Original Article

Myopathy in Patients Taking Atorvastatin: A Pilot Study

K. Manoj, N. Jain, S. V. Madhu

Department of Endocrinology, Centre for Diabetes Endocrinology and Metabolism, University College of Medical Sciences (University of Delhi) and GTB Hospital, New Delhi, India

Abstract

Aim: This study aims to investigate the prevalence and risk factors of statin-induced myopathy. **Subjects and Methods:** A total of 200 patients aged ≥ 40 years and taking atorvastatin 10 mg/day or more for at least 2 weeks were recruited in the study. A detailed history of participants and anthropometry of study participants was recorded, and features of myopathy were explained. Biochemical investigations along with thyroid stimulating hormone (TSH) and Vitamin D were done in all patients. **Results:** Mean age of study population was 54.81 ± 9.10 years. Sixty-five percent (65.5%) of atorvastatin users had coronary heart disease, 62.5% were hypertensive, 38% had diabetes. Thirty-five percent (35.5%) patients were taking 10 mg/day atorvastatin, 45% were taking 20 mg/day, and 19.5% were taking 40 mg/day. The overall frequency of myopathy among statin users was 7.5% which was significantly higher with increasing dose of atorvastatin (1.4% in 10 mg/day group, 10% in 20 mg/day group, and 12.8% in 40 mg/day, $P < 0.05$). The frequency of atorvastatin-related myopathy was higher in females 8.65% compared to 6.25% in males. Serum TSH levels in patients with myopathy were 4.05 ± 7.76 μIU/ml while in those without myopathy were 3.13 ± 2.88 μIU/ml ($P = 0.649$). Serum 25-hydroxy Vitamin D levels were measured in 66 patients randomly. Mean levels in patients with myopathy were 15.98 ± 12.94 ng/ml and without myopathy were 10.20 ± 5.64 ng/ml ($P = 0.285$). **Conclusion:** The present study demonstrates that a significantly higher number of patients taking atorvastatin develop myopathy in real life clinical condition. The frequency of myopathy increases with increase in atorvastatin dose.

Keywords: Atorvastatin, myopathy, thyroid stimulating hormone, Vitamin D

Introduction

There is an increase in the global burden of noncommunicable diseases.[1] Diabetes and cardiovascular diseases contribute to major morbidity and mortality.[1] Statins have been found to be most important drug with pleotropic drug action.[2,3] Hence, it has been prescribed to several patients to reduce cardiovascular and cerebrovascular comorbidity.[4] Although the drug is well tolerated still there are some dose limiting side effects including gastrointestinal intolerance, myopathy, elevated liver enzymes, and peripheral neuropathy.[5] Several clinical studies have documented various degrees of myopathies from subtle symptoms to severe rhabdomylosis leading to discontinuation of drug.[6,7] This adverse effect is augmented by old age, female sex, hepatic and renal insufficiency, and hypothyroidism.[8] Concomitant use of fibrates, azoles, macrolides, verapamil, cyclosporine, and amiodarone enhances the myopathy caused by statins.[9] Muscle symptoms associated with statin use have been inconsistently associated with biopsy and electrographic changes. Earlier only few studies have reported statin leading to inflammatory and necrotizing myopathy where biopsy changes did not revert on stopping the medication. The present study was carried out in atorvastatin users to determine the incidence of myopathy and associated risk factors in them.

Statins have been found to reduce the cardiovascular and cerebrovascular morbidity, and its effect increases with increase in dose of drug, simultaneously the adverse effects also increase with an increase in the dose. The present study has therefore been undertaken to investigate the prevalence and risk factors of statin-induced myopathy.

Subjects and Methods

The study was approved by Institutional Ethics Committee-Human Research, University College of Medical Sciences and GTB Hospital, Delhi, India. All the guidelines

Address for correspondence: Dr. S. V. Madhu, Department of Endocrinology, Centre for Diabetes Endocrinology and Metabolism, University College of Medical Sciences (University of Delhi) and GTB Hospital, Dilshad Garden, New Delhi - 110 095, India.
E-mail: drsvmadhu@gmail.com

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of the Institutional Ethical Committee were followed during the study.

A total of 200 patients aged ≥40 years and taking atorvastatin 10 mg/day or more for at least 2 weeks were recruited in the study. Patients with a history of alcohol abuse (210 g/week in males and 140 g/week in females) and or with liver diseases were excluded from the study. Other confounding factors were also taken into consideration such as the previous history of myopathy, myositis, polyneuropathy, peripheral vascular disease, and acute febrile episodes. Patients with chronic illnesses like HIV/AIDS, malignancy and other connective tissue disorders were also excluded from the study. Participants taking drugs (such as corticosteroids, amphetamine, cocaine heroine, cimetidine, and penicillamine) were also excluded.

Eligible participants were counseled and a written informed consent was obtained from all study participants. A simple questionnaire was designed including history of illnesses, treatment and alcohol and smoking consumption. Compliance with atorvastatin and features of myopathy were explained to study participants. Patients were advised to come with prescription papers, investigation reports, and medications. Next morning after confirming the compliance with statin, height and weight were recorded for body mass index (BMI), and other general physical examination was done. On the prefixed scheduled date, patients were asked to come after overnight fasting for the following investigations; hemoglobin, fasting plasma glucose, kidney function test, liver function test, serum electrolytes along with serum calcium and phosphorus, lipid profile (serum total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], very-LDL [VLDL], and triglyceride), thyroid stimulating hormone (TSH) and Vitamin D. Two hours postprandial plasma glucose after the breakfast was also measured. Samples for TSH and Vitamin D estimation were stored at −20° centigrade unless analyzed.

Hemoglobin was measured by cyanhemoglobin method and plasma glucose by glucose oxidase method. Serum urea was estimated by enzymatic method, serum creatinine by modified Jaffe`s method, serum sodium, potassium and calcium by ISE ion selective electrode method and serum phosphorus by spectrophotometric method. Serum billirubin was estimated by Diazo method, and serum liver enzymes were estimated by enzymatic method. Total serum cholesterol was estimated by the method of Allain *et al*., serum triglyceride by the method of Werener and Gabriesulsen and HDL-cholesterol (HDL-C) by commercially available 3rd generation direct homogenous assay kit (Autopure HDL-C Accurex Biomedicals, India). The estimation of LDL-cholesterol was done by Friedwald equation, LDL = (Total CHL – [HDL-C + TG/5]) and VLDL = TG/5.

TSH was measured by commercially available RIA kit (Beckman Coulter Inc., Czech Republic). Analytical sensitivity of the assay was 0.04 mIU/L. The antibody used in this assay had extremely low cross reactivity against related molecules. Intra- and inter-assay coefficients of variation were below or equal to 8.6% for serum samples. 25 (OH) Vitamin D was measured by commercially available RIA kit (Diasorin, USA). The coefficient of variation within assay was <12% and analytic sensitivity of the assay was <1.5 ng/ml.

Statistical analysis

Student's *t*-test was used to compare continuous variables and Chi-square test to compare categorical variables between the groups. One-way ANOVA followed by Turkey's test was applied to compare baseline clinical characteristics and biochemical parameters among patients on different doses. Data were considered significantly different if $P < 0.05$.

Results

The study was carried out in 200 atorvastatin users which include 96 (48%) males and 104 (52%) females. The mean age of the study population was 54.81 ± 9.10 years, which was similar in males (54.79 ± 9.16 years) and females (54.82 ± 9.12 years). Their mean BMI was 25.25 ± 3.69 kg/m^2 and was also similar in male (25.31 ± 3.69 kg/m^2) and in female subjects (25.31 ± 3.69 kg/m^2). Systolic and diastolic blood pressures between two groups (atorvastatin users with and without myopathy) were comparable. Furthermore, biochemical parameters were also comparable between two groups.

Sixty-five point five percent of the patients (n = 131) had coronary heart disease, 62.5% (n = 125) were hypertensive, 38% (n = 76) were diabetic. None of the recruited patients were taking any drug which was known to cause myopathy except calcium channel blockers (CCB); this included the drugs such as amiodarone, azole antifungals, cyclosporine, and macrolide antibiotics. Among those taking CCBs, there was no patient taking verapamil or diltiazam, which have been reported to increase the risk of rhabdomyolysis. All these patients were on amlodipine. No evidence of chronic liver or kidney disease was found in any of the patients studied. Only 3.5% (n = 7) patients reported significant alcohol consumption, whereas 20% (n = 40) gave a history of smoking. There was no family history of myalgia, evidence of statin intolerance in the past or history of raised creatinine kinase (CK) levels in any of the study subjects.

Among the 200 patients studied, 7.5% of total patients (n = 15) developed myopathy. Further when these patients were divided into three groups based on the dose of atorvastatin they were taking. Various demographic parameters, biochemical parameters, and risk factors except a few were comparable between these three groups [Tables 1 and 2]. In terms of doses 35.5% (n = 71) were taking 10 mg atorvastatin per day, 45% (n = 90) were taking 20 mg atorvastatin per day and remaining 19.5% (n = 39) were taking 40 mg atorvastatin per day.

Among the group of patients (n = 71) taking 10 mg atorvastatin per day, only 1 (1.4%) patient developed myopathy who was taking 10 mg atorvastatin per day for the past 18 months for

Table 1: Comparison of baseline clinical characteristics in patients with myopathy taking different doses of atorvastatin

Characteristics	Patients on 10 mg/day atorvastatin (*n*=71)	Patients on 20 mg/day atorvastatin (*n*=90)	Patients on 40 mg/day atorvastatin (*n*=39)	*P*
Age (years)	54.99±9.60	55.23±9.34	53.51±7.60	0.605
BMI (kg/m^2)	25.43±3.76	24.98±3.49	25.70±4.05	0.556
Systolic BP (mmHg)	138.86±15.52	137.31±17.69	137.38±17.07	0.828
Diastolic BP (mmHg)	78.03±11.26	77.42±9.38	76.10±9.09	0.629
Pulse rate (/min)	87.21±10.38	84.89±10.85	83.05±11.46	0.136

All values are given in mean±SD. SD: Standard deviation, BP: Blood pressure, BMI: Body mass index

Table 2: Comparison of biochemical parameters between patients taking different doses

Parameters	Patients on 10 mg/day atorvastatin (*n*=71)	Patients on 20 mg/day atorvastatin (*n*=90)	Patients on 40 mg/day atorvastatin (*n*=39)	*P*
Hemoglobin (g/dL)	12.84±1.53	12.40±1.40	12.79±1.26	0.111
Fasting plasma glucose (mg/dL)	109.17±29.12	107.32±28.56	109.21±34.97	0.910
PP plasma glucose (mg/dL)	151.44±42.21	149.21±43.27	149.21±39.21	0.938
Blood urea (mg/dL)	24.07±6.51	25.04±7.50	25.31±6.99	0.632
Serum creatinine (mg/dL)	0.79±0.020	0.80±0.17	0.83±0.16	0.496
Serum sodium (mEq/L)	139.86±3.75	139.82±5.63	139.21±5.88	0.824
Serum potassium (mEq/L)	3.95±0.50	3.96±0.51	4.03±0.45	0.738
Serum calcium (mg/dL)	8.65±0.46	8.79±0.48	8.79±0.53	0.155
Serum phosphorous (mg/dL)	3.02±0.51	3.19±0.51	2.91±0.62	0.017
Serum total bilirubin (mg/dL)	0.63±0.15	0.64±0.14	0.66±0.15	0.501
Serum direct bilirubin (mg/dL)	0.15±0.05	0.17±0.04	0.18±0.45	0.003
Serum SGOT (IU/L)	30.08±9.92	31.24±9.80	28.08±10.64	0.256
Serum SGPT (IU/L)	32.56±10.41	30.42±9.66	30.87±9.85	0.387
Serum ALP (IU/L)	96.56±24.79	93.58±22.74	89.21±18.00	0.267
Serum HDL (mg/dl)	37.08±3.81	37.38±4.31	38.92±4.52	0.076
Serum total cholesterol (mg/dL)	194.01±20.07	174.69±24.56	152.33±18.84	<0.001
Serum triglyceride (mg/dL)	135.54±21.15	128.43±16.76	121.23±18.02	0.001
Serum VLDL (mg/dL)	27.30±4.36	25.67±3.39	24.26±3.55	0.001
Serum LDL (mg/dL)	129.63±18.81	111.64±23.42	89.15±17.65	<0.001
Serum TSH (μIU/mL)	4.43±8.90	4.08±7.55	2.93±3.72	0.600
Serum 25-(OH) D (ng/mL)	16.03±13.67	16.52±13.69	12.16±6.41	0.573

All values are given in mean±SD. SD: Standard deviation, PP: Postprandial, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, ALP: Alkaline phosphatase, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, LDL: Low-density lipoprotein, TSH: Thyroid-stimulating hormone, 25-(OH) D: 25-hydroxyvitamin D

coronary heart disease. Among the group of patients (n = 90) taking 20 mg atorvastatin per day, 10% (n = 9) developed myopathy and among the group of patients (n = 39) taking 40 mg atorvastatin per day, 12.82% (n = 5) developed myopathy [Figure 1].

Among the 15 patients who developed myopathy, 93% (n = 14) complained of pain. The pain was diffuse in nature in all the 14 patients. Seven patients complained of pain in upper limbs, and remaining 7 patients complained of pain in lower limbs. Fourteen percent (n = 2) of the patients with myopathy also complained of muscle cramps which involved lower limbs. Another 14% (n = 2) patients complained of weakness which involved upper limbs. All patients continued to have symptoms till the day of recruitment. However, no patient complained of stiffness. CK levels were marginally elevated in only 1% (n = 2) patients while on atorvastatin treatment, and both these patients were asymptomatic. None of the patients studied developed rhabdomyolysis while on statin therapy. The shortest interval between the beginning of therapy and onset of symptoms was 7 days and longest interval recorded was 2 years with the median interval being 90 days. Five patients developed symptoms within 1 month of starting therapy.

Total cholesterol, triglyceride, and LDL were found to significantly higher in patients taking 10 mg of atorvastatin compared to other patients taking higher doses of atorvastatin [Table 2]. Serum TSH and Vitamin D levels were also comparable between the three groups [Table 2].

Risk factors analysis

On risk factor analysis (male sex, duration of treatment, other comorbidities such as coronary artery diseases, hypertension and diabetes and smoking) *per se* has not shown any accountability in the causation of myopathy. Hypothyroid state and Vitamin D deficiency were also equally distributed among patients on different doses of atorvastatin [Table 3].

Table 3: Comparison of risk factor between patients with and without myopathy

Characteristics	Number of patients with myopathy (*n*=15) (%)	Number of patients without myopathy (*n*=185) (%)	*P*
Males (*n*=96)	6 (40.00)	90 (48.64)	0.519
Females (*n*=104)	9 (60.00)	95 (51.35)	0.519
<3 months duration (*n*=23)	2 (13.33)	21 (11.35)	0.683
>3 months duration (*n*=177)	13 (86.66)	164 (88.64)	0.683
CAD (*n*=131)	11 (73.33)	120 (64.86)	0.507
Hypertension (*n*=125)	7 (46.66)	118 (63.78)	0.188
Diabetes (*n*=76)	7 (46.66)	69 (37.29)	0.472
Smoking (*n*=40)	3 (20.00)	37 (20.00)	1.000
Calcium channel blocker (*n*=50)	3 (20.00)	47 (25.40)	0.766
Hypothyroidism (*n*=48)	2 (13.33)	46 (24.86)	0.529
Vitamin D deficiency (*n*=51)	6 (40.00)	45 (24.32)	0.323

CAD: Coronary artery disease

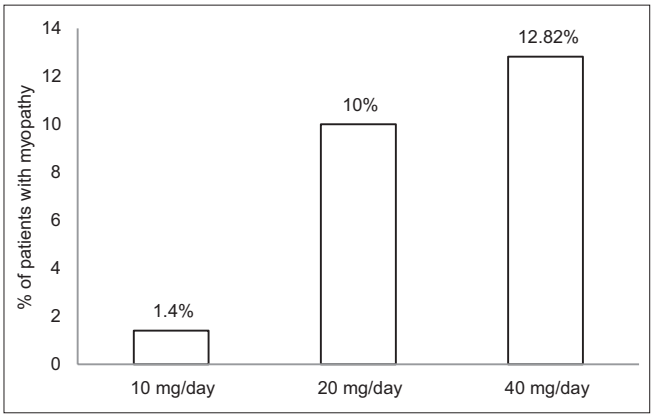

Figure 1: Incidence of myopathy in patients taking different doses of atorvastatin

Discussion

The present study was designed to observe the incidence of myopathy and myositis in real life clinical scenario in patients with all their comorbidities and concomitant medications. To the best of our knowledge, a similar study for the evaluation of risk factors and prevalence of myopathy in statin users has not been done in our India, and therefore all the comorbidities in the patients such as coronary artery disease, hypertension, diabetes mellitus, chronic kidney disease and liver disease were included for evaluation. Further, those who smoked or consumed alcohol or were on concurrent medications with an increased risk of myopathy were also included in the analysis to study their contribution to the risk of myopathy. In addition, serum CK levels, thyroid function test and Vitamin D levels have also been evaluated. This design allowed a comprehensive evaluation of various risk factors which could affect statin-associated myopathy in common clinical situations.

Study participants who were evaluated for atorvastatin-induced myopathy were middle-aged (mean age was 55 years), divided almost equally among both genders, were mildly overweight and had significant comorbidities such as coronary artery disease, diabetes mellitus and hypertension. Relatively, small proportions of them were smokers and had consumed alcohol while none had coexisting kidney or liver disease. Patients were taking 10–40 mgs of atorvastatin per day for the duration ranging from 15 days to 11 years.

The principal finding of the present study is that 7.5% (15/200) of atorvastatin-treated patients had myopathy and incidence of myopathy increases with increase in doses of atorvastatin. The most common complaint was pain which was reported by 93% of patients with myopathy. Pain was equally distributed between upper and lower extremities. Two patients complained of cramps in the lower limbs, and another two patients complained of weakness in the upper limbs. None of the patients complained of stiffness. The shortest interval between beginning the atorvastatin treatment and onset of symptoms was 7 days with a median period of 90 days. However, 5 patients out of 15 had the onset of symptoms within 1 month of beginning the therapy.

The incidence of myopathy in atorvastatin users in our study slightly differ from what has been reported earlier.[10,11] The previous large, observational study – the PRIMO, reported 14.9% incidence of myopathy among patients taking high-dose atorvastatin (40 mg and 80 mg per day). However, our study showed a slightly lower incidence of myopathy (12.8%) among the patients taking 40 mg per day atorvastatin. This slight difference may be explained by the fact that none of the patients in our study was taking 80 mg per day of atorvastatin. We also observed lower incidence of muscle weakness 14% compared to findings of PRIMO study (25%). However, we cannot comment on these differences with certainty as we had small number of patients with myopathy (n = 15) and a large sample size could have better characterized the muscle symptoms.

In the present study, mean age of patients with myopathy and without myopathy was comparable. This finding suggests that myopathy in statin users are independent phenomena and is not influenced by age. This notion is further supported by earlier study findings.[10] However, few studies in literature

reported in contrast to our findings and have shown higher incidence (>42%) of musculoskeletal symptoms in older age group.[12] Some of the researchers have attributed this reported higher incidence of musculoskeletal symptoms to a higher incidence of degenerative disease in older age group.[12] However, as reported by the PRIMO study physically active patients are more likely to develop myopathy, and older age group patients are less physically active and have a sedentary lifestyle leading to a decreasing incidence of myopathy in this age group.

The results of our study are in contrast to one observational study in literature that has reported much higher prevalence of myopathy among statin users. Cooper *et al*. have reported a high incidence (65%) of muscles symptoms among statin users.[13] These patients belonged to a high age group (mean age 64.7 ± 12.1 years) who were likely to have frequent nonspecific musculoskeletal symptoms. The TNT study which compared high-dose atorvastatin (80 mg) to low-dose atorvastatin (10 mg) found no difference in the incidence of myalgia (4.8% vs. 4.7%, respectively) in high dose and low dose atorvastatin group.[14] however, Gujral *et al*. have reported no significant difference in myalgia among patients on low to moderate dose statin (71%) compared to high dose statin (61%), the effect of dose might have been nullified by higher mean age and longer duration of therapy in patients taking low to moderate dose of statin.[13] The incidence of myopathy observed in our study also contrasted with very low incidence of this adverse effect being described in various randomized controlled trials. These studies have reported low incidence of myalgia that is 1%–5% of patients in both the statin and placebo groups.[5,15]

In the present study, we found that a quarter of patients (48/200) with higher TSH levels (>4 μIU/ml). Only 2 patients (4.16%) in this group had myopathy in contrast to the total incidence of 7.5% in the entire study population. There was no significant difference in the incidence of hypothyroidism between patients with or without statin-induced myopathy. This is in contrast to the findings of the PRIMO study.[10] They found a significant difference between these two groups ($P = 0.04$). The lack of significant difference in our study may be due to relatively smaller sample size. In this study, we also measured serum Vitamin D level in 66 patients. Out of these, 51 patients had Vitamin D deficiency. While serum Vitamin D levels were comparable in patients with and without myopathy, Vitamin D deficiency was observed in a larger proportion of patients who developed myopathy as compared to those without muscle symptoms. However, this did not achieve statistical significance. This finding is similar to an earlier study conducted by Eisen *et al*. who reported muscle-related symptoms in 39% patients ($n = 106$) but did not find any significant difference in Vitamin D level among patients with or without myalgia.[16] In a retrospective medical record review done by Margenhagen *et al.*, they have reported lower incidence of adverse muscle events in the patients treated with high-dose simvastatin (80 mg) who also had a higher Vitamin D level. They suggested that correction of 25-hydroxyvitamin D levels before statin therapy initiation may mitigate one risk factor in the development of statin-related myalgia.[16] In our study, we found myopathy only in patients with Vitamin D deficiency and patients with adequate Vitamin D levels did not develop myopathy but due to the limited number of patients in which Vitamin D levels were measured, we cannot conclude with certainty regarding the risk of myopathy attributed to Vitamin D deficiency. However, Vitamin D estimation in all 200 subjects could have demonstrated more strongly the risk potential of Vitamin D deficiency with respect to atorvastatin-induced myopathy.

Furthermore, we did not find smoking or alcohol abuse to be significant risk factors for the development of statin-associated myopathy. However, in the PRIMO study, smokers had a lower incidence of myopathy compared to nonsmokers although this decreased risk was attributed to sedentary lifestyles among smokers. We did not include the detailed evaluation of physical activity and quality of life. Detailed information on these aspects could have thrown more light on clinical significance of atorvastatin-related myopathy.

Mechanism of statin-induced myopathy

There are several mechanisms postulated for statin-induced myopathy. Statin decreases cholesterol content of cell membrane so decreases its stability.[17] it has been also hypothesized that it reduces the production of ubiquinone (coenzyme Q 10), which is a component of respiratory chain in inner mitochondrial membrane.[18] This deficiency lead to abnormal energy metabolism and thus muscle weakness.[19] statins also prevent the formation of penylated proteins which include Ras, Rac, and Rho GTP-binding proteins.[9]

Management of statin-induced myopathy

There is not a single conscience for the management for statin-induced myopathy. All guideline recommend determining serum CK levels on the onset of myopathy only not in asymptomatic patients.[5] For a symptomatic rise in serum CK levels >10 times the upper limit of normal, immediate discontinuation of drug is recommended.[5,20] If CK levels are in between 3 and 10 times the normal levels, there are different opinions among different guidelines stating suspension of statins till there is an improvement in symptoms.[20]

Limitations

A large sample size could have yielded more information about the relationship of various risk factors with myopathy. This study also did not include the detailed evaluation of physical activity and quality of life.

Conclusion

Myopathy symptoms were found in a significant number of patients taking atorvastatin and the incidence of myopathy increases with increase in dose of atorvastatin. Further, though benefits of statins continue to outweigh their adverse effects. However, possible alternate options including statin switching,

nonstatin drugs, change in dosing regimens may also be considered to reduce the incidence of myopathy.

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Conflicts of interest

There are no conflicts of interest.

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