International Journal of Advances in Pharmacy Medicine and Bioallied Sciences
An International, Peer-reviewed, Indexed, Open Access, Multi-disciplinary Journal
www.biomedjournal.com
ISSN 2348-2109

Original Research Article

# Comparative dose efficacy study of atorvastatin on lipid profile and incidence of adverse effects in dyslipidemic patients

B.V.S. Lakshmi[1*], Ram Babu[2], M. Sudhakar[1], E. Yashita[3], B. Varshita[3], V. Swapna[3], K. Vennela[3].

[1]Department of Pharmacology, Malla Reddy College of Pharmacy (Affiliated to Osmania University), Dhulapally , Secunderabad- 500014, Telangana, INDIA.
[2]Department of General Medicine, Malla Reddy Institute of Medical Sciences, Suraram, Hyderabad, Telangana, INDIA.
[3]Department of Pharmacy Practice, Malla Reddy College of Pharmacy (Affiliated to Osmania University), Dhulapally , Secunderabad- 500014, Telangana, INDIA.

ARTICLE INFO

*Article History:*
Received 02 Feb 2018
Revised 20 Feb 2018
Accepted 10 March 2018

*Keywords:*
Atorvastatin,
Dyslipidemic patients,
Incidence of adverse effects,
DASH diet,
Lipid levels,
Simple randomization.

ABSTRACT

**Background:** Cardiovascular diseases (CVD) are the major cause of morbidity and mortality in our society with Dyslipidemia contributing significantly to atherosclerosis. Thus measurement of plasma lipids would help in identifying people at risk for CVD.
**Materials and methods:** The study included 158 consecutive Dyslipidemic patients above 25 years of age. Patient selection was done by simple random sampling into three equal groups (A, B, C) who were newly prescribed with Atorvastatin 10mg, 20mg, 40mg respectively and their sociodemographic, height, weight, and physical activities were collected from patient's Medical Records. In week 9 each group is divided into further two subgroups i.e. control group (drug therapy + subjects regular diet) and experimental group (drug therapy + DASH diet) and recorded the data of those subjects and the efficacy was determined and compared.
**Results:** In the present study, the % mean change of all three doses (10mg, 20mg and 40mg) reduced the lipid levels (TC, LDL, TG, VLDL) from baseline to week 8. A dose-dependent response was apparent with greater decreases achieved by patients receiving the higher doses (20 and 40 mg) of Atorvastatin when compared to the lower dose (10mg). The present study also showed that the patient groups who followed the DASH diet along with Atorvastatin (experimental group) had the significant reduction in lipid levels when compared to that of patient groups who followed their regular diet with Atorvastatin (control group).
**Conclusion:** In the present study, the results showed that the effects of Atorvastatin on lipid profile was similar-considering 40mg and 20mg dosages of the drug and thus administration of the lower dose of the drug (20mg) might be more preferable. In the second phase of the present study, Atorvastatin Experimental group (following DASH diet + drug) was found to be most effective at reducing lipid levels when compared to control group (following subjects regular diet + drug).

*AUTHOR FOR CORRESPONDENCE
E-mail address: adithya.neha@gmail.com



## INTRODUCTION

The Cardiovascular diseases (CVD) are the major cause of morbidity and mortality in our society with dyslipidemia, defined as the process of either hypercholesterolemia or hypertriglyceridemia. cholesterol, triglycerides, and phospholipids are the major lipids in the body, and they are transported as

complexes of lipid and proteins known as lipoproteins. Plasma lipoproteins are spherical particles with surfaces that consist largely of phospholipids, free cholesterol, and protein and cores that consist mostly of triglyceride and cholesterol ester. The three major classes of lipoproteins found in serum are low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), and very low-density lipoproteins (VLDLs). Intermediate density lipoprotein resides between VLDL and LDL and is included in the LDL measurement in routine clinical measurement. Abnormalities of plasma lipoproteins can result in a predisposition to coronary, cerebrovascular, and peripheral vascular arterial disease. Accumulating evidence over the last decades had linked elevated total and LDL and reduced HDL to the development of coronary heart disease (CHD). Premature coronary atherosclerosis, leading to the manifestations of ischemic heart disease, is the most common and significant consequence of hyperlipidemia. Thus measurement of plasma lipids would help in identifying people at risk for CVD (Grundy et al., 1999). The statins have been shown to reduce the risk of stroke by approximately 30% in patients with coronary artery disease and elevated plasma lipids. The National Cholesterol Education Program (NCEP) considers ischemic stroke or TIA to be a coronary "equivalent" and has recommended the use of statins to achieve a low-density lipoprotein (LDL) concentration of less than 100 mg/dL (Grundy et al., 1999). Statin therapy is an effective way to reduce stroke risk and should be considered in all ischemic stroke patients (Pearson et al., 2002). The aim of the present study was to ascertain the best efficacious dose among the different doses of atorvastatin (10 mg, 20 mg, 40 mg) to find out the influence of cholesterol-lowering diet (DASH DIET) on patient status with the help of a diet chart and to conduct the patient counseling regarding the usage of atorvastatin and lifestyle modifications needed in lowering the lipid levels using patient information leaflet.

## MATERIALS AND METHODS

### Study design

This is a prospective, observational, comparative study. This analysis used patient-reported data and was conducted for a period of six months at a Multi-specialty tertiary care teaching hospital. Ethical approval was obtained from the authorities of the ethical committee after submission of the study protocol. The Institutional Human Ethical Committee approval code of the study is IHEC/MRIMS/23/2017.

### Study population

A Total of 181 cases were collected out of which 23 patients dropped out, 158 patients were included in the study. The reason for patient dropout was lost to follow up (n=8), death (n=1), withdrawal of informed consent (n=2), not following the dash diet regimen (n=10) and others/administrative (n=2).

Patient selection was done by simple random sampling into three equal groups (A, B, C) who were newly prescribed with atorvastatin 10 mg, 20 mg, 40 mg respectively and their efficacy was determined and compared (Week 0 to week 8). Divided each group into further two subgroups i.e. control group (drug therapy + subjects regular diet) and experimental group (drug therapy + DASH diet) and recorded the data of those subjects. The efficacy was determined and compared for these subgroups (week 9 to week 25). The prevalence of adverse effects was determined at each review (review 1 and review 2) and compared.

### Data collection

The data for these patients was obtained from the patient profile forms and a well-designed questionnaire was used to collect the data of the recruited patients prospectively. The questionnaire included sociodemographic characteristics such as age, gender, weight and marital status. The second part included lifestyle habits such as smoking and alcohol. The third part included details regarding patient condition such as blood pressure, their diet control and any other health condition. The fourth part included the details of Atorvastatin prescribed and biochemistry laboratory investigations such as total cholesterol, HDL, LDL and TG levels (in mg/dl). The final part included symptoms of the patient and their Quality Of Life.

### Statistical analysis

Results were presented as the mean ± standard deviation for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. The comparison of efficacy between the experimental and control group of the study was done with unpaired t-test (Student's t-test) using IBM SPSS Statistics 20 version. Student's t-test was used to ascertain the significance of differences between mean values of two continuous variables .$P < 0.05$ was considered statistically significant.

## RESULTS & DISCUSSION

A Total of 181 cases were collected out of which 23 patients dropped out, 158 patients were included in the study. Patient selection was done by simple random sampling into three equal groups (A, B, C) who were newly prescribed with atorvastatin 10 mg, 20 mg, 40

mg respectively and their efficacy was determined and compared (week 0 to week 8) Divided each group into further two subgroups i.e. control group (drug therapy + subjects regular diet) and experimental group (drug therapy + DASH diet) and recorded the data of those subjects. The efficacy was determined and compared for these subgroups (week 9 to week 25). The results of the study were as follows:

**Table 1.** Sociodemographic and baseline CHD risk factors.

| Demographic / baseline characteristics | Atorvastatin 10mg (n=50) | Atorvastatin 20mg (n=56) | Atorvastatin 40 mg (n=52) | Total (n=158) |
|---|---|---|---|---|
| **Mean age (mean ± SD)** | 54.82 ± 8.83 | 54.84 ± 10.38 | 54.63 ± 11.89 | |
| **Gender** [n (%)] | | | | |
| Male | 26 (52%) | 26 (46.42%) | 32 (61.53%) | 84 (53.16%) |
| Female | 24 (48%) | 30 (53.57%) | 19 (36.53%) | 73 (46.2%) |
| **Marital status** [n (%)] | | | | |
| Married | 48 (96%) | 54 (96.4%) | 47 (90.3%) | 149 (98%) |
| Unmarried | 2 (4%) | 2 (3.57%) | 5 (9.61%) | 9 (5.69%) |
| **CHD risk factors** [n (%)] | | | | |
| Male ≥45 years | 19 (38%) | 23 (41.07%) | 25 (48.07%) | 67 (42.4%) |
| Female ≥55 years | 22 (44%) | 24 (42.85%) | 13 (25%) | 59 (37.3%) |
| Cigarette smokers | 8 (16%) | 8 (14.2%) | 8 (15.38%) | 24 (15.1%) |
| Alcoholics | 11 (22%) | 10 (17.85%) | 13 (25%) | 34 (21.5%) |
| Cigarette smokers + alcoholics | 8 (16%) | 6 (10.71%) | 5 (9.61%) | 19 (12%) |
| Hypertension* | 17 (34%) | 21 (37.5%) | 23 (44.2%) | 61 (38.6%) |
| Diabetes | 10 (20%) | 12 (21.4%) | 12 (23.07%) | 24 (21.5%) |
| Hypertension + diabetes | 13 (26%) | 14 (25%) | 9 (17.3%) | 36 (22.7%) |
| HDL-C (<40mg / dL) | 8 (16%) | 22 (39.28%) | 26 (50%) | 56 (35.4%) |
| BMI [n (%)] | | | | |
| Over weight | 11 (22%) | 18 (32.1%) | 20 (38.4%) | 49 (31.01%) |
| Obese | 6 (12%) | 8 (14.2%) | 2 (3.84%) | 16 (10.1%) |

**blood pressure >140/90mmgHg or taking Antihypertensive medication; BMI – body mass index*

There were more men than women, more married that unmarried & ages ranged from 25 to 84years. No significant differences (P <0.05) in baseline CHD risk factors were evident among the treatment groups.

## Population demographics

Demographic and baseline characteristics of the study participants are shown in (Table 1). Overall, demographic characteristics were mostly similar for each treatment group. There were more men than women, more married than unmarried & ages ranged from 25 to 84 years. No significant differences (P <0.05) in baseline CHD risk factors were evident among the treatment groups (Table 1). The most frequently occurring risk factors were male sex aged >45 years (n = 158, 42.4%) and hypertension (n = 158, 38.6%). A total of 24 (21.5%) patients had a history of diabetes. Patients with habits of only smoking, only alcoholism and smoking + alcoholism recorded were 15.1%, 21.5% & 12% respectively. It is evident from demographic data (Table 1) which have the patient characteristics that many of patients had more than two risk factors for cardiovascular diseases. For instance, the patients were diabetic, hypertensive and most of them were over 55years old. In addition, over 1/3rd of the patients were overweight and obese (31.01%, 10.1%).

## Lipid profile

In the present study, the results revealed that all three doses (10 mg, 20 mg, 40 mg) reduce the lipid levels (TC, LDL, TG, VLDL) from baseline to week 8 (Table 2). A dose-dependent response was apparent with greater decreases achieved by patients receiving the higher doses (20 and 40 mg) of atorvastatin when compared to the lower dose (10 mg). An increase in HDL-C from baseline to week 8 was also observed in all treatment groups (Table 2). This was similar to the study Conducted by (Biggerstaff and Wooten, 2006). An increase in the total cholesterol level, was observed with statins taken at night, LDL-C is an important marker for the risk of developing heart disease. Most abundant type, LDL carries approximately 65% of the total circulating cholesterol. Inhibition of cholesterol biosynthesis, increased uptake and degradation of low-density lipoproteins (LDL) leads to inhibition of the secretion of lipoproteins & inhibition of LDL oxidation. Statins have antiatherosclerotic effects that correlate positively with the percent decrease in LDL cholesterol. It has been reported in a study by, that atorvastatin increases high-density lipoprotein cholesterol (HDL-C) more in patients with low than in those with high baseline HDL-C levels. In contrary, our present study resulted in the higher increase in HDL-C levels in higher Atorvastatin doses (20 mg & 40 mg) than in lower dose

(10 mg). Statins inhibit hepatic synthesis of apolipoprotein-100, determining the reduction of the synthesis and secretion of triglyceride-rich lipoproteins(Rydén et al., 2013).

**Table 2.** Mean percentage change in lipid parameters from baseline (week 0 to week 8).

| Lipid variables | Atorvastatin 10mg (n=50) | Atorvastatin 20 mg (n=56) | Atorvastatin 40 mg(n=52) |
|---|---|---|---|
| **TC** | -17.66* | -22.11* | -24.63* |
| **HDL** | 4.82 | 5.98* | 6.19* |
| **LDL** | -32.25* | -39.36* | -42.95* |
| **VLDL** | -78.35* | -80.00* | -85.40* |
| **TG** | -9.78 | -12.32* | -13.36* |
| **TC/HDL** | -25.97* | -27.33* | -31.26* |
| **Non-HDL** | -4.90 | -7.84* | -9.50* |

The results are represented as % mean change,*p-value <0.05.

Mean percentage change in lipid levels after 8 weeks. In the present study, the % mean change of all three doses (10mg, 20mg and 40mg) reduced the lipid levels (TC, LDL, TG, VLDL) from baseline to week 8. A dose-dependent response was apparent with greater decreases achieved by patients receiving the higher doses (20 and 40 mg) of Atorvastatin when compared to lower dose (10mg).

## Cholesterol ratio and non-HDL

The TC/HDL cholesterol ratio, known as the atherogenic or Castelli index and non-HDL is of great interest as major predictors of cardiovascular disease. The evidence derived from large observational studies, including the Framingham Study, the LRCP and the PROCAM suggests that the total/HDL cholesterol ratio is a more powerful coronary risk predictor than independently-used total cholesterol, LDL cholesterol and HDL cholesterol. In fact, several studies have suggested that a decrease in total-cholesterol/HDL-cholesterol ratio is linked to a reduction in the risk of morbidity and mortality in cardiovascular diseases (Lemieux et al., 2001). It is proposed that the ability of this ratio to predict risk is explained by the fact that it is a relevant cumulative marker of the cluster of metabolic abnormalities found in individuals with high TG, low HDL-C Dyslipidemia (Koenig et al., 1999). This condition has been shown to be the consequence of obesity and insulin resistance and is also commonly associated with an increased concentration of small, dense LDL particles (Superko, 1997).

Non-HDL cholesterol, which is total cholesterol minus HDL cholesterol, is a measure of the cholesterol in LDL, IDL and VLDL particles. In our present study, the % mean change from baseline to week 8 TC/HDL cholesterol ratios was found to be -25.97 in 10 mg, -27.33 in 20 mg & -31.26 in 40mg. All these values were statistically significant. And the % mean change of non-HDL from baseline to week 8 was recorded as -4.90, -7.84 and -9.50 in 10, 20 & 40 mg respectively (Figure 1-3). This implies that the risk of heart diseases was lowered in all the subjects. The reduction in cholesterol synthesis with atorvastatin therapy causes a reduction in intracellular cholesterol concentrations and a subsequent upregulation of hepatocyte LDL receptors. These receptors recognize and bind with apolipoproteins B and E on the surface of circulating very-low-density lipoprotein (VLDL) and LDL particles (Lamarche et al., 1996), resulting in uptake and degradation by the cells. Atorvastatin also lowers circulating VLDL and LDL levels by reducing the secretion of VLDL and VLDL-like lipoproteins from the liver, thus reducing the quantities of lipoprotein available to serve as the substrate for conversion to atherogenic remnant particles (Ray et al., 2009).

## Influence of DASH diet

The present study also showed that the patient groups who followed the DASH diet along with atorvastatin (experimental group) had the significant reduction in lipid levels when compared to that of patient groups who followed their regular diet with atorvastatin (control group). Similar results were reported in a study by (Karuna et al., 2015). Intake of high-fibre diet (>25gms/day) reduces cholesterol levels. The mechanism of action for this benefit is the increased viscosity of gel-forming fibres that trap bile and its cholesterol component. The trapped bile is then eliminated in the stool. Replacing saturated fats with unsaturated fats helps to lower the levels of TC and LDL cholesterol in the blood (Beynen and Katan, 1989). Low-carbohydrate diets seek to minimize insulin release while favouring release of glucagon. It has been demonstrated that consumption of n-6 and n-3 PUFAs (Poly Unsaturated Fatty Acids) decreases blood triglycerides by increasing fatty acid oxidation through activation of PPARalpha (Peroxisome proliferator-activated receptor alpha) or by reducing the activation of SREBP-1 (Sterol regulatory element-binding transcription factor 1) inhibiting lipogenesis. Dietary PUFAs activate PPARalpha and PPARgamma (Peroxisome proliferator-activated receptor gamma)

increasing lipid oxidation and decreasing insulin resistance leading to a reduction of hepatic steatosis (Mattson et al., 1985). Relative to the control diet, the DASH diet resulted in the significantly lower mean of total cholesterol (TC), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and the higher mean of high-density lipoprotein (HDL) (Table 1). In addition, our present study showed significant reductions in TC/HDL cholesterol ratio and non-HDL. From this, we infer that the DASH diet is likely to reduce coronary heart disease risk. Quality of Life assessment, the majority of the study population was satisfied with the therapy (Figure 4).

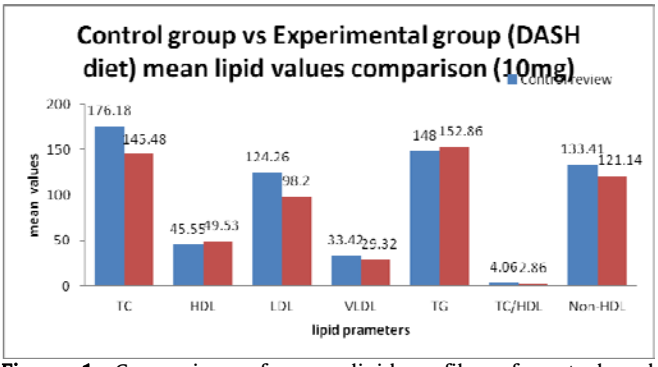


**Figure 1.** Comparison of mean lipid profiles of control and experimental group (10mg). In our present study, the mean lipid values of 10mg treatment group were found to be decreased in TC, LDL, VLDL, TC/HDL and non-HDL levels of experimental group when compared to that of control group.

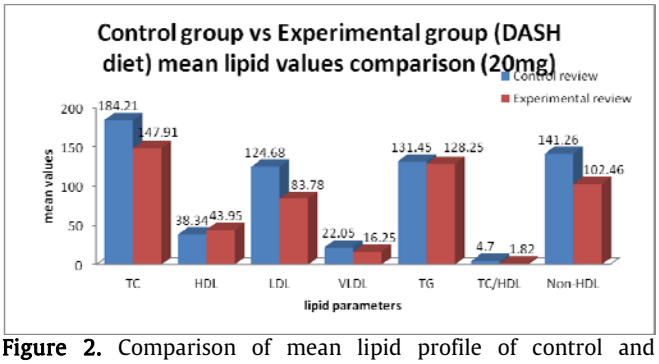


**Figure 2.** Comparison of mean lipid profile of control and experimental groups using Atorvastatin 20mg [control (n=27), Experimental (n=29)].

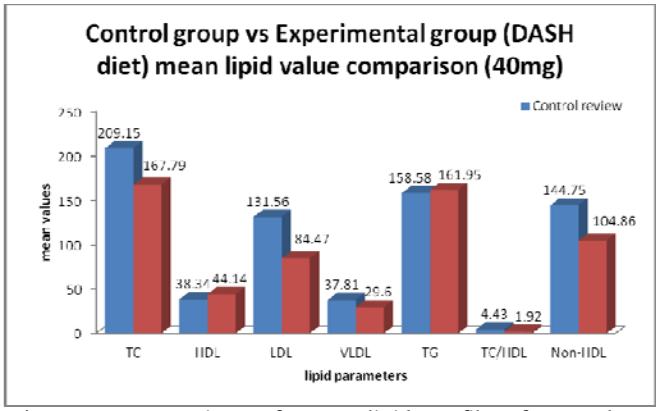


**Figure 3.** Comparison of mean lipid profile of control and experimental groups using Atorvastatin 40mg [control (n=25), Experimental (n=27)]

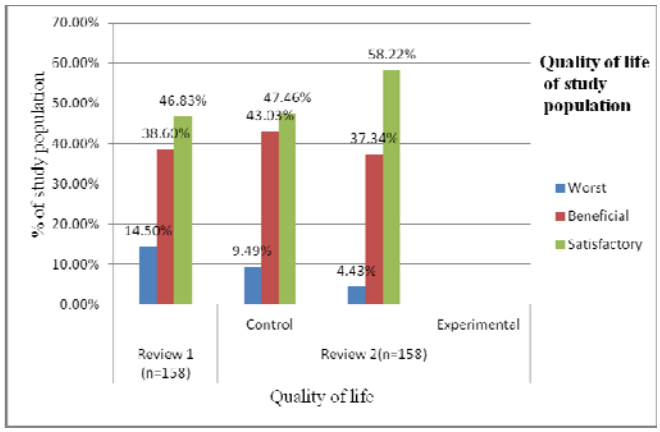


**Figure 4.** Graphical representation of distribution of study population based on quality of life. Majority of the study population were satisfied with the therapy (46.83%) in review 1 and in review 2.In review 2, majority of experimental group population were satisfied with the therapy (58.22%) compared to control group (47.46%).

Worldwide, cardiovascular disease is estimated to be the leading cause of death and loss of disability-adjusted life years (DALYs). Although age-adjusted cardiovascular death rates have declined in several developed countries in the past decades, rates of cardiovascular diseases have raised greatly in low and middle income countries, with about 80% of the burden now occurring in those countries. In view of this, all efforts need to be taken to clearly understand the role of risk factors in the emerging epidemic, for its effective control. Presence of dyslipidemia even among the young adults as observed in the study is distressing and thus screening right from younger ages may help promote lifestyle changes that can prevent or slow atherogenesis. More importantly, a healthy lifestyle should be included right from childhood stage to prevent this epidemic. Several randomized controlled trials have shown that effective treatment of dyslipidaemia reduces the rate of morbidity and mortality. The prevalence of dyslipidemia is very high in India, which calls for urgent life style intervention strategies to prevent and manage this important cardiovascular risk factor. The ICMR-INDIAB study shows that obesity, dysglycemia and hypertension were strongly associated with dyslipidemia. Statins significantly reduce cardiovascular events in a broad population of patients with hyperlipidemia Total of 181 cases were collected out of which 23 patients dropped out, 158 patients were included in the study. Patient selection was done by simple random sampling into three equal groups (A, B, C) who were newly prescribed with atorvastatin 10 mg, 20 mg, 40 mg respectively and their efficacy was determined and compared (week 0 to week 8). Divided each group into further two subgroups i.e. control group (drug therapy + subjects regular diet) and experimental group (drug therapy + subjects regular diet) and experimental group (drug

therapy + DASH diet) and recorded the data of those subjects. The efficacy was determined and compared for these sub groups (week 9 to week 25). The prevalence of adverse effects was determined at each review (review 1 and review 2) and compared. Demographic and baseline characteristics of the study participants are shown in Table 1. Overall, demographic characteristics were mostly similar for each treatment group. There were more men than women, more married than unmarried & ages ranged from 25 to 84years. No significant differences (P <0.05) in baseline CHD risk factors were evident among the treatment groups (Table 1). The most frequently occurring risk factors were male sex aged >45 years (n = 158, 42.4%) and hypertension (n = 158, 38.6%). A total of 24 (21.5%) patients had a history of diabetes. Patients with habits of only smoking, only alcoholism and smoking + alcoholism recorded were 15.1%, 21.5% & 12% respectively. It is evident from demographic data (Table 1) which have the patient characteristics that many of patients had more than two risk factors for cardiovascular diseases. For instance, the patients were diabetic, hypertensive and most of them were over 55years old. In addition, over 1/3$^{rd}$ of the patients were overweight and obese (31.01%, 10.1%).

## CONCLUSIONS

The present study revealed that statin therapy is effective in allowing LDL-C goal achievement and improving the lipid profile in dyslipidemias. Many of patients had more than two risk factors for cardiovascular diseases. For instance, the patients were diabetic, hypertensive and most of them were over 55years old. In addition, over 1/3rd of the patients were overweight and obese (31.01%, 10.1%). In the present study, the results showed that the effects of atorvastatin on lipid profile was similar considering 40 mg and 20 mg dosages of the drug and thus administration of the lower dose of the drug (20mg) might be more preferable. In the second phase of the present study, Experimental group (following DASH diet + drug) was found to be most effective at reducing lipid levels when compared to control group (following subject's regular diet + drug). Atorvastatin therapy had shown the significant reduction in cholesterol ratio (TC/HDL), non-HDL which implies that the risk of heart diseases was lowered in the patients. The lowering of TG's is another important goal of reducing cardiovascular risk among diabetic patients. In the current study, the greatest reductions in TG's were -12.32% and -13.36 % mean change with 20 mg and 40 mg respectively. It thus appears that, in relation to this factor (TG's), atorvastatin 20 mg and 40 mg doses are similarly effective at reducing it. In this study, the subjects were experiencing more adverse effects while using atorvastatin 40 mg than other two doses (10 mg & 20 mg). But there were no significant side effects reported in this study with any of the dose (10 mg, 20 mg & 40 mg). Based on the results from cholesterol drugs and adverse effects questionnaire Quality of Life assessment, the majority of the study population were satisfied with the therapy. Overall, the use of lower dose drug therapy (20 mg) along with dietary modification (DASH diet) rather than 40 mg dose therapy would lower the incidence of side effects.

Further in-depth investigation regarding these doses should be done to prove efficacy in the larger population.

## CONFLICT OF INTEREST

None declared.

## REFERENCES

Beynen AC, Katan MB. Impact of dietary cholesterol and fatty acids on serum lipids and lipoproteins in man, in Vergroesen AJ, Crawford MA (Eds): The Role of Fats in Human Nutrition. London, Academic Press Ltd., 1989.

Biggerstaff KD, Wooten JS. Understanding lipoproteins as transporters of cholesterol and other lipids. Advances in Physiology Education. 2006; 28(1-4): 105-106.

Grundy SM, Pasternak R, Greenland P. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations. Circulation. 1999; 100–101:1481–149.

Lemieux I, Lamarche B, Couillard C, Pascot A, Cantin B, Bergeron J et al. Total Cholesterol/HDL Cholesterol Ratio vs. LDL Cholesterol/HDL Cholesterol Ratio as Indices of Ischemic Heart Disease Risk in Men The Quebec Cardiovascular Study. Archives of Internal Medicine. 2001; 161(22): 2685-2692.

Karuna S, Pranity S, Ritika S. Effect of High Fibre and Omega-3 Rich Diet on Hypercholesterolemia Patients. Journal of Nutrition and Food Sciences. 2015. 5:412.

Koenig W, Sund M, Fröhlich M, Fischer HG, Löwel H, Döring A et al. C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. Circulation. 1999; 99:237-242.

Lamarche B, Moorjani S, Lupien PJ, Cantin B, Bernard PM, Dagenais GR et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Québec cardiovascular study. Circulation. 1996;94(3):273-8.

Mattson FH, Grundy SM. Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man. Journal of Lipid Research, 1985; 26:194-202.

Pearson TA, Blair SN, Daniels SR. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update. Circulation. 2002;106:388–391.

Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. Arteriosclerosis, Thrombosis, and Vascular Biology. 2009; 29(3) 423–430.

Rydén L, Grant PJ, Anker SD. ESC guidelines on diabetes, pre-diabetes and cardiovascular diseases developed in collaboration with the EASD. European Heart Journal. 2013; 34:3035-3087.

Superko HR. The new thinking on lipids and coronary artery disease. Current Opinion in Cardiology. 1997; 12: 180-187.