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Original Research Article

Effect of atorvastatin and metformin combination therapy in type 2 diabetic dyslipidemias

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ABSTRACT

Background: Dyslipidaemia is a major risk factor for cardiovascular complications in patients with type 2 diabetes mellitus and affects 10-73% of this population. In type 2 diabetes mellitus, increased efflux of free fatty acids from adipose tissue and impaired insulin mediated skeletal muscle uptake of free fatty acids, increases fatty acid flux to the liver and also decreased glucose utilization in muscle that leads to acute elevation of free fatty acids. Lipid profile which is altered in diabetes state is one of the significant factors in development of cardiovascular diseases. The derangements seen in serum lipid profile includes: increased total cholesterol (TC), triglycerides (TG) and low-density lipoprotein (LDL) and decreased high-density lipoprotein cholesterol (HDL) concentration. Hence with the aforementioned views the present study had been planned to evaluate the effect of atorvastatin and metformin combination therapy in type 2 diabetic dyslipidemias.
Methods: Study design, observational prospective study, with duration of 4-5 months and sample size of 30 patients with type 2 diabetes mellitus are taken with mild to moderate dyslipidemias. The study subjects received combination therapy of metformin 500 mg/day along with atorvastatin 20mg/day, there effect is seen on serum lipid profile and fasting blood glucose levels (FBS).
Results: There was a significant mean decrease in TC, LDL , TG , FBS by 31.7 mg/dl ($p<0.05$), 28.5 mg/dl (p value <0.05), 19.5 mg/dl ($p<0.05$), 9.13 mg/dl ($p<0.05$) respectively and rise in HDL by 1.7 mg/dl ($p<0.05$)), no significant decrease in VLDL ($p>0.05$).
Conclusions: Combination of atorvastatin and metformin was effective in reduction of TC, LDL, TG and FBS and elevation of HDL levels in type-2 diabetic dyslipidemias.

Keywords: Dyslipidemias, Type-2 diabetes mellitus, Atorvastatin, Metformin, Lipid profile, Fasting blood glucose

INTRODUCTION

Diabetes mellitus is a mumgltifaceted disease which is characterized by hyperglycemia, lipoprotein abnormalities and altered intermediary metabolism, and generation of free radicals often worsen the complications of diabetes mellitus.[1] The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014.[2] Type 2 diabetes often accompanies along with other metabolic abnormalities such as obesity, hypertension and hypercoagulability, this group of eccentric abnormalities has been referred to as the metabolic syndrome and it has been related with high risk for atherosclerosis.[3]

The major risk factor for cardiovascular complications in patients with type-2 diabetes mellitus (T2 DM) is dyslipidaemia and it affects 10-73% of this population.[4] Diabetic dyslipidemias commonly manifests as raised low-density lipoprotein cholesterol (LDL-C), decreased

high-density lipoprotein cholesterol (HDL-C) levels, elevated triglyceride (TG) levels. In type-2 diabetes mellitus and insulin resistance, increased efflux of free fatty acids from adipose tissue and impaired insulin mediated skeletal muscle uptake of free fatty acids increases fatty acid flux to the liver and also decreased glucose utilization in muscle was analogous with elevation of free fatty acids.[5,6]

The present study had been planned to evaluate the effect of atorvastatin and metformin combination therapy in type-2 diabetic dyslipidemias which is given as first line treatment in the management of dyslipidemias.[7]

METHODS

This was an observational prospective study, study period from November 2018 to March 2019. The present study was started after obtaining approval from the Institutional Ethics Committee, Gandhi Medical College. Patients were explained about study purpose and procedure, after screening 30 patients were enrolled and written informed consent was obtained from every patient.

Inclusion criteria

Inclusion criteria were patients with type-2 diabetes mellitus in the age group of 35-65 years, both sexes, only type-2 diabetes mellitus patients on oral hypoglycemic drugs with FBS >110-<250 mg/dl, and patients with mild to moderate dyslipidemias.

Exclusion criteria

Exclusion criteria were patients with type-1 diabetes mellitus and with type-2 diabetes mellitus on insulin, patients with uncontrolled diabetes (FBS >250 mg/dl) and uncontrolled hypertension (sys >160 and diastolic >100) and gestational diabetes mellitus.

After baseline investigations (lipid profile, FBS), patients were started on atorvastatin 20 mg OD and metformin 500 mg OD by the clinician and the follow up was done after 12 weeks to see their effect on lipid profile and FBS.

Statistical analysis

Data was collected, tabulated and analysed by using SPSS software with appropriate statistical tests. Paired t test was applied to compare values before and after 12 weeks treatment parameters and p (probability) value obtained is used to quantify statistical significance of evidence.

RESULTS

There was a significant mean decrease in TC, LDL, TG, FBS by 31.7 mg/dl ($p<0.05$), 28.5 mg/dl (p value <0.05), 19.5 mg/dl ($p<0.05$), 9.13 mg/dl ($p<0.05$) respectively and rise in HDL by 1.7 mg/dl ($p<0.05$), no significant decrease in VLDL ($p>0.05$). The combination therapy of metformin 20 mg and atorvastatin 500 mg for 12 weeks resulted in fall of TC by 13.8%, decrease in LDL by 19.4% and reduction in TG by 12.3% and decline in fasting blood sugar FBS by 6.4% and rise in HDL by 4%.

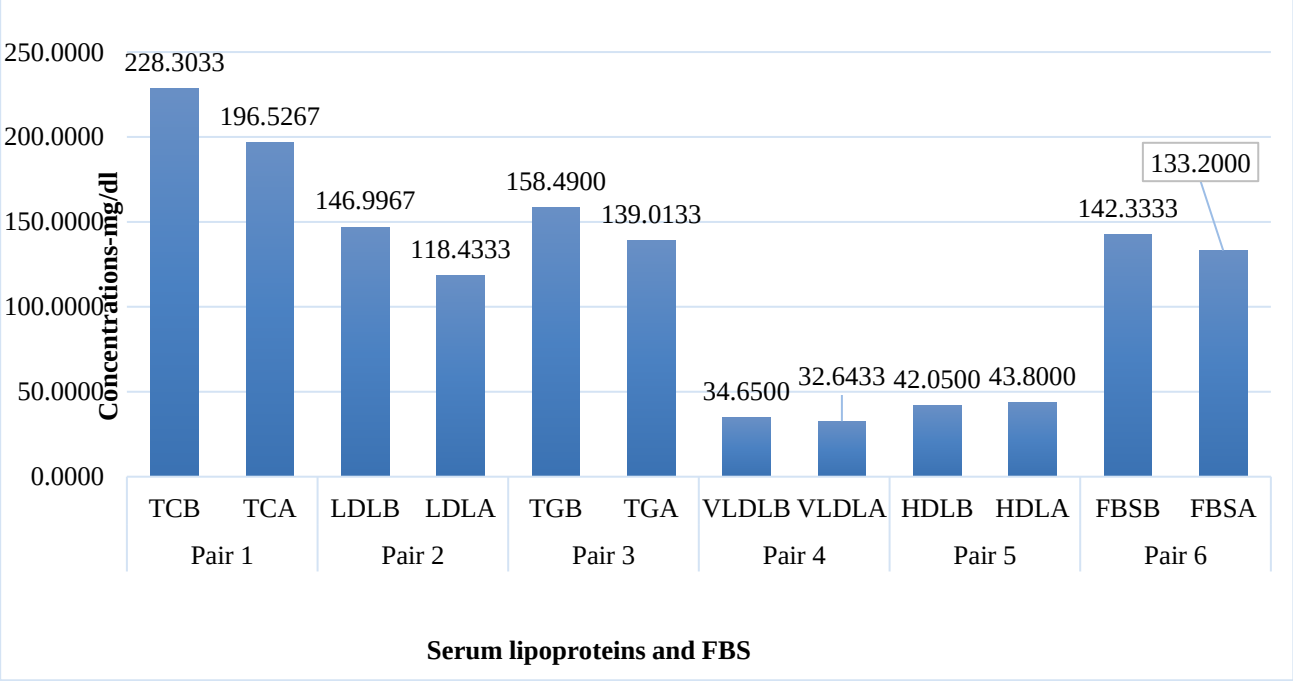

Figure 1: The mean variations of serum lipoproteins and fasting blood sugar at (A) baseline using paired t-test and (B) after 12 weeks of treatment.

Table 1: Paired samples statistics.

Variables		Mean	N	SD	SEM
Pair 1	TCB	228.3033	30	22.48395	4.10499
	TCA	196.5267	30	17.38265	3.17362
Pair 2	LDLB	146.9967	30	27.46366	5.01416
	LDLA	118.4333	30	19.11252	3.48945
Pair 3	TGB	158.4900	30	38.65555	7.05750
	TGA	139.0133	30	33.46350	6.10957
Pair 4	VLDLB	34.6500	30	13.01624	2.37643
	VLDLA	32.6433	30	9.65072	1.76197
Pair 5	HDLB	42.0500	30	9.89273	1.80616
	HDLA	43.8000	30	9.19295	1.67840
Pair 6	FBSB	142.3333	30	36.88177	6.73366
	FBSA	133.2000	30	30.12892	5.50076

DISCUSSION

Diabetes mellitus is associated with a considerably increased risk of premature atherosclerotic cardiovascular disease. Intensive glycemic control has essentially failed to significantly improve cardiovascular outcomes in clinical trials. Dyslipidemia is common in diabetes and there is strong evidence that cholesterol lowering improves cardiovascular outcomes, even in patients with apparently unremarkable lipid profiles.

Statins are the first line therapy to reduce atherosclerotic cardio vascular disease by decreasing LDL-C by 30-49% or at least 50% depending on risk level in diabetic dylipidemias.[8] Metformin is the first line drug in type-2 diabetes mellitus. The combination of metformin and atorvastatin is synergistic as metformin enhances the anti-adipogenic effects of atorvastatin. Metformin increase atorvastatin mediated inhibition of STAT3 signaling and metformin enhances atorvastatin mediated TGF-β/Smad3 signaling.[9] In present study we found the combination of atorvastatin and metformin was effective in reduction of TC, LDL, TG and FBS and elevation of HDL levels in type-2 diabetic dyslipidemias.

In a study conducted by Balsubramanian et al to assess efficacy, safety and tolerability of a fixed dose combination of atorvastatin 10 mg and metformin SR 500 mg in adult Indian patients with diabetic dyslipidaemia.[10] Therapy with the fixed dose combination of atorvastatin 10 mg and metformin SR 500 mg resulted in a significant reduction in the mean plasma fasting and postprandial glucose levels (35 and 38.8% respectively) and there was a steep fall in the HbA1c levels from baseline levels of 8.76% to 6.74% (23.1%). In present study the combination therapy of metformin 20 mg and atorvastatin 500 mg for 12 weeks resulted in fall of fasting blood sugar (FBS) by 6.4% and HbA1c could not be done due to financial constraints.

In a study conducted by Balsubramanian et al there was also a significant ($p<0.05$) reduction in mean total cholesterol 31.2%, LDL cholesterol 35.4%, VLDL cholesterol 19.6% and a significant increase HDL cholesterol 9.5%.[10] In present study there was also a significant reduction in mean total cholesterol 13.8%, LDL cholesterol 19.4%, TG 12.3% and a rise in HDL cholesterol 4%. In both the aforementioned studies there was a significant decline in following parameters FBS, TC, LDL, TG, and a moderate rise in HDL with the combination therapy of metformin and atorvastatin.

CONCLUSION

It can be concluded that combination therapy is more efficacious than monotherapy. The enhanced effect of combination could be due to beneficial pleotropic effects of atorvastatin improving endothelial function, decreasing oxidative stress and inflammation, and inhibiting the thrombogenic response. However, more studies are required to confirm our findings and provide conclusive results regarding the potential benefit from combined treatment of atorvastatin and metformin in patients with type-2 diabetes mellitus.

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