslipidemia has shown a favorable influence on glucose homeostasis.13 Studies have supported re-evaluation of fibrates as an add-on strategy to statins in order to reduce cardiovascular risk in diabetic patients with dyslipidemia.14 In recent years, real-world evidence analysis has shown that the statin and fibrate can cause a reduction of approximately 30% in stroke risk compared with the control group.15 The previous findings of studies have suggested a possible beneficial role of fibrates in cardiovascular risk reduction especially in patients with an atherogenic dyslipidemia who are closely associated with metabolic syndrome and insulin resistance.16

However, the use of fibrate-statin combination in nondiabetic patients with dyslipidemia and their effect on glycemic parameters are not well studied so far. Moreover, the most of these studies have been conducted on diabetic subjects or on patients with impaired glucose profile. Therefore, selection of a non-diabetic cohort is crucial for a clear understanding of statins-Fenofibrate's effect on blood glucose levels. Hence, this study was designed to determine the effects fenofibrate along with atorvastatin or rosuvastatin on norm glycemic patients who are newly diagnosed with dyslipidemia.

STUDY POPULATION

Study design: This was a randomized, prospective, open labeled, parallel group, single-center, and 24 weeks clinical study. It was conducted on patients newly diagnosed with dyslipidemia attending medicine clinic of J.N. Medical College & Hospital, A.M.U., Aligarh, a tertiary level hospital in India from May 2017 to September 2018.

Inclusion criteria: non-diabetic dyslipidemic patients of age > 20 years with definite indication for starting hypolipidemic drugs were included in the study.

Exclusion criteria: Patients with significant kidney diseases, abnormal liver function tests (alanine transaminase [ALT] >2× upper limit of normal [ULN], aspartate transaminase >2× ULN or total bilirubin >2× ULN and/or direct bilirubin >ULN) and other significant systematic illnesses were excluded from the study. Patients with an existing diagnosis of diabetes or with previous statin exposure were also excluded from the study. The patients on medications known to affect blood glucose parameters were also excluded from the study.

The primary endpoint was to observe the change in glycemic parameters (fasting blood glucose, 2hour postprandial plasma glucose and HbA1c) from baseline values. The secondary endpoint was to determine the safety and tolerability profiles of these drugs by assessing adverse effects.

Diagnosis of dyslipidemia was made according to National Cholesterol Education Program-Adult Treatment Panel IV guidelines.17 Patients were screened for diabetes mellitus according to American Diabetes Association guidelines (ADA, 2017).18 They were followed up at 12 and 24 weeks to assess the effects of atorvastatin-fenofibrate and rosuvastatin-fenofibrate on FPG, 2 hours PPG and HbA1c. All the necessary investigations were done if and when required.

Written and informed consent was obtained from all patients before enrolling them in the study. Ethical clearance for the study protocol was obtained from the Institutional Ethics Committee (IEC) of J.N. Medical College and Hospital, AMU, Aligarh on 18.05.2017 with registration number 626/FM. The study was also registered with clinical trial registry of India.

Patients were advised to remain on a stable diet as per NCEP ATP-IV guidelines, 2015. All adverse events experienced by the patients were

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recorded at each visit. Adverse drug reactions were assessed using Naranjo Adverse Drug Reaction Probability Scale19 and severity was assessed using Modified Hartwig and Siegel scale.20 The eligible patients were divided into two groups Group-1 (Atorvastatin 10 mg & Fenofibrate 160 mg/day) and Group-2(Rosuvastatin 10 mg & Fenofibrate 160 mg/day).

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS-23 software and charts were prepared using Microsoft Excel 2013. For descriptive statistics; frequency, percentage and graphs were used to present the study results. Repeated Measure Analysis of variance (RM-ANOVA) followed by Bonferroni post-hoc test was used to analyze the change in parameters from baseline values at different time points during follow up. All the values were expressed as mean ±SE. P<0.05 was considered to be statistically significant.

RESULTS

A total of 40 patients were enrolled, out of which 05 patients (2 patients of Group-1 and 3 patients of Group-2) failed to complete the study. Finally, 35 patients were analyzed 18 patients in Group-1 and17 in Group-2. The mean age and Body Mass Index (BMI) of patients in Group-1 and Group-2 were 44.78±13.65 and 53.59 ±10.70 and 27.77 ± 3.07 and 27.71 ± 3.75 kg/m2 respectively. There were 14 males (40%) and 21(60%) females out of 35 patients.

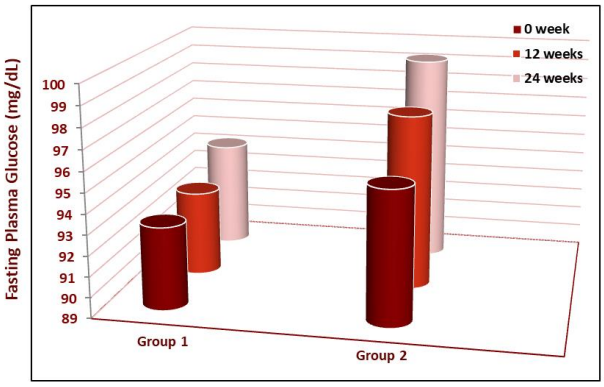

Figure 1: Effect of Atorvastatin-Fenofibrate and Rosuvastatin-Fenofibrate combination on FPG levels

In Group-1(Atorvastatin-Fenofibrate), at a baseline (0 weeks) the mean FPG was 93.06 mg/dl which increased to 93.16 mg/dl at 12 weeks and 94.22 mg/dl at 24 weeks. In Group-2 (Rosuvastatin-Fenofibrate), at 0 weeks, the mean FPG was 95.54 mg/dl which increased to 97.60 mg/dl at 12 weeks and 99.24 mg/dl at 24 weeks. However, the increase in mean values of FPG, when compared to baseline values (0 weeks) was found to be insignificant (p>0.05) at both time points (i.e. 12 and 24 weeks) in both the groups (Intragroup comparison).

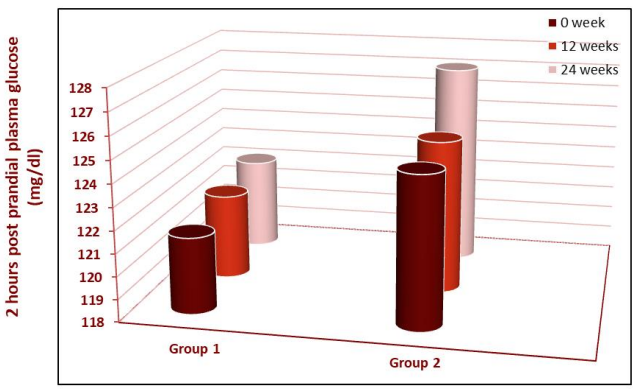

Figure 2: Effect of Atorvastatin-Fenofibrate and Rosuvastatin-Fenofibrate combination on 2hours PPG levels

In Group-1, at 0 week, the mean PPG was 121.40 mg/dL which increased to 121.81 mg/dL at 12 weeks and 122.12 mg/dL at 24 weeks. In Group-2, at 0 week, the mean PPG was 124.72 mg/dL which increased to 124.85 mg/dL at 12 weeks and 127.08 mg/dL at 24 weeks. The increase in mean values of 2 hours PPG, when compared to a baseline values (0 weeks) was found to be insignificant (p>0.05) in both the groups at 12 weeks as well as 24 weeks.

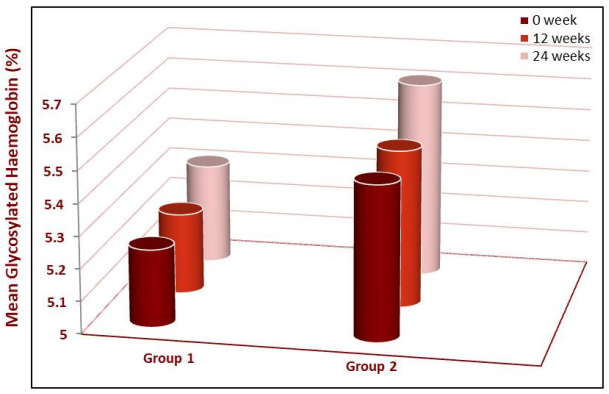

Figure 3: Effect of Atorvastatin-Fenofibrate and Rosuvastatin-Fenofibrate combination on HbA1c levels

The mean HbA1c in Group-1increased from 5.24% at a baseline (0 week) to 5.25% at 12 weeks and 5.31% at 24 weeks, respectively while in Group-2 the increased was from 5.48% at baseline (0 week) to 5.49% at 12 weeks and 5.61% at 24 weeks, respectively (p>0.05). The increase in mean values of HbA1c, when compared to a baseline (0 weeks) was insignificant (p>0.05) in both the Groups at 12 and 24 weeks.

The changes in blood urea and serum creatine were also analyzed. In Group-1 and Group-2 the mean blood urea (mg/dL) was 23.28, 24.23, and 25.08 and 30.42, 31.59, and 32.79 (mg/dL) at a baseline (0 week), 12 and 24 weeks respectively. In Group-1 and Group-2 the mean serum creatinine was 0.84, 0.87, 0.88 and 0.94, 1.02, 1.03 at a baseline (0 week), 12 weeks and 24 weeks respectively.

Table1: Effect of Atorvastatin-Fenofibrate and Rosuvastatin-Fenofibrate combination on Liver Function Test

Biochemical parameters	Group-1 (Mean ± SE)		Group-2 (Mean ± SE)	
	Baseline	24 weeks	Baseline	24 weeks
Total bilirubin (mg/dL)	1.03 ±0.12	1.23 ±0.08	0.97 ±0.11	1.19 ±0.11
Aspartate Transaminase (AST) (IU/L)	29.58 ±1.28	32.96 ±1.17	31.41 ±1.70	35.12 ±1.73
Alanine Transaminase (ALT) (IU/L)	31.21 ±2.08	34.33 ±1.81	38.00 ±3.88	40.77 ±3.98
Alkaline Phosphatase (ALP) (IU/L)	55.79 ±5.45	59.75 ±5.19	46.59 ±4.98	51.06 ±4.95
Intragroup comparison P-value (0-24 weeks)	P<0.05		P<0.05	

Table 2: Effect of Atorvastatin-Fenofibrate and Rosuvastatin-Fenofibrate combination on lipid profile

Biochemical parameters (mg/dL) Mean ± SE	Group-1		Group-2	
	Baseline	24 weeks	Baseline	24 weeks

Total cholesterol (TC)	207.47 ±7.69	169.85 ±5.83	212.60 ±8.76	164.88 ±7.40
Triglycerides (TG)	219.61 ±10.24	158.61 ±5.39	238.52 ±19.80	155.93 ±7.72
High Density Lipoprotein (HDL)	41.92 ±2.16	46.70 ±1.35	40.13 ±2.03	44.36 ±1.83
Low Density Lipoprotein (LDL)	138.63 ±8.95	108.14 ±7.77	140.23 ±10.85	103.36 ±9.53
Very Low-Density Lipoprotein (VLDL)	42.27 ±1.75	32.61 ±1.35	39.14 ±1.92	29.63 ±1.75
Intragroup comparison P value (0-24 weeks)	P<0.05		P<0.05	

SAFETY ASSESSMENT

Adverse events reported by the patients were assessed using Naranjo's ADR Probability Scale and Modified Hartwig and Siegel scale. A total of 6 patients in Atorvastatin-Fenofibrate group and 7 patients in Rosuvastatin-Fenofibrate Group experienced adverse events. The adverse events observed were body pain, nausea, dyspepsia, weakness and GI upset. No adverse event required discontinuation of therapy. The adverse events were mild in severity according to Modified Hartwig and Siegel scale in all the cases. On Naranjo's ADR Probability Scale, events were possible (Score=1-4) in 4 cases of Group-1 and Group-2 each. The events were probable (Score=5-8) in 2 cases of Group-1 and 3 cases in Group-2. The occurrence of adverse events was similar in the Groups.

DISCUSSION

Diabetes mellitus and dyslipidemia are an independent risk factor for atherosclerotic cardiovascular and cerebrovascular diseases.18,21 In the present work, we studied the effects of combination therapy of Atorvastatin-Fenofibrate and Rosuvastatin-Fenofibrate on blood glycemic parameters in non-diabetic patients with dyslipidemia. In both the groups i.e. Atorvastatin 10 mg in combination with Fenofibrate 160 mg (Group-1) and Rosuvastatin 10 mg in combination with Fenofibrate 160 mg (Group-2), the mean FPG showed statistically insignificant ($p>0.05$) increase at both time points, i.e. 12 and 24 weeks. However, in our previously published study when Atorvastatin alone at the doses of 10 mg and 20 mg was used in nondiabetic patients with dyslipidemia the statistically significant increase in FPG were observed.12

Bezafibrate decreases blood glucose level, HbA1C, insulin resistance and reduces the incidence of T2DM compared to placebo.22Atorvastatin-Fenofibrate and Rosuvastatin-Fenofibrate combinations showed statistically nonsignificant ($p>0.05$) increase in 2 hours PPG and HbA1c at both time points, i.e.,12 and 24 weeks. However, Atorvastatin and Rosuvastatin when used without the addition of Fenofibrate statistically significant ($p<0.05$) increase in 2 hours PPG and HbA1c levels at 24 weeks of study were found as compared with their baseline values. Atorvastatin at the dose of 10 mg and 20 mg led to an increase of 0.12% and 0.18% in mean HbA1c levels, respectively. The increase in mean HbA1c by Rosuvastatin 5 mg and 10 mg was 0.20% and 0.23%, respectively.12

These observed findings of the present study may be due to the insulin sensitizing effect of Fenofibrate studied by Yong et al; in the year 1999 on insulin sensitivity in non-diabetic males with low HDL/dyslipidemic syndrome.23 The pleiotropic effects Fenofibrate have also been suggested in the metabolic syndrome and in patients with impaired glucose tolerance13,24 Krysiak in prediabetic patients has found that Fenofibrate can decrease post-challenge and fasting plasma glucose scores, HOMA (homeostasis model assessment) index scores and HbA1c levels.

Fibrates have been reported to reduce the triglyceride content in skeletal muscle, which has been correlated with improved insulin sensitivity. Finally, PPARα activation suppresses monocyte production of inflammatory cytokines, including IL-6 and TNF-α, thereby improving insulin resistance.

This study, although with small sample size may suggest a possible reduction in the risk of diabetogenic effect of statins in combination with Fenofibrate in nondiabetic patients with dyslipidemia and these new observations might change clinical approach to treatment in such patients.

CONCLUSION

Statins one of the most widely prescribed groups of drugs have shown their beneficial role in primary and secondary prevention of cardiovascular disease in a number of trials but current reports of increased risk of type 2 diabetes with statin therapy are of concern. In the current study of 24 weeks the Atorvastatin-Fenofibrate and Rosuvastatin-Fenofibrate combinations have shown statistically insignificant increase in mean FPG, 2 hours PPG and HbA1c levels($p>0.05$). These findings suggest that fibrates have a favorable influence on glucose homeostasis.

This study was limited by a small sample size and single center design. More such prospective studies are needed with a large cohort to elucidate the risk reduction to develop diabetes with Statins-Fenofibrate combinations. These observations might help clinicians to consider the risk associated different statins when they are contemplating the treatment for individuals particularly in prediabetics with dyslipidaemia.

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