Original Research Article

A Comparative study on the effect of Atorvastatin-Vitamin D versus Atorvastatin on serum LDL levels

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Abstract

Background: Background: Hyperlipidemia is a well documented risk factor for atherosclerosis, responsible for significant amount of ischemic strokes and cardiovascular disease globally. Studies have shown that vitamin D supplementation with atorvastatin has synergistic effects in lowering serum cholesterol concentrations and ameliorating statin-induced myalgia and myopathy. **Objective:** To estimate the effect of fixed dose combination of 1000 I.U of Vitamin D3 and Atorvastatin 10 mg per day for 3 months on serum LDL levels in hyperlipidemic patients compared to those on Atorvastatin 10 mg per day alone. **Methodology:** A Prospective multiple arm analytical observational study was conducted with ethics committee approval. medical details and reports of serum lipid profile investigation, routinely checked at 6 weeks intervals in patients of cardiology department, were collected from 97 recruited patients for 3 months after obtaining written informed consent. We have recorded the plasma glucose levels and HbA1c levels in hyperlipidemic patients who have diabetes also twice at 12 weeks interval**.** Patients were asked to report adverse drug reactions, if any, by regular telephonic enquiry and at each clinical visit **Results:** There was a significant reduction in LDL cholesterol levels in both study groups at 12 weeks compared to baseline. No significant difference was observed between the two groups. The plasma glucose levels of diabetic dyslipidemic patients in both the groups were well controlled and the HbA1c values were not different between the two treatment groups. Both the treatments were well tolerated throughout the study period. 3 patients taking Atorvstatin alone complained of myalgia at the end of 12 weeks, which was not accompanied by elevated creatine kinase levels. **Conclusion:** Fixed dose combination of vitamin D with atorvastatin did not improve serum lipid levels in hyperlipidemic patients compared to atorvastatin alone. In this study both the treatment groups provide significant improvement in lipid profile. Large studies are required in future for evaluating the effect of Vitamin D on lipid profile**.**

Key Word: serum lipid levels, hyperlipidemic.

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INTRODUCTION

Hyperlipidemia is the presence of elevated levels of lipids or lipoproteins in the blood. It is an important modifiable risk factor for atherosclerosis leading to 17.3 million deaths per year, likely to be more than 23.6 million by 2030.[1] Globally, about 56% of ischemic heart disease and 18% of strokes are due to raised cholesterol levels. [2] The Indian subcontinent is home to 20% of the world's population. Cardiovascular diseases (CVD) have become the leading cause of death in India like the developed countries. However, coronary artery disease (CAD) is affecting Indians at least 5-6 years earlier than people of

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western countries. A recent survey by Indian Council for Medical Research (ICMR) showed that 79% of population they studied had at least one lipid abnormality with regional variations. [3] Reduction of serum cholesterol levels is one of the most important strategies in the prevention and treatment of CAD. This may be achieved by dietary and lifestyle modifications such as restriction of dietary fat intake and regular bodily exercise. However, most patients of hyperlipidemia frequently require lipid-lowering medications to achieve target serum lipid levels. HMG-CoA reductase inhibitors (statins), the most commonly prescribed lipid-lowering medications are also the most frequently prescribed drugs worldwide. Among the various statins, atorvastatin is the single most commonly prescribed statin. Several clinical trials in the primary and secondary prevention of CVDs have demonstrated the beneficial effects of atorvastatin in reducing the risk of death and major cardiovascular events compared to other statins. [4] Treatment of hyperlipidemia with statins may cause dose-related adverse -effects such as elevation of hepatic transaminase levels, myalgia, myositis and uncommonly rhabdomyolysis. Myalgia has also been shown to be associated with vitamin D deficiency and to resolve with its correction . [5] Based on these studies, pharmaceutical companies have introduced fixed dose combinations of atorvastatin and vitamin D in India, which are being prescribed widely by clinicians. Recently, vitamin D has been increasingly shown to influence the risk of several disorders including cardiovascular diseases. [6] Specifically, vitamin D may have a beneficial influence on dyslipidemia and vascular calcification, two important predictors of cardiovascular disease. [7] In spite of being a sunny tropical country, the Indian population has been found to have high prevalence of (70%) of Vitamin D deficiency. [8] Studies exploring the effect of concomitant vitamin D administration on the hypolipidemic effectiveness of statins are scarce in the literature and specifically absent in the Indian population. Therefore, we conducted this observational study to explore the effectiveness of fixed dose combinations of atorvastatin and vitamin D in improving serum lipid levels compared to treatment with atorvastatin alone.

MATERIAL AND METHODS

We conducted a prospective analytical observational study at the departments of Cardiology and Pharmacology of Sree Gokulam Medical College and Research Foundation (SGMCandRF), Venjaramoodu, Trivandrum during January 2014 to July 2015. The study population was recruited consecutively from hyperlipidemic patients attending the outpatient department of department of Cardiology.

Inclusion Criteria:

1. Patients aged between 18-80 Years
2. Patients of both the genders
3. Hyperlipidaemic patients who were prescribed either Atorvastatin 10 mg/day or a fixed dose combination of Atorvastatin 10 mg + Vitamin D3 1000 IU per day by the treating cardiologist.

Exclusion Criteria:

1. Hyperlipidemic patients on any dose of Atorvastatin other than 10mg/day or any other cholesterol lowering drug.
2. Patients who required or were already on vitamin D with or without calcium for prevention or treatment of bone diseases.

The study was approved by institutional ethics committee of SGMCandRF vide approval no. IEC NO:09/84/11/2013/ dated.The patients were recruited after obtaining written informed consent. Demographic details, medical history and treatment particulars were collected from the recruited participants using a case record form. The reports of serum lipid profile investigation, routinely ordered by the treating cardiologist at 6 weeks intervals in these patients, were collected from the recruited patients. Serum lipid levels were estimated using SIEMENS RxL Integrated Autoanalyzer System in Biochemistry laboratory of SGMCand RF. LDL Cholesterol was estimated using SIEMENS ALDL Flex reagent Catridge with an intra-assay variance of 1.6%.HbA1c were estimated using BIO-RAD – D10 analyser in Biochemistry laboratory. Patients were asked to report adverse drug reactions, if any, by regular telephonic enquiry and at each clinical visit. Glycated haemoglobin (HbA_1c) and Blood Glucose levels (FBS & 2hr PPBS) were monitored twice at 12 weeks interval in diabetic hyperlipidemic patients The outcome measures were 1.Change in serum LDL cholesterol levels at the end of 6 weeks and 12 weeks in hyperlipidemic patients 2.Change in blood glucose levels and HbA_{1C} levels at the end of 12 weeks in hyperlipidemic diabetic patients and 3.comparison of adverse drug reactions in hyperlipidemic patients on combination of 1000 I.U of vitamin D_3 and atorvastatin 10 mg per day compared to those on atorvastatin 10 mg per day alone. The data was entered into Microsoft® Excel worksheet and statistical analysis done using freely available online statistical software. Quantitative variables were reported as mean ±SD (for normal distribution) or median with interquartile range (Q1, Q3) (for non-normal distribution) and categorical variables as counts (n) and frequencies (%). Comparison of results between the treatment groups was done using independent samples t –test for normally distributed data or Wilcoxon Rank-sum test for non-normal data. Categorical variables were compared using Chi-square test or Fischer's exact test. Comparison of

quantitative variable within the same group was done using repeated measures ANOVA. A p-value less than 0.05 was considered statistically significant.

RESULTS

The study consecutively monitored 97 hyperlipidemic patients in whom the study drugs were prescribed by the treating cardiologist from January 2014 to July 2015. In our study, the mean age and BMI of patients were 53 ± 6 yrs and 25.7 ± 1 kg/m^2, respectively. Of the 97 hyperlipidemic patients, 13 (13%) were diabetic, 23 (23%) had coronary artery disease and 13 (13%) were hypertensive. Among these hyperlipidemic patients, 48 were prescribed Atorvastatin alone and 49 were prescribed Atorvastatin - Vitamin D fixed dose combination (FDC) by the treating cardiologist . The baseline characteristics of patients in the two treatment groups were similar as shown in Table 1. Significant reductions in serum LDL cholesterol were observed in both the treatment groups at 6 and 12 weeks of treatment compared to respective baseline values (Table 2). However, these outcome measures were not different between the two treatment groups at 6 or 12 weeks of treatment. On post-hoc sub-group analyses ,the values indicated that there was no difference in percentage reduction in LDL cholesterol between the two treatment groups at 6 or 12 weeks. (Table 3)

Table 1: Baseline characteristics and baseline lipid profile values of the two treatment groups

Sr no	Parameters	Atorvastatin (n=48) [mean ± SD or median (Q1,Q3) or n(%)]	Atorvastatin–Vitamin D fixed dose combination (n=49) [mean ± SD or median (Q1,Q3) or n(%)]
1		Gender	
	Male	25 (52%)	27 (55%)
	Female	23 (47%)	22 (44%)
2	Age (year)	54 ± 7	51 ± 5
3	**BMI (kg/m^2)**	25 ± 1	25 ± 1
4	**Co morbidities [n (%)]**		
	Patients with Diabetes mellitus **[n (%)]**	8 (16%)	5 (10%)
5	Patients with Coronary artery disease **[n (%)]**	13 (27 %)	10 (20%)
6	**Patient with Hypertension [n (%)]**	7 (14 %)	6 (12 %)

Table 2: Outcome measures at baseline and after 6 and 12weeks of treatment in the two treatment groups

Outcome measure	Time-point	Atorvastatin (n = 48) [mean ± SD or median (Q1,Q3)]	Atorvastatin-Vitamin D FDC (n=49) [mean ± SD or median (Q1,Q3)]
LDL cholesterol (mg/dL)	Baseline	160 ± 27	170 ± 26
	6 weeks	122 ± 21#	126 ± 21#
	12 weeks	106 ± 22#	111 ± 19#

#: p-value<0.05 with respect to baseline value of same group

Table 3: Percentage reduction in LDL cholesterol at different time-points in the two treatment groups

Outcome measure	Time-point compared	Percentage reduction in Atorvastatin group [mean± SD] (n=48)	Percentage reduction in Atorvastatin – Vitamin D FDC group [mean ± SD] (n=49)
LDL Cholesterol	Baseline - 6 weeks	23±11	25 ±9
	6 weeks – 12 weeks	12 ± 7	11± 9
	Baseline – 12 weeks	32±12	34± 11

DISCUSSION

Our study showed that combining vitamin D with atorvastatin did not improve serum lipid levels in hyperlipidemic patients compared to atorvastatin alone. However, among the patients who did show improvement in lipid profile, vitamin D combined with atorvastatin showed higher percentage rise in HDL cholesterol level compared to those patients taking atorvastatin alone. The mean age and BMI of the patients in our study were comparable to that reported in previous studies. 9-11 Among 97 hyperlipidemic patients, 13 % had diabetes mellitus, 13% had hypertension and 23% had coronary

artery disease. In a study done in North India among dyslipidemic patients, 22% had hypertension,16% had diabetes which was higher than our study. 12. In our study, the baseline mean LDL Cholesterol was 165 ± 27 mg/dL ,which was higher compared to a previous study done in North India 9 and this value was lower compared to that reported from Tamilnadu.22. In the present study, both treatment groups showed significant reduction in LDL-C, at the end of 12 weeks of the study. In our study, the mean percentage reduction of TC and LDL Cholesterol over 6 weeks of therapy were higher compared to a previous study done in Lucknow (-11% and -14%).[23] The mean percentage reduction in LDL cholesterol in the present study was higher (30%) compared to a previous Indian study, by Jyothi et al 9 and lower than 49% reported by Canna et al24. A recent study done in North India also showed the significant reduction of all the lipid values from baseline with Atorvastatin 10 mg over 12 weeks. The mean percentage reduction in LDL was 31% which was almost similar to our stud25. It has been documented that Atorvastatin 10 mg reduces LDL cholesterol by 31-35% regardless of the baseline cholesterol levels.[25] In the present study, the mean percentage reduction of LDL Cholesterol values from baseline (Table no 3) were maximum at 12 weeks of therapy. This may be because of the confounding factors on lipid profile like dietary habits, sedentary lifestyle, primary dyslipidemia, smoking, drugs which alter lipid profile (eg:beta blockers), compliance to medication etc were not considered for the study. There was no significant difference in reduction of LDL were observed between two study groups. The results of our study showed that patients of hyperlipidemia on both the treatments achieved similar reductions in LDL Cholesterol levels at 6 weeks and 12 weeks of treatment. There was no differences between the two treatments with respect to hypolipidemic effectiveness or safety over the period of 12 weeks. Various clinical studies had revealed the unfavourable effects of statin on glucose metabolism and pointed out the risk of new-onset diabetes in statin users.[26] However, this remains controversial. A metanalysis showed that the effects of statins on glycated haemoglobin (HbA1c) had little clinical significance in view of its benefits in diabetic patients.[27] However, in the current study, the plasma glucose levels of diabetic dyslipidemic patients in both the groups were well controlled and the HbA1c values were not different between the two treatment groups. Both the treatments were well tolerated by the patients. 3 patients from Atorvastatin treated group complained of myalgia at 12 weeks which was not accompanied by elevated creatine kinase levels This result was comparable to a previous Indian study after 12 weeks of treatment with Atorvastatin 10mg[25]. These patient did not need any reduction in dose or change in medication for the same. Therefore, the Atorvastatin-vitamin D FDC appears to be associated with lower risk of myalgia than atorvastatin alone. However, larger and longer studies as well as pharmacovigilance are required to further explore this aspect.

CONCLUSION

Fixed dose combination of vitamin D with atorvastatin did not improve serum lipid levels in hyperlipidemic patients compared to atorvastatin alone. Both the treatments were well tolerated by the patients.The plasma glucose levels and HbA1c of diabetic dyslipidemic patients in both the treatment groups were well controlled. Larger interventional studies are required in future for further exploring the impact of Vitamin D on lipid profile.

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