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Original Research Article

## Prospective, randomized, open label comparative study of efficacy of atorvastatin versus atorvastatin with vitamin D3 in patients with dyslipidemia attending tertiary care hospital

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### ABSTRACT

**Background:** Cardiovascular diseases are one of the most important group of diseases causing premature mortality and morbidity. Dyslipidemia is an independent risk factor for cardiovascular diseases and is a disorder of lipoprotein metabolism. Various research studies support role of vitamin D against dyslipidemia. Vitamin D concentration positively correlates with HDL cholesterol and negatively with serum LDL and triglyceride levels. Vitamin D supplementation to Atorvastatin appeared to have increased cholesterol lowering activity more than either substance did alone.

**Methods:** The study was conducted in an outpatient department of general medicine for a duration of 12 weeks in a tertiary care hospital. Total of 100 patients with dyslipidemia were selected based on measurement of lipid profile. Out of 100 patients, 50 patients under group A were treated with atorvastatin 10mg and balance 50 patients under group B treated with atorvastatin and Vitamin D3 1000 IU/day orally. Patients were followed up monthly for 3 months and lipid profile was assessed at baseline and at the end of study. The baseline characteristics were similar in both study groups.

**Results:** On comparing groups at the end of 12 weeks mean LDL, triglycerides and VLDL were significantly reduced in group B than group A with  $p < 0.001$ . The mean HDL level too increased in group B than group A with  $p < 0.001$ .

**Conclusions:** Fasting plasma lipid profile improvement was higher in the atorvastatin with vitamin D3 group compared to atorvastatin group.

**Keywords:** Atorvastatin, Vitamin D3, Dyslipidemia, Lipid profile

### INTRODUCTION

Dyslipidemia, defined as an elevated total or low-density lipoprotein (LDL) cholesterol level, or low levels of high-density lipoprotein (HDL) cholesterol, is an important risk factor for coronary heart disease (CHD) and stroke.<sup>1</sup> Cardiovascular diseases are one of the most common group of diseases causing increased mortality and morbidity in both developing and developed countries. Cardiovascular diseases (CVDs) are the leading cause of death globally. An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. Of these

deaths, 85% were due to heart attack and stroke. Out of the 17 million premature deaths (under the age of 70) due to non-communicable disease in 2019, 38% were caused by CVDs.<sup>2</sup> It is important to detect cardiovascular diseases as early as possible so that management with counseling and pharmacotherapy can begin. The causes for dyslipidemia may be primary or secondary. Primary cause is mainly genetic and it is inherited. Secondary causes are the most important and it accounts for approximately 30-40% of all dyslipidemia. Hypothyroidism, nephrotic syndrome, chronic kidney diseases, primary biliary cholangitis, obstructive jaundice, diabetes and obesity are secondary

causes for dyslipidemia. Drugs which cause dyslipidemia will also come under secondary cause, that can be divided into the drugs that increases LDL-C levels and triglyceride levels.<sup>3</sup> Some of the drugs are hormones (anabolic steroids, glucocorticoids, oral contraceptives, tamoxifen), amiodarone, thiazide diuretics, retinoids etc. A large proportion of individuals in the society have dyslipidemia, often associated with modifiable risk factors. The primary and the most important way to prevent atherosclerotic vascular diseases is to promote a healthy life style modifications throughout their life. All adults should consume a healthy diet such as vegetables, fruits, nuts, and whole grains and mainly to avoid and quit tobacco usage. They should also be advised to minimize the intake of trans-fatty acid foods and caloric restrictions are recommended. They should engage in at least 150 minutes per week of accumulated moderate intensity physical activity.<sup>4</sup> The prevalence of dyslipidemia in India is increasing, that calls for urgent life style modification strategies. This is aimed to prevent and manage this important cardiovascular risk factor.

Indian subcontinent is home to 20% of the world's population. CVDs have become the leading cause of death in India like developed countries. The national cholesterol education program adult treatment panel III (NCEP ATP III) and American heart association (AHA) guidelines recommend the use of statins for primary prevention of CAD based on individual risk factor profile and LDL-C.<sup>5</sup>

#### ATP III classification of IDL, total and HDL cholesterol (mg/dl)<sup>(a)</sup>

**LDL cholesterol:** Primary target of therapy, <100-optimal, 100-129-Near optimal/above optimal, 130-159-Borderline high, 160-189-High, >190-very high

**Total cholesterol:** <200-Desirable, 200-239-Borderline high, >240-High

**HDL cholesterol:** <40-Low, >60-High

<sup>(a)</sup>2020 National cholesterol education program (NCEP) guidelines.

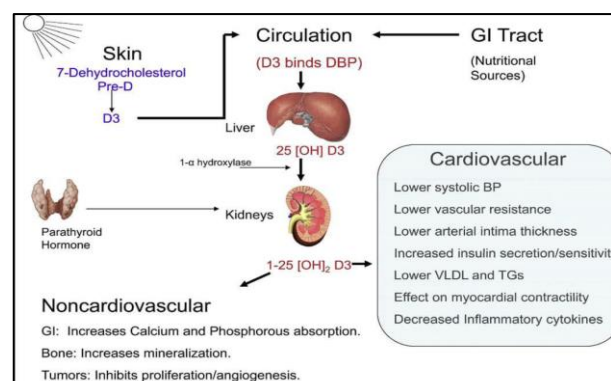
Dyslipidemia was diagnosed using NCEP guidelines. The most common abnormalities, hypercholesterolemia-13.95, hypertriglyceridemia-29.5%, low HDL-C-72.3%, high LDL-C-11.8% and 79% had abnormalities in one of the lipid parameters.<sup>6</sup>

Recent studies have reported that high cholesterol is present in 25-30% of urban and 15-20% rural subjects.<sup>7</sup> The risk factor for dyslipidemia includes diabetes, hypertension, chronic kidney disease, physical inactivity.

Vitamin D deficiency affects more than one billion population worldwide. This pandemic of vitamin D deficiency can mainly be attributed to lifestyle changes (for example reduced physical activity, fast food) and

environmental factors. Low serum vitamin D level is linked to the cause of obesity, hyperlipidemia, hypertension and insulin resistance.<sup>8</sup> Inadequate exposure to sunlight may also lead to vitamin D deficiency. Ultraviolet-B (UVB) rays in the sunlight induce vitamin D synthesis in the skin.

The increasing prevalence of vitamin D deficiency is an important health problem in the community. Vitamin D deficiency and insufficiency is a global issue that afflicts more than one billion children and adults worldwide.<sup>9</sup> Vitamin D deficiency is an independent risk factor for mortality in general population.<sup>10</sup> Many studies suggested the role of vitamin D in many of the diseases like type 2 diabetes mellitus, hypertension, cardiovascular diseases, dyslipidemia, and auto immune diseases. When there is a low Vitamin D level it will increase the severity of fibromyalgia because low vitamin D levels itself will cause muscle weakness.<sup>11</sup> Normal suggested and supplementation of vitamin D 1000 IU/day. Adequate vitamin D levels are required for good vascular health. In addition to its beneficial effect on bones by increasing intestinal calcium absorption it also has beneficial vascular effect.<sup>12,13</sup> Vitamin D deficiency may increase the risk of cardiovascular diseases through three mechanisms. 1) Mainly vitamin D deficiency will cause imbalance between anti-inflammatory and pro inflammatory cytokines, which was studied in in-vitro studies. 2) Endothelial cells have receptors for vitamin D whose stimulation will inhibit cell proliferation.<sup>14</sup> 3) Association between hypertension and vitamin D deficiency is mainly by the activation of renin-angiotensin-aldosterone system.<sup>15</sup> Vitamin D have an influence on dyslipidemia and vascular calcification, two important predictors of cardiovascular disease.<sup>16</sup>



**Figure 1: Metabolic and biological actions of vit D.**

The main management of dyslipidemia is to lower LDL-C levels and to increase HDL-C levels. The management can be either pharmacological or non-pharmacological ways. Before starting the treatment, we have to rule out the secondary cause and treat accordingly. The non-pharmacological methods mainly include, life style modification, exercise and weight reduction and to stop alcohol intake, increase intake of foods rich in fiber content, and antioxidants.

Pharmacological management like drug therapy comes into account when dietary modifications fail to lower LDL cholesterol levels, so NCEP recommends the use of cholesterol lowering agents if lipid levels remain elevated after six months of dietary therapy. Drugs such as bile acid-binding resins (Cholestyramine, cholestipol) and HMG-CoA reductase inhibitors (statins), fibric acid analogues (clofibrate, gemfibrozil) can be used.

Statins are the most commonly prescribed drug in the world and it is used for conditions like cardiovascular diseases, diabetes, peripheral vascular diseases, cerebrovascular diseases for longer duration. Among the statins the most commonly used statin is atorvastatin and it is most effective in treating dyslipidemia. The main mechanism of action of statins is by inhibiting the HMG-CoA enzyme. This enzyme is involved in biosynthesis of cholesterol in our body and it is a rate limiting enzyme. Once the enzyme is inhibited, the conversion from HMG-CoA to mevalonate is prevented, which is precursor for cholesterol synthesis and thereby reducing the cholesterol production in our body.

Recent studies also suggest the use of statins may lower the risk of stroke, dementia, and Alzheimer's diseases, may improve bone density in postmenopausal women and even prevent prostate cancer. These broad actions may lead to their pleiotropic effects which are unrelated to lipid lowering actions. Some of these actions includes: improved endothelial function, reduced vascular inflammation, antithrombotic action, enhanced fibrinolysis, immune suppression, reduced platelet aggregation, stabilization of atherosclerotic plaque. Drugs like itraconazole, cyclosporine and erythromycin which inhibit CYP3A4 can vastly increase the plasma levels of many toxins and thus increase the risk of their toxicity. Grape fruit juice inhibits intestinal degradation of statins and can result in 8-10-fold increase in the levels of statins. The most common adverse effect is muscle pain and liver toxicity. Therefore, statins are contraindicated in patients with Liver diseases and during Pregnancy and Lactation, because cholesterol is essential for fetal development.

Small amount of cholesterol is normally present in all the cells and it is an important constituent of plasma cell membrane. Cholesterol is also the precursor for many steroid hormones, androgens, mineralocorticoids, glucocorticoids. Statins helps in lowering the blood cholesterol levels, but by inhibiting cholesterol synthesis it may affect the normal plasma membrane function of many cells and it may produce muscle pain, joint pain, and some CNS related problems. Co-enzyme Q is an important component of electron transport chain in mitochondria, which in turn will produce energy in form of ATP. Statins by inhibiting this important enzyme may produce myalgia, chronic fatigue syndrome, hypertension, cardiomyopathy.

Gupta et al did study on cultured cells with vitamin D3. At concentrations greater than 2 micrograms/ml, the hydroxylated forms of vitamin D3 caused an accumulation

of methyl sterols indicating an inhibition of lanosterol demethylation. Vitamin D3, however, had little effect on lanosterol demethylation. A second site of inhibition occurs at 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate limiting enzyme in cholesterol biosynthesis at concentrations less than 2 micrograms/ml. All vitamin D3 compounds, except 1,25-dihydroxy vitamin D3, inhibited HMG-CoA reductase activity in a concentration dependent manner.<sup>17</sup>

Statin is mainly used in cardiovascular diseases, however statin induced myopathy is a major reason for statin discontinuation and non-adherence by the patients. Vitamin D deficiency which will cause muscle weakness may be a confounder for statin induced myopathies. Supplementation of vit D may improve statin tolerance.<sup>18</sup>

In spite of being a sunny tropical country, the Indian population has been found to have high prevalence of (70%) of vitamin D deficiency.<sup>19</sup> Studies exploring the effect of concomitant vitamin D administration on the hypolipidemic effectiveness of statins are scarce in literature and specifically absent in Indian population. Therefore, this study was conducted to explore the effectiveness of combining atorvastatin and vitamin D in reducing serum cholesterol levels compared to treatment with atorvastatin alone.

### ***Aims and objectives***

The aim and objectives of the study were to compare the efficacy of atorvastatin and vitamin D3 combination with atorvastatin on lipid profile in dyslipidemia patients.

## **METHODS**

### ***Study center***

This study was carried out in patients attending general medicine OPD of tertiary hospital Visakhapatnam

### ***Collaborating departments***

Collaborating departments were department of pharmacology, department of medicine, and department of biochemistry.

### ***Study population***

Patients attending general medicine OPD and who were diagnosed to have dyslipidemia.

### ***Sample size***

A total 100 patients were participated in the study.

### ***Study design***

It is a single centered prospective, randomized, open label comparative study in patients with dyslipidemia.

**Study duration**

The study was conducted from December 2020 to February 2021 (3 months).

**Efficacy parameters**

Efficacy parameters used were-total cholesterol, LDL, TG, VLDL, and HDL cholesterol levels evaluated at baseline and at 3<sup>rd</sup> month

**Inclusion criteria**

All the patients with age group from 30 to 60 years of both male and female, patients with total cholesterol levels 200-239 mg/dl, patients with hypertension and patients willing to give written and informed consent included in study.

**Exclusion criteria**

Patients with total cholesterol level >240 mg/dl, pregnant and lactating women, patient with hypothyroidism, patient with diabetes and clinically significant gastrointestinal, renal, respiratory and cardiovascular dysfunctions, patient already on atorvastatin, patients with history of allergy/hypersensitivity to drugs and patients with history of alcohol and drug abuse were excluded from the study.

The 100 patients who were diagnosed with dyslipidemia have been included in the study. The patients were diagnosed to have dyslipidemia only after checking the laboratory values. Out of 100 patients studied, 50 were treated with atorvastatin 10 mg/day orally considered as group-A and the remaining 50 patients were treated with atorvastatin 10 mg and vitamin D3 1000IU/day orally considered as group-B. In atorvastatin group 25 were normotensive with dyslipidemia and 25 were hypertensive with dyslipidemia, similarly in atorvastatin with vitamin D3 group 25 were normotensive and 25 were hypertensive. Patients were included in the study only after fulfilling the inclusion and exclusion criteria. Patients were well informed about the study what we are going to do, drugs given to them and purpose of the study and explained in local languages. Patients were informed both verbally and in writing by the investigator about the nature, significance, and the risk of study before enrollment. Informed consent was obtained from all the patients personally. The contact details of the investigator were given to patients involved in the study to report in case of adverse effects.

Both the groups A and B were given their respective tablets. Follow up of the patients were done monthly by monitoring the health status and the compliance was also checked by counting the empty drug strips. Adverse drug reactions were also assessed during their visits. The treatment efficacy was monitored by doing lipid profile at baseline and at the end of 3<sup>rd</sup> month of the therapy. Other biochemical parameters like complete hemogram, liver function test, renal function test, thyroid function tests,

urine tests were done at the time of inclusion to rule out associated co morbidities. The results at the end of the study were tabulated and analyzed statistically.

**Statistical analysis**

Data were entered in Microsoft excel sheet and analyzed by unpaired t test and independent t test.

**RESULTS**

The 100 patients were recruited for the study. No dropouts. All 100 participants who were recruited for the study continued to attend till final follow up.

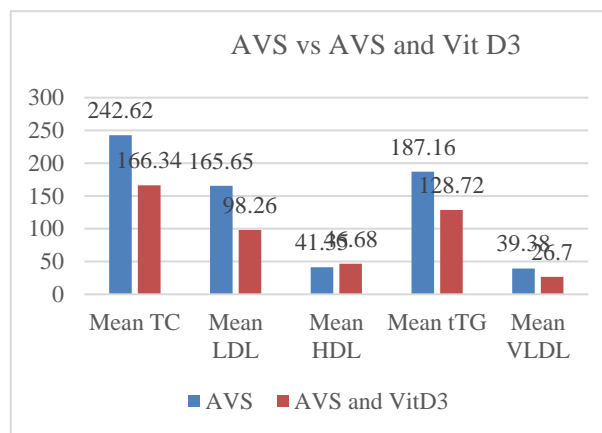
Age range was from 30 to 60 years. Gender wise number of men-55 and women-45.

**Table 1: Effect of atorvastatin on lipid profile in group A, (n=50).**

Lipid profile	Before AVS		After AVS	
	Mean	SD	Mean	SD
<b>Total cholesterol</b>	242.61	21.285	196.68	21.120
<b>LDL</b>	162.32	18.216	125.67	15.320
<b>HDL</b>	41.36	3.523	45.26	2.925
<b>TG</b>	195.86	48.526	166.52	44.968
<b>VLDL</b>	41.18	9.218	34.13	9.143

**Table 2: Effect of atorvastatin and vitamin D on lipid profile in group B, (n=50).**

Lipid profile	Before AVS and vit. D3		After AVS and vit D3	
	Mean	SD	Mean	SD
<b>Total cholesterol</b>	242.62	18.115	166.34	10.616
<b>LDL</b>	165.65	17.361	98.26	8.918
<b>HDL</b>	41.35	2.128	46.68	3.016
<b>TG</b>	187.16	48.261	128.72	34.815
<b>VLDL</b>	39.38	9.165	26.70	8.012



**Figure 2: Comparing atorvastatin (group-A) and AVS with vit D3 (group B).**

**Table 3: T' test comparison of lipid profile in both group A and group B, (n=50).**

Lipid profile	AVS and vit D3		AVS		T test	Df
	Mean	SD	Mean	SD		
<b>Total cholesterol</b>	166.34	10.616	196.68	21.120	9.075	98
<b>LDL</b>	98.26	8.918	125.67	15.320	10.933	98
<b>HDL</b>	46.68	3.016	45.26	2.925	2.389	98
<b>TG</b>	128.72	34.815	166.52	44.968	4.699	98
<b>VLDL</b>	26.70	8.012	34.13	9.143	4.321	98

**Table 4: T test comparison in hypertensive patients in group A and group B, (n=25).**

Lipid profile	AVS and vit D3		AVS		T test	Df
	Mean	SD	Mean	SD		
<b>Total cholesterol</b>	165.10	9.813	187.72	1.805	16.030	98
<b>LDL</b>	96.81	10.146	116.01	14.327	7.733	98
<b>HDL</b>	48.12	2.261	47.12	2.105	2.289	98
<b>TG</b>	98.93	19.183	40.012	45.956	4.271	98
<b>VLDL</b>	19.58	3.516	27.066	8.912	5.525	98

Unpaired t test was conducted in order to compare the effect of atorvastatin and vitamin D3 combination with Atorvastatin on lipid profile in both the groups.

The test indicated that the reduction in serum LDL, TG, VLDL and increase in HDL cholesterol was higher in group-B compared to group-A as the  $p < 0.001$  and it is statistically significant.

In order to compare the effect of atorvastatin and vit D3 combination with atorvastatin on lipid profile hypertensive patients with dyslipidemia by using unpaired t test.

The test indicated that the reduction in serum LDL, TG, VLDL and increase in HDL cholesterol were higher for patients in group-B compared to group-A as  $p < 0.001$  and it is statistically significant.

## DISCUSSION

Coronary heart disease remains the most leading cause of death among the middle aged and elderly population worldwide. High blood pressure, high cholesterol level and smoking are the key risk factors to the cardio vascular diseases. Several other medical conditions like diabetes, overweight and obesity, and life style choices like unhealthy diet, physical inactivity, excessive alcohol use put people under high risk for heart diseases.

Life style changes are an integral part of prevention and treatment of dyslipidemia like calorie reduction is the key to weight loss and dyslipidemia treatment, followed by smoking cessation, abstinence from alcohol, physical activity, role of yoga and stress management. Public awareness is essential to address this epidemic

Most of the dyslipidemia patients will be asymptomatic for several years and blood lipid levels are not always routinely evaluated, unless they suffer from sudden cardio

vascular morbidity. Lipid association of India expert recommend screening for dyslipidemia by 20 years of age or at the time of college admission/at earliest opportunity for the purpose of early detection of high-risk individuals.

The most effective and potent drug for treating dyslipidemia is statins. Statins are used because of its proven safety profile and efficacy. Statins are highly efficacious at lowering LDL-C, with reduction ranges from 20%-55%.<sup>20</sup> Among statins Atorvastatin is the commonly prescribed drug. The main mechanism of action of statins is by inhibiting the enzyme essential for cholesterol biosynthesis that is HMG-CoA reductase.

Vitamin D3 has very good effect on blood lipid profile levels. The main action is, it lowers the levels of TGs in lipid profile. It lowers TG levels by two mechanisms mainly in patients with CKD. One by reducing the hepatic TG formation and secretion through hepatocellular calcium. Second mechanism is it suppress the TG levels by lowering the serum parathyroid hormone (PTH) levels, by increased peripheral removal of TG. Therefore, vitamin D3 is essential and the oral recommended dose is 1000IU/day. Vitamin D3 also has several beneficial pleiotropic effects like statins.

Abhima et al study with fixed dose combination of vitamin D3 1000IU and atorvastatin 10 mg per day for 3 months showed significant mean percentage increase in HDL levels compared to atorvastatin group.

JB Schwartz department of clinical pharmacology, university of California showed that atorvastatin and vit D has synergistic effect on cholesterol concentration.<sup>21</sup>

Ahmed et al, from Jewish hospital Cincinnati showed that vitamin D reduced statin induced Myalgia. It is one of the adverse effects of statin which leads to failure of compliance.

Rasa et al showed that the cardioprotective effect of vitamin D is by promoting the formation of large HDL particles which helps in reverse cholesterol transport.<sup>22</sup>

Maki et al demonstrated the significant relationship between HDL-C and vitamin D.<sup>23</sup>

Hence the present study was taken to know the effects of atorvastatin and vitamin D3 combination in patients with dyslipidemia as this combination helps to significantly reduce the bad cholesterol levels and increase the good cholesterol levels and it improves the patient compliance too and in long run, the patients will be benefited by the pleiotropic effects of statins as well as vitamin D.

The 100 patients with dyslipidemia were selected for our study from outpatient department of general medicine. Their details such as socio demographic, clinical and lab data were collected. The patients were explained about the study in local language and the drugs were given orally. Before starting the therapy investigations such as fasting plasma lipid profile and liver function tests were done. At the end of the study treatment efficacy were assessed in both the groups.

At the end of the study the mean total cholesterol was reduced significantly in atorvastatin vitamin D3 group than in atorvastatin group with  $p < 0.001$ . The mean LDL-C, TG, VLDL were reduced significantly in atorvastatin vitamin D3 group than in atorvastatin group with  $p < 0.001$ . The mean HDL-C in atorvastatin vitamin D3 group was 46.68 and in atorvastatin group was 45.26 with  $p < 0.001$ . This significant reduction in total cholesterol, TG, LDL, VLDL can be due to hepatic reduction in the formation of TGs and suppressive effect on parathyroid levels.<sup>24</sup>

Fasting plasma lipid profile was significantly improved in both groups, but the improvement was more significant in atorvastatin and vitamin D3 group

Atorvastatin and vitamin D3 treated group (group-B) showed better response when compared to only atorvastatin (group A).

### Limitations

Under ideal circumstances the number of participants in this study should have been  $> 200$  and the duration of the study must be at least 6 months. But, because of the challenges of the pandemic (COVID) we have to limit this to three months duration and 100 participants.

### CONCLUSION

Supplementation of vitamin D3 along with atorvastatin in dyslipidemia patients proved to have better response on lipid profile compared to only atorvastatin. Vitamin D supplementation seems to have synergistic effects on cholesterol concentrations.

Large robust clinical trials have to be carried out to understand the complex ways in which statins and vitamin D might affect each-others properties and actions.

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